
Cervical cancer remains one of the leading causes of cancer-related deaths worldwide. Here we report the extensive molecular characterization of 228 primary cervical cancers, one of the largest comprehensive genomic studies of cervical cancer to date. We observed notable APOBEC mutagenesis patterns and identified SHKBP1, ERBB3, CASP8, HLA-A and TGFBRII as novel significantly mutated genes in cervical cancer. We also discovered amplifications in immune targets CD274 (also known as PD-L1) and PDCD1LG2 (also known as PD-L2), and the BCAR4 long non-coding RNA, which has been associated with response to lapatinib. Integration of human papilloma virus (HPV) was observed in all HPV18-related samples and 76% of HPV16-related samples, and was associated with structural aberrations and increased target-gene expression. We identified a unique set of endometrial-like cervical cancers, comprised predominantly of HPV-negative tumours with relatively high frequencies of KRAS, ARID1A and PTEN mutations. Integrative clustering of 178 samples identified keratin-low squamous, keratin-high squamous and adenocarcinoma-rich subgroups. These molecular analyses reveal new potential therapeutic targets for cervical cancers.


Hematopoietic stem cell (HSC) transplantation represents a curative treatment for various hematological disorders. However, delayed reconstitution of innate and adaptive immunity often causes fatal complications. HSC maintenance and lineage differentiation are supported by stromal niches, and we now find that bone marrow stroma cells (BMSCs) are severely and permanently damaged by the pre-conditioning irradiation required for efficient HSC transplantation. Using mouse models, we show that stromal insufficiency limits the number of donor-derived HSCs and B lymphopoiesis. Intra-bone transplantation of primary, but not cultured, BMSCs quantitatively reconstitutes stroma function in vivo, which is mediated by a multipotent NT5E+ (CD73)+ ENG- (CD105)- LY6A+ (SCA1)+ BMSC subpopulation. BMSC co-transplantation doubles the number of functional, donor-derived HSCs and significantly reduces clinically relevant side effects associated with HSC transplantation including neutropenia and humoral immunodeficiency. These data demonstrate the potential of stroma recovery to improve HSC transplantation.


BACKGROUND: Bacteria/biofilm on breast implant surfaces has been implicated in capsular contracture and breast implant-associated anaplastic large-cell lymphoma (ALCL). Macrotextured breast implants have been shown to harbor more bacteria than smooth or microtextured implants. Recent reports also suggest that macrotextured implants are associated with a significantly higher incidence of breast implant-associated ALCL. Using techniques to reduce the number of bacteria around implants, specifically, the 14-point plan, has successfully minimized the occurrence of capsular contracture. The authors hypothesize that a similar effect may be seen in reducing the risk of breast implant-associated ALCL. METHODS: Pooled data from eight plastic surgeons assessed the use of macrotextured breast implants (Biocell and polyurethane) and known cases of breast implant-associated ALCL. Surgeon adherence to the 14-point plan was also analyzed. RESULTS: A total of 42,035 Biocell implants were placed in 21,650 patients; mean follow-up was 11.7 years (range, 1 to 14 years). A total of 704 polyurethane implants were used, with a mean follow-up of 8.0 years
The overall capsular contracture rate was 2.2 percent. There were no cases of implant-associated ALCL. All surgeons routinely performed all 13 perioperative components of the 14-point plan; two surgeons do not routinely prescribe prophylaxis for subsequent unrelated procedures. CONCLUSIONS: Mounting evidence implicates the role of a sustained T-cell response to implant bacteria/biofilm in the development of breast implant-associated ALCL. Using the principles of the 14-point plan to minimize bacterial load at the time of surgery, the development and subsequent sequelae of capsular contracture and breast implant-associated ALCL may be reduced, especially with higher-risk macrotextured implants.

CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, IV.


BACKGROUND: The purpose of this study was to estimate the gap between the available and the ideal supply of human resources (physicians, nurses, and health promoters) to deliver the guaranteed package of prevention and health promotion services at urban and rural primary care facilities in Mexico. METHODS: We conducted a cross-sectional observational study using a convenience sample. We selected 20 primary health facilities in urban and rural areas in 10 states of Mexico. We calculated the available and the ideal supply of human resources in these facilities using estimates of time available, used, and required to deliver health prevention and promotion services. We performed descriptive statistics and bivariate hypothesis testing using Wilcoxon and Friedman tests. Finally, we conducted a sensitivity analysis to test whether the non-normal distribution of our time variables biased estimation of available and ideal supply of human resources. RESULTS: The comparison between available and ideal supply for urban and rural primary health care facilities reveals a low supply of physicians. On average, primary health care facilities are lacking five physicians when they were estimated with time used and nine if they were estimated with time required (P < 0.05). No difference was observed between available and ideal supply of nurses in either urban or rural primary health care facilities. There is a shortage of health promoters in urban primary health facilities (P < 0.05). CONCLUSION: The available supply of physicians and health promoters is lower than the ideal supply to deliver the guaranteed package of prevention and health promotion services. Policies must address the level and distribution of human resources in primary health facilities.


This paper provides an overview of the discussion and presentations from the Workshop on the Management of Large CryoEM Facilities held at the New York Structural Biology Center, New York, NY on February 6-7, 2017. A major objective of the workshop was to discuss best practices for managing cryoEM facilities. The discussions were largely focused on supporting single-particle methods for cryoEM and topics included: user access, assessing projects, workflow, sample handling, microscopy, data management and processing, and user training.


We have analyzed a set of quinolinequinones with respect to their reactivities, cytotoxicities, and anti-HIV-1 properties. Most of the quinolinequinones were reactive with glutathione, and several acted as sulfhydryl crosslinking agents. Quinolinequinones inhibited binding of the HIV-1 matrix protein to RNA to varying degrees, and several quinolinequinones showed the capacity to crosslink HIV-1 matrix proteins in vitro, and HIV-1 structural proteins in virus particles. Cytotoxicity assays yielded quinolinequinone CC50 values in the
low micromolar range, reducing the potential therapeutic value of these compounds. However, one compound, 6,7-dichloro-5,8-quinolinequinone potently inactivated HIV-1, suggesting that quinolinequinones may prove useful in the preparation of inactivated virus vaccines or for other virucidal purposes.


OBJECTIVE: Acute invasive fungal sinusitis (AIFS) is a frequently fatal infection for which extensive and debilitating surgical debridement is a mainstay of therapy. Resulting defects are often composite in nature, mandating free tissue-transfer reconstruction. Outcomes data for free flap reconstruction are limited. The purpose of this study was to examine surgical outcomes and survival in patients undergoing free flap transfer following invasive fungal sinusitis. STUDY DESIGN: Retrospective case series. METHODS: Between 1995 and 2015, patients undergoing operative debridement for AIFS were identified. Surgical records were used to identify survivors of acute infection who subsequently underwent free flap reconstructive surgery. Patient demographics, cause of immune compromise, defect description, flap type, perioperative complications, indications for revision surgery, functional outcomes, and long-term survival were reviewed. RESULTS: Forty-four patients were treated for AIFS, of those, 30 (68%) survived acute infection. Ten patients underwent maxillectomy, six with orbital exenteration, and were designated candidates for reconstruction. Eight patients underwent reconstruction. Median time from debridement to reconstruction was 67.5 days. Flap types included latissimus dorsi, scapula, anterolateral thigh, rectus, radial forearm, and fibula. Median follow-up was 7.7 months. No perioperative complications were encountered, and all subjects remained disease-free, able to speak and eat normally without prosthetic supplementation. Seven patients (87%) are currently alive. CONCLUSION: Reconstruction of defects left by invasive fungal sinusitis using free-tissue transfer resulted in successful flap survival, with no disease recurrence for all defects and flap types reviewed. Survivors of AIFS are able to tolerate midface reconstruction, with favorable functional outcomes and survival rates. LEVEL OF EVIDENCE: 4. Laryngoscope, 127:815-819, 2017.


INTRODUCTION: The World Health Organization (WHO) and other health agencies have concluded that yellow fever booster vaccination is unnecessary since a single dose of vaccine confers lifelong immunity. Areas covered: We reviewed the clinical studies cited by health authorities in their investigation of both the safety profile and duration of immunity for the YFV-17D vaccine and examined the position that booster vaccination is no longer needed. We found that antiviral immunity may be lost in 1-in-3 to 1-in-5 individuals within 5 to 10 years after a single vaccination and that children may be at greater risk for primary vaccine failure. The safety profile of YFV-17D was compared to other licensed vaccines including oral polio vaccine (OPV) and the rotavirus vaccine, RotaShield, which have subsequently been withdrawn from the US and world market, respectively. Expert commentary: Based on these results and recent epidemiological data on vaccine failures (particularly evident at >10 years after vaccination), we believe that current recommendations to no longer administer YFV-17D booster vaccination be carefully re-evaluated, and that further development of safer vaccine approaches should be considered.


OBJECTIVES: The aim of this in vitro study was to analyze the effect of the incorporation of two anti-caries agents into dental adhesives on the reduction of the virulence of Streptococcus mutans and on the adhesion to dentin.
METHODS: Apigenin (1mM) and tt-Farnesol (5mM) were added separately and in combination to a self-etch adhesive (CS3 - Clearfil S3 Bond Plus) and to an etch-and-rinse adhesive (OPT - OptiBond S). Biofilm of S. mutans was grown on adhesive-coated hydroxyapatite disks for 115h and bacterial viability, dry-weight, alkali soluble, water soluble, intracellular polysaccharides and protein were quantified. Bond strength and dentin-adhesive interface were performed to analyze the effects of the incorporation on the physical properties and to identify changes in hybrid layer morphology. RESULTS: Addition of Apigenin and Apigenin+tt-Farnesol to CS3, and Apigenin or tt-Farnesol to OPT reduced the dry-weight of S. mutans biofilm. Insoluble polysaccharide decreased with the addition of Apigenin to CS3 and tt-Farnesol to OPT. Intracellular polysaccharide decreased with addition of Apigenin and Apigenin+tt-Farnesol to CS3. No changes in dentin bond strength, resin-dentin interfacial morphology, total amount of protein and soluble polysaccharide were observed with the additions. SIGNIFICANCE: Biofilms that are less cariogenic around dental restorations could decrease secondary caries formation; in addition, the reduction of virulence of S. mutans without necessarily killing the microorganism is more unlikely to induce antimicrobial resistance.


Neuronal elements distributed throughout the cardiac nervous system, from the level of the insular cortex to the intrinsic cardiac nervous system, are in constant communication with one another to ensure that cardiac output matches the dynamic process of regional blood flow demand. Neural elements in their various ‘levels’ become differentially recruited in the transduction of sensory inputs arising from the heart, major vessels, other visceral organs and somatic structures to optimize neuronal coordination of regional cardiac function. This White Paper will review the relevant aspects of the structural and functional organization for autonomic control of the heart in normal conditions, how these systems remodel/adapt during cardiac disease, and finally how such knowledge can be leveraged in the evolving realm of autonomic regulation therapy for cardiac therapeutics.
Aims The majority of sudden cardiac arrests (SCAs) occur in patients with left-ventricular (LV) ejection fraction (LVEF) >35%, yet there are no methods for effective risk stratification in this sub-group. Since abnormalities of LV geometry can be identified even with preserved LVEF, we investigated the potential impact of LV geometry as a novel risk marker for this patient population. Methods and results In the ongoing Oregon Sudden Unexpected Death Study, SCA cases with archived echocardiographic data available were prospectively identified during 2002-15, and compared with geographical controls. Analysis was restricted to subjects with LVEF >35%. Based on established measures of LV mass and relative wall thickness (ratio of wall thickness to cavity diameter), four different LV geometric patterns were identified: normal geometry, concentric remodelling, concentric hypertrophy, and eccentric hypertrophy. Sudden cardiac arrest cases (n = 307) and controls (n = 280) did not differ in age, sex, or LVEF, but increased LV mass was more common in cases. Twenty-nine percent of SCA cases presented with normal LV geometry, 35% had concentric remodelling, 25% concentric hypertrophy, and 11% eccentric hypertrophy. In multivariate model, concentric remodelling (OR 1.76; 95%CI 1.18-2.63; P = 0.005), concentric hypertrophy (OR 3.20; 95%CI 1.90-5.39; P < 0.001), and eccentric hypertrophy (OR 2.47; 95%CI 1.30-4.66; P = 0.006) were associated with increased risk of SCA. Conclusion Concentric and eccentric LV hypertrophy, but also concentric remodelling without hypertrophy, are associated with increased risk of SCA. These novel findings suggest the potential utility of evaluating LV geometry as a potential risk stratification tool in patients with preserved or moderately reduced LVEF. © 2016 The Author.

In this research agenda on the acute and critical care management of trauma patients, we concentrate on the major factors leading to death, namely haemorrhage and traumatic brain injury (TBI). In haemostasis biology, the results of randomised controlled trials have led to the therapeutic focus moving away from the augmentation of coagulation factors (such as recombinant factor VIIa) and towards fibrinogen supplementation and administration of antifibrinolytics such as tranexamic acid. Novel diagnostic techniques need to be evaluated to determine whether an individualised precision approach is superior to current empirical practice. The timing and efficacy of platelet transfusions remain in question, while new blood products need to be developed and evaluated, including whole blood variants, lyophilised products and novel red cell storage modalities. The current cornerstones of TBI management are intracranial pressure control, maintenance of cerebral perfusion pressure and avoidance of secondary insults (such as hypotension, hypoxaemia, hyperglycaemia and pyrexia). Therapeutic hypothermia and decompressive craniectomy are controversial therapies. Further research into these strategies should focus on identifying which subgroups of patients may benefit from these interventions. Prediction of the long-term outcome early after TBI remains challenging. Early magnetic resonance imaging has recently been evaluated for predicting the long-term outcome in mild and severe TBI. Novel biomarkers may also help in outcome prediction and may predict chronic neurological symptoms. For trauma in general, rehabilitation is complex and multidimensional, and the optimal timing for commencement of rehabilitation needs investigation. We propose priority areas for clinical trials in the next 10 years.
save millions of lives through cancer prevention. As the main providers of cancer care worldwide, our patients, their families, and our communities look to us for guidance regarding all things cancer related, including cancer prevention. Through this statement and accompanying recommendations, ASCO hopes to increase awareness of the tremendous global impact of human papillomavirus (HPV)-caused cancers, refocus the discussion of HPV vaccination on its likely ability to prevent millions of cancer deaths, and increase HPV vaccination uptake via greater involvement of oncology professionals in ensuring accurate public discourse about HPV vaccination and calling for the implementation of concrete strategies to address barriers to vaccine access and acceptance.


Objective To describe the cost, length of stay, and incidence of postoperative hemorrhage associated with Down syndrome (DS) patients undergoing tonsillectomy in a national sample of inpatient children. Study Design This study uses a national cross-sectional cohort to analyze children with and without DS undergoing tonsillectomy with or without adenoidectomy. Setting 2012 Healthcare Cost and Utilization Project Kids' Inpatient Database. Subjects and Methods The database was analyzed for postoperative hemorrhage and respiratory compromise, length of stay, and total charges of hospital stay. These outcomes were compared between patients with DS vs patients without DS. Results In total, 7512 patients were identified who underwent tonsillectomy: 7159 patients without DS and 353 patients with DS. The non-DS group was younger with a median age of 3 years (range, 0-18) compared with a DS median age of 4 years (range, 0-20), P = .004. The DS group had a significant increase in postoperative hemorrhage compared with non-DS (10 [2.8%] vs 87 [1.2%], respectively), P = .024. However, the DS and non-DS groups were comparable for respiratory complications (5 [1.4%] vs 106 [1.5%], respectively), P = .922. Median length of stay was significantly increased in the DS group (1 [interquartile range (IQR), 1-3]) compared with the non-DS group (1 [IQR, 1-2]), P < .001. Median charges for hospital stay totaled $17,451 (IQR, $11,901-$24,949) for the DS group compared with $14,395 (IQR, $9739-$21,890) for the non-DS group, P < .001. Conclusion Across the United States, children with DS hospitalized for tonsillectomy have an increased length of stay and cost of care. These data also suggest an increased risk of postoperative hemorrhage during the initial admission without an increased risk of respiratory complications.


Background Previous reports suggest that patients with Parkinson disease (PD) have elevated rates of complications following spine surgery; however, these reports are limited by small patient series. In this study, we used the National Inpatient Sample (NIS) database to compare in-hospital complications following elective lumbar spine surgery in patients with a diagnosis of PD and patients without PD. Methods The NIS database was accessed to identify patients with PD and those without PD who underwent lumbar spine surgery. All patients identified had a diagnosis code consistent with degenerative lumbar spine pathology. The patients were evaluated for the presence or absence of PD and divided into 4 lumbar spine procedure groups: decompression alone, lateral fusion, posterior fusion, and anterior fusion technique. Propensity score matching (PSM) was performed for the PD versus non-PD patients in each procedure group to control for confounding demographic variables, and in-hospital complications were compared between the 2 groups. Results Between 2001 and 2012, a total of 613,522 lumbar spine surgery patient episodes were identified, of which 4492 (0.7%) involved a diagnosis of PD. Following PSM for patient age, sex, and race, the patients with PD were at increased risk for acute postoperative hemorrhagic anemia, increased blood transfusion requirements, and increased genitourinary, neurologic, and cardiac complications compared with the patients without PD. Conclusions PSM analysis of the NIS database demonstrated that patients with PD are
at increased risk for acute in-hospital complications and greater blood transfusion requirements than those without PD. Surgeons should be aware of the increased risks and differing requirements when treating spinal pathology in patients with PD. © 2017 Elsevier Inc.


Alcohol is a human carcinogen. A causal link has been established between alcohol drinking and cancers of the upper aerodigestive tract, colon, liver and breast. Despite this established association, the underlying mechanisms of alcohol-induced carcinogenesis remain unclear. Various mechanisms may come into play depending on the type of cancer; however, convincing evidence supports the concept that ethanol’s major metabolite acetaldehyde may play a major role. Acetaldehyde can react with DNA forming adducts which can serve as biomarkers of carcinogen exposure and potentially of cancer risk. The major DNA adduct formed from this reaction is N (2)-ethyldideoxyguanosine, which can be quantified as its reduced form N (2)-ethyl-dG by LC-ESI-MS/MS. To investigate the potential use of N (2)-ethyl-dG as a biomarker of alcohol-induced DNA damage, we quantified this adduct in DNA from the oral, oesophageal and mammary gland tissues from rhesus monkeys exposed to alcohol drinking over their lifetimes and compared it to controls. N (2)-Ethyl-dG levels were significantly higher in the oral mucosa DNA of the exposed animals. Levels of the DNA adduct measured in the oesophageal mucosa of exposed animals were not significantly different from controls. A correlation between the levels measured in the oral and oesophageal DNA, however, was observed, suggesting a common source of formation of the DNA adducts. N (2) -Ethyl-dG was measured in mammary gland DNA from a small cohort of female animals, but no difference was observed between exposed animals and controls. These results support the hypothesis that acetaldehyde induces DNA damage in the oral mucosa of alcohol-exposed animals and that it may play role in the alcohol-induced carcinogenic process. The decrease of N (2)-ethyl-dG levels in exposed tissues further removed from the mouth also suggests a role of alcohol metabolism in the oral cavity, which may be considered separately from ethanol liver metabolism in the investigation of ethanol-related cancer risk.


By expressing vesicular glutamate transporters at high levels in plasma membrane and applying voltage clamp methods, Eriksen et al. (2016) have identified a Cl(-) channel in the transporter that is coactivated by protons and Cl(-).


BACKGROUND: In an effort to reduce the disease burden in rural Rwanda, decrease poverty associated with expenditures for fuel, and minimize the environmental impact on forests and greenhouse gases from inefficient combustion of biomass, the Rwanda Ministry of Health (MOH) partnered with DelAgua Health (DelAgua), a private social enterprise, to distribute and promote the use of improved cookstoves and advanced water filters to the poorest quarter of households (Ubudehe 1 and 2) nationally, beginning in Western Province under a program branded Tubeho Neza (“Live Well”). The project is privately financed and earns revenue from carbon credits under the United Nations Clean Development Mechanism. METHODS:
During a 3-month period in late 2014, over 470,000 people living in over 101,000 households were provided free water filters and cookstoves. Following the distribution, community health workers visited nearly 98% of households to perform household level education and training activities. Over 87% of households were visited again within 6 months with a basic survey conducted. Detailed adoption surveys were conducted among a sample of households, 1000 in the first round, 187 in the second. RESULTS: Approximately a year after distribution, reported water filter use was above 90% (+/-4% CI) and water present in filter was observed in over 76% (+/-6% CI) of households, while the reported primary stove was nearly 90% (+/-4.4% CI) and of households cooking at the time of the visit, over 83% (+/-5.3% CI) were on the improved stove. There was no observed association between household size and stove stacking behavior. CONCLUSIONS: This program suggests that free distribution is not a determinant of low adoption. It is plausible that continued engagement in households, enabled by Ministry of Health support and carbon financed revenue, contributed to high adoption rates. Overall, the program was able to demonstrate a privately financed, public health intervention can achieve high levels of initial adoption and usage of household level water filtration and improved cookstoves at a large scale.


OBJECTIVES/HYPOTHESIS: To determine whether the application of laser-assisted techniques for the treatment of Zenker’s diverticulum would reduce the failure rate of endoscopic procedures without compromising safety or durability. STUDY DESIGN: Cohort study with long-term follow-up. METHODS: We performed a single-institution review of 106 consecutive patients in whom endoscopic laser-assisted diverticulotomy (ELD) or endoscopic stapler-assisted diverticulotomy (ESD) was attempted. The Eating Assessment Tool was collected pre- and postoperatively. Long-term follow-up was conducted on average 2.4 years postoperatively. RESULTS: The decision to use either ELD or ESD was made intraoperatively. An endoscopic procedure was successfully completed in 103 of 106 patients (97.2%). Eighty-three patients underwent ELD, 20 underwent ESD, and only three required use of an open approach. No serious complications occurred. Postoperatively, there was a significant reduction in dysphagia symptoms. At follow-up, most individuals had dysphagia scores within the normal range (69%) and were eating a regular diet (73%). Fourteen patients (14%) required revision. Compared to historical data from our institution for ESD alone, the addition of ELD resulted in a reduction in the failure rate without an increase in serious complications. Recurrence rates and long-term outcomes were equivalent. CONCLUSION: Through careful patient selection, appropriate workup, and judicious use of techniques, it was possible to perform endoscopic surgery in a majority of patients without serious complications. Both approaches resulted in short- and long-term symptom management with high levels of satisfaction. LEVEL OF EVIDENCE: 4. Laryngoscope, 126:2705-2710, 2016.


This consensus guideline discusses the electrocardiographic phenomenon of beat-to-beat QT interval variability (QTV) on surface electrocardiograms. The text covers measurement principles, physiological basis, and clinical value of QTV. Technical considerations include QT interval measurement and the relation between QTV and heart rate variability. Research frontiers of QTV include understanding of QTV physiology, systematic evaluation of the link between QTV and direct measures of neural activity, modelling of the QTV dependence on the variability of other physiological variables, distinction between QTV and general T wave shape variability, and assessing of the QTV utility for guiding therapy. Increased QTV appears to be a risk marker of arrhythmic and cardiovascular death. It remains to be established whether it can guide therapy alone or in combination with other risk factors. QT interval variability has a possible role in non-invasive assessment of tonic sympathetic activity.
Vagus nerve stimulation (VNS) currently treats patients with drug-resistant epilepsy, depression, and heart failure. The mild intensities used in chronic VNS suggest that primary visceral afferents and central nervous system activation are involved. Here, we measured the activity of neurons in the nucleus of the solitary tract (NTS) in anesthetized rats using clinically styled VNS. Our chief findings indicate that VNS at threshold bradycardic intensity activated NTS neuron discharge in one-third of NTS neurons. This VNS directly activated only myelinated vagal afferents projecting to second-order NTS neurons. Most VNS-induced activity in NTS, however, was unsynchronized to vagal stimuli. Thus, VNS activated unsynchronized activity in NTS neurons that were second order to vagal afferent C-fibers as well as higher-order NTS neurons only polysynaptically activated by the vagus. Overall, cardiovascular-sensitive and -insensitive NTS neurons were similarly activated by VNS: 3/4 neurons with monosynaptic vagal A-fiber afferents, 6/42 neurons with monosynaptic vagal C-fiber afferents, and 16/21 polysynaptic NTS neurons. Provocatively, vagal A-fibers indirectly activated C-fiber neurons during VNS. Elevated spontaneous spiking was quantitatively much higher than synchronized activity and extended well into the periods of nonstimulation. Surprisingly, many polysynaptic NTS neurons responded to half the bradycardic intensity used in clinical studies, indicating that a subset of myelinated vagal afferents is sufficient to evoke VNS indirect activation. Our study uncovered a myelinated vagal afferent drive that indirectly activates NTS neurons and thus central pathways beyond NTS and support reconsideration of brain contributions of vagal afferents underpinning therapeutic impacts.

NEW & NOTEWORTHY Acute vagus nerve stimulation elevated activity in neurons located in the medial nucleus of the solitary tract. Such stimuli directly activated only myelinated vagal afferents but indirectly activated a subpopulation of second- and higher-order neurons, suggesting that afferent mechanisms and central neuron activation may be responsible for vagus nerve stimulation efficacy.


OBJECTIVE: To determine whether providing remote neurologic care into the homes of people with Parkinson disease (PD) is feasible, beneficial, and valuable. METHODS: In a 1-year randomized controlled trial, we compared usual care to usual care supplemented by 4 virtual visits via video conferencing from a remote specialist into patients’ homes. Primary outcome measures were feasibility, as measured by the proportion who completed at least one virtual visit and the proportion of virtual visits completed on time; and efficacy, as measured by the change in the Parkinson’s Disease Questionnaire-39, a quality of life scale. Secondary outcomes included quality of care, caregiver burden, and time and travel savings. RESULTS: A total of 927 individuals indicated interest, 210 were enrolled, and 195 were randomized. Participants had recently seen a specialist (73%) and were largely college-educated (73%) and white (96%). Ninety-five (98% of the intervention group) completed at least one virtual visit, and 91% of 388 virtual visits were completed. Quality of life did not improve in those receiving virtual house calls (0.3 points worse on a 100-point scale; 95% confidence interval [CI] -2.0 to 2.7 points; p = 0.78) nor did quality of care or caregiver burden. Each virtual house call saved patients a median of 88 minutes (95% CI 70-120; p < 0.0001) and 38 miles per visit (95% CI 36-56; p < 0.0001). CONCLUSIONS: Providing remote neurologic care directly into the homes of people with PD was feasible and was neither
more nor less efficacious than usual in-person care. Virtual house calls generated great interest and provided substantial convenience. CLINICALTRIALS.GOV IDENTIFIER: NCT02038959. CLASSIFICATION OF EVIDENCE: This study provides Class III evidence that for patients with PD, virtual house calls from a neurologist are feasible and do not significantly change quality of life compared to in-person visits. The study is rated Class III because it was not possible to mask patients to visit type.


Background: Continuous glucose monitoring (CGM), which studies have shown is beneficial for adults with type 1 diabetes, has not been well-evaluated in those with type 2 diabetes receiving insulin. Objective: To determine the effectiveness of CGM in adults with type 2 diabetes receiving multiple daily injections of insulin. Design: Randomized clinical trial. (The protocol also included a type 1 diabetes cohort in a parallel trial and subsequent second trial.) (ClinicalTrials.gov: NCT02282397). Setting: 25 endocrinology practices in North America. Patients: 158 adults who had had type 2 diabetes for a median of 17 years (interquartile range, 11 to 23 years). Participants were aged 35 to 79 years (mean, 60 years [SD, 10]), were receiving multiple daily injections of insulin, and had hemoglobin A1c (HbA1c) levels of 7.5% to 9.9% (mean, 8.5%). Intervention: Random assignment to CGM (n = 79) or usual care (control group, n = 79). Measurements: The primary outcome was HbA1c reduction at 24 weeks. Results: Mean HbA1c levels decreased to 7.7% in the CGM group and 8.0% in the control group at 24 weeks (adjusted difference in mean change, -0.3% [95% CI, -0.5% to 0.0%]; P = 0.022). The groups did not differ meaningfully in CGM-measured hypoglycemia or quality-of-life outcomes. The CGM group averaged 6.7 days (SD, 0.9) of CGM use per week. Limitation: 6-month follow-up. Conclusion: A high percentage of adults who received multiple daily insulin injections for type 2 diabetes used CGM on a daily or near-daily basis for 24 weeks and had improved glycemic control. Because few insulin-treated patients with type 2 diabetes currently use CGM, these results support an additional management method that may benefit these patients. Primary Funding Source: Dexcom.


Computed tomography (CT) lung density is an accepted biomarker for emphysema in alpha-1 antitrypsin deficiency (AATD), although concerns for radiation exposure limit its longitudinal use. Serum proteins associated with emphysema, particularly in early disease, may provide additional pathogenic insights. We investigated whether distinct proteomic signatures characterize the presence and progression of emphysema in individuals with severe AATD and normal forced expiratory volume in 1 second (FEV1). QUANTitative lung CT UnMasking emphysema progression in AATD (QUANTUM-1) is a multicenter, prospective 3-year study of 49 adults with severe AATD and FEV1 post-bronchodilator values (Post-BD) >80% predicted. All participants received chest CT, serial spirometry, and contributed to the serum biobank. Volumetric imaging display and analysis (VIDA) software defined the baseline 15th percentile density (PD15) which was indexed to CT-derived total lung capacity (TLC). We measured 317 proteins using a multiplexed immunoassay (Myriad Discovery MAP(R) panel) in 31 individuals with a complete dataset. We analyzed associations between initial PD15/TLC, PD15/TLC annual decline, body mass index (BMI), and protein levels using Pearson’s product moment correlation. C-reactive protein (CRP), adipocyte fatty acid-binding protein (AFBP), leptin, and tissue plasminogen activator (tPA) were found to be associated with baseline emphysema and all but leptin were associated with emphysema progression after adjustments were made for age and sex. All 4 proteins were
associated with BMI after further adjustment for multiple comparisons was made. The relationship between these proteins and BMI, and further validation of these findings in replicative cohorts require additional studies.


Importance: Early-life epilepsies are often a consequence of numerous neurodevelopmental disorders, most of which are proving to have genetic origins. The role of genetic testing in the initial evaluation of these epilepsies is not established. Objective: To provide a contemporary account of the patterns of use and diagnostic yield of genetic testing for early-life epilepsies. Design, Setting, and Participants: In this prospective cohort, children with newly diagnosed epilepsy with an onset at less than 3 years of age were recruited from March 1, 2012, to April 30, 2015, from 17 US pediatric hospitals and followed up for 1 year. Of 795 families approached, 775 agreed to participate. Clinical diagnosis of the etiology of epilepsy were characterized based on information available before genetic testing was performed. Added contributions of cytogenetic and gene sequencing investigations were determined. Exposures: Genetic diagnostic testing. Main Outcomes and Measures: Laboratory-confirmed pathogenic variant. Results: Of the 775 patients in the study (367 girls and 408 boys; median age of onset, 7.5 months [interquartile range, 4.2-16.5 months]), 95 (12.3%) had acquired brain injuries. Of the remaining 680 patients, 327 (48.1%) underwent various forms of genetic testing, which identified pathogenic variants in 132 of 327 children (40.4%; 95% CI, 37%-44%): 26 of 59 (44.1%) with karyotyping, 32 of 188 (17.0%) with microarrays, 31 of 114 (27.2%) with epilepsy panels, 11 of 33 (33.3%) with whole exomes, 4 of 20 (20.0%) with mitochondrial panels, and 28 of 94 (29.8%) with other tests. Forty-four variants were identified before initial epilepsy presentation. Apart from dysmorphic syndromes, pathogenic yields were highest for children with tuberous sclerosis complex (9 of 11 [81.8%]), metabolic diseases (11 of 14 [78.6%]), and brain malformations (20 of 61 [32.8%]). A total of 180 of 446 children (40.4%), whose etiology would have remained unknown without genetic testing, underwent some testing. Pathogenic variants were identified in 48 of 180 children (26.7%; 95% CI, 18%-34%). Diagnostic yields were greater than 15% regardless of delay, spasms, and young age. Yields were greater for epilepsy panels (28 of 96 [29.2%]; P < .001) and whole exomes (5 of 18 [27.8%; P = .02] than for chromosomal microarray (8 of 101 [7.9%]). Conclusions and Relevance: Genetic investigations, particularly broad sequencing methods, have high diagnostic yields in newly diagnosed early-life epilepsies regardless of key clinical features. Thorough genetic investigation emphasizing sequencing tests should be incorporated into the initial evaluation of newly presenting early-life epilepsies and not just reserved for those with severe presentations and poor outcomes.


BACKGROUND: Using positron emission tomography (PET) imaging, we sought to determine whether normal age or exercise training cause changes in the cardiac sympathetic nervous system function in male or female healthy volunteers. METHODS: Healthy sedentary participants underwent PET studies before and after 6 months of supervised exercise training. Presynaptic uptake by the norepinephrine transporter-1 function was measured using PET imaging of [(11)C]-meta-hydroxyephedrine, a norepinephrine analog, and expressed as a permeability-surface area product (PSnt in mL/min/mL). Postsynaptic function was measured as beta-adrenergic receptor density (beta'max in pmol/mL tissue) by imaging the beta-receptor antagonist [(11)C]-CGP12177. Myocardial blood flow (MBF in mL/min/mL tissue) was measured by imaging [(15)O]-water.
This study was initiated to determine whether the noradrenergic (NE) neurons of the locus coeruleus (LC) could mediate the stimulatory action of androgens on serotonin-related gene expression in male macaques. These experiments follow our observations that serotonin neurons lack androgen receptors (ARs), and yet respond to androgens. Male Japanese macaques (Macaca fuscata) were castrated for 5-7 months and then treated for 3 months with [1] placebo, [2] T (testosterone), [3] DHT (dihydrotestosterone; non-aromatizable androgen) plus ATD (steroidal aromatase inhibitor), or [4] FLUT (Flutamide; androgen antagonist) plus ATD (n=5/group). The noradrenergic (NE) innervation of the raphe was determined with immunolabeling of axons with an antibody to dopamine-beta-hydroxylase (DBH). Immunolabeling of tyrosine hydroxylase (TH) dendrites and corticotropin releasing hormone (CRH) axons innervating the LC was also determined. Due to the longer treatment period employed, the expression of the cognate nuclear receptors was sought. Androgen receptor (AR), estrogen receptor alpha (ERalpha) and estrogen receptor beta (ERbeta) immunostaining was accomplished. Quantitative image analysis was applied and immunopositive neurons or axons with boutons were measured. Double-label of NE neurons for each receptor plus TH determined whether the receptors were localized in NE neurons. Androgens with or without aromatase activity significantly stimulated DBH axon density in the raphe (ANOVA, p=0.006), and LC dendritic TH (ANOVA, p<0.0001), similar to serotonin-related mRNA expression in the raphe. There were significantly more AR-positive neurons in TH and DHT+ATD-treated groups compared to placebo or FLUT+ATD-treated groups (ANOVA, p=0.0014). There was no difference in the number of positive-neurons stained for ERalpha or ERbeta. The CRH axon density in the LC was significantly reduced with aromatase inhibition, suggesting that CRH depends on estrogen, not androgens (ANOVA, p=0.0023). Double-immunohistochemistry revealed that NE neurons did not contain AR. Rather, AR-positive nuclei were found in neighboring cells that are likely neurons. However, >80% of LC NE neurons contained ERalpha or ERbeta. In conclusion, the LC NE neurons may transduce the stimulatory effect of androgens on serotonin-related gene expression. Since LC NE neurons lack AR, the androgenic effect of androgens on serotonin would be mediated by the estrogenic actions of aromatizable androgens.
stimulation of dendritic TH and axonal DBH may be indirectly mediated by other neurons. Estrogen, either from metabolism of T or from de novo synthesis, appears necessary for robust CRH innervation of the LC, which differs from female macaques.


BACKGROUND: This qualitative study investigated gender power inequalities as they contribute to relationship dynamics and HIV-serostatus disclosure among men and women living with HIV in Durban, South Africa. HIV serodiscordance among men and women within stable partnerships contributes to high HIV incidence in southern Africa, yet disclosure rates remain low. Given the emphasis on prevention for HIV-serodiscordant couples, this research supports the urgent need to explore how best to support couples to recognize that they are part of this priority population and to access appropriate prevention and treatment. METHODS: Thirty-five in-depth individual interviews were conducted with 15 HIV-positive men and 20 HIV-positive women (not couples) receiving care at public-sector clinics near Durban. A structured coding scheme was developed to investigate men's and women's attitudes toward HIV-serostatus disclosure and behaviors of sharing (or not sharing) HIV serostatus with a partner. Narratives were analyzed for barriers and facilitators of disclosure through the lens of sociocultural gender inequality, focusing on reasons for non-disclosure. RESULTS: Among 35 participants: median age was 33 years (men) and 30 years (women); average years since HIV diagnosis was 1 (men) and 1.5 (women). Four themes related to gender inequality and HIV-serostatus disclosure emerged: (1) Men and women fear disclosing to partners due to concerns about stigma and relationship dissolution, (2) suspicions and mistrust between partners underlies decisions for non-disclosure, (3) unequal, gendered power in relationships causes differential likelihood and safety of disclosure among men and women, and (4) incomplete or implicit disclosure are strategies to navigate disclosure challenges. Findings illustrate HIV-serostatus disclosure as a complex process evolving over time, rather than a one-time event. CONCLUSION: Partner communication about HIV serostatus is infrequent and complicated, with gender inequalities contributing to fear, mistrust, and partial or implicit disclosure. Relationship dynamics and gender roles shape the environment within which men and women can engage successfully in the HIV-serostatus disclosure process. Integrated interventions to reduce barriers to trustful and effective communication are needed for HIV-affected men and women in partnerships in which seeking couples-based HIV counseling and testing (CHCT) is challenging or unlikely. These data offer insights to support HIV-serostatus disclosure strategies within relationships over time.


BACKGROUND: There is an evidence gap regarding the use of regional anaesthesia (epidural, spinal, or combined epidural/spinal anaesthesia) and associated complications by maternal body mass index (BMI). We examine associations between regional anaesthesia, mode of delivery, and regional anaesthesia complications by pre-pregnancy BMI categories among term deliveries. METHODS: Retrospective cohort study of births in California, 2007-2010, utilizing linked birth certificate data and patient discharge data. Outcomes were mode of delivery (among laboured deliveries) and select regional anaesthesia complications. Multivariable Poisson regression was used to adjust for maternal characteristics. RESULTS: In women undergoing labour (i.e. laboured delivery), women with higher BMI categories were more likely to receive regional analgesia in a dose-response fashion (adjusted risk ratio [RR] 1.10, 95% confidence interval [CI] 1.10, 1.11 for primiparous women with category I obesity), and in those receiving regional anaesthesia, were less likely to deliver vaginally (e.g. RR 0.85, 95% CI 0.84, 0.85 for the same category of women). Regional anaesthesia complications displayed a complex relationship with maternal BMI, with women in intermediate obesity categories having decreased odds as compared to normal-weight women, and women in the highest BMI category having a twofold increased risk of complications (RR 2.34, 95% CI 1.37, 4.02 for primiparous...
women). CONCLUSION: Labouring women in higher BMI categories were more likely to receive regional anaesthesia and more likely to deliver via caesarean compared to normal weight women and women without regional anaesthesia. Rates of anaesthesia complications were highest among women in the highest BMI category.


Purpose To describe a fully automated segmentation method that yields object-based morphologic estimates of enlarged perivascular spaces (ePVSs) in clinical-field-strength (3.0-T) magnetic resonance (MR) imaging data. Materials and Methods In this HIPAA-compliant study, MR imaging data were obtained with a 3.0-T MR imager in research participants without dementia (mean age, 85.3 years; range, 70.4-101.2 years) who had given written informed consent. This method is built on (a) relative normalized white matter, ventricular and cortical signal intensities within T1-weighted, fluid-attenuated inversion recovery, T2-weighted, and proton density data and (b) morphologic (width, volume, linearity) characterization of each resultant cluster. Visual rating was performed by three raters, including one neuroradiologist, after established single-section guidelines. Correlations between visual counts and automated counts, as well session-to-session correlation of counts within each participant, were assessed with the Pearson correlation coefficient r. Results There was a significant correlation between counts by visual raters and automated detection of ePVSs in the same section (r = 0.65, P < .001; r = 0.69, P < .001; and r = 0.54, P < .01 for raters 1, 2, and 3, respectively). With regard to visual ratings and whole-brain count consistency, average visual rating scores were highly correlated with automated detection of total burden volume (r = 0.58, P < .01) and total ePVS number (r = 0.76, P < .01). Morphology of clusters across 28 data sets was consistent with published radiographic estimates of ePVS; mean width of clusters segmented was 3.12 mm (range, 1.7-13.5 mm). Conclusion This MR imaging-based method for multimodal autoidentification of perivascular spaces yields individual whole-brain morphologic characterization of ePVS in clinical MR imaging data and is an important tool in the detailed assessment of these features. (c) RSNA, 2017 Online supplemental material is available for this article.


Purpose of the Study: Studying the brain through autopsy is an essential component of Alzheimer’s disease research. Racial and ethnic minorities are underrepresented in Alzheimer’s research generally and, in particular, in the number of completed brain autopsies. We explored beliefs about and attitudes toward brain donation among African American, Chinese, Caucasian, and Latino research subjects and their family members through focus groups at 4 NIH-funded Alzheimer’s Disease Centers. Design and Methods: Eighteen focus groups were conducted with 61 research subjects and 34 family members. Because the primary purpose of the focus groups was to identify the range of considerations that may influence the decision to participate in brain donation, data from focus groups were pooled and then analyzed. Results: We found that many of the concerns, attitudes, and beliefs about brain donation were similar across the 4 ethnic groups. Concerns and attitudes fell into 3 categories: (a) concerns and misconceptions about brain research and the process of brain removal, (b) religious beliefs, and (c) the role of the family. Implications: Our findings suggest that interventions to enhance enrollment in brain donation that target factors identified in this study are likely to be relevant to people from a broad range of backgrounds and ethnicities. Nonetheless, we observed some potential differences among racial/ethnic groups that may affect how research volunteers and their families approach a decision about donating their brain for research. Further study is warranted to explore these and other possible culturally distinct attitudes and beliefs about brain donation. © 2016 The Author.

BACKGROUND: Konzo is an irreversible upper-motor neuron disorder affecting children dependent on bitter cassava for food. The neurocognitive ability of children with konzo over time has yet to be fully documented. METHODS: We did a longitudinal study in a konzo outbreak zone continuously affected by konzo since 1990, in the district of Kahemba, southern Bandundu Province, Congo. We enrolled children with a record of neurological diagnosis of konzo in Kahemba town. For all study children with konzo enrolled in the final sample for the baseline assessment, a neurological exam was done by neurologists to confirm konzo diagnosis using the 1996 WHO criteria at 2 years and 4 years. In the initial baseline sample for each child with konzo, we attempted to get consent from a comparison child without konzo (1996 WHO criteria) within 2 years of age, from a neighbouring household who met inclusion criteria. The neuropsychological assessments were the Kaufman Assessment Battery for Children, second edition (KABC-II), and the Bruininks-Oseretsky Test of Motor Proficiency, second edition (BOT-2). FINDINGS: Data collection occurred between Oct 12, 2011, and Aug 14, 2015, in the town of Kahemba. 123 children from the Congo with konzo and 87 presumably healthy children without konzo from neighbouring households were enrolled. The planned assessments were completed by 76 children with konzo and 82 children without konzo at 2-year follow-up, and by 55 children with konzo and 33 children without konzo at 4-year follow-up. Boys with konzo did worse than those without konzo on the KABC-II Learning (p=0.0424) and on the Mental Processing Index (MPI; p=0.0111) assessments at 2-year follow-up, but girls did not. These differences observed in boys might have been caused by stunting. At 4-year follow-up, the difference in KABC-II MPI score between boys or girls with or without konzo was not significant. Both boys and girls with konzo had lower scores on BOT-2 than children without konzo at both follow-up times (p<0.0001). These differences were not attenuated when controlling for physical growth. Boys with and without konzo declined on BOT-2 fine motor proficiency at 2-year follow-up (boys with konzo p=0.0076; boys without konzo p=0.0224) and KABC-II MPI performance at 2-year follow-up and 4-year follow-up (2 years: boys with konzo p<0.0001, boys without konzo p=0.0213; 4 years: boys with konzo p=0.0256, boys without konzo p=0.10), but that was not the case for the girls with scores remaining stable regardless of konzo status. For boys, increases in urinary thiocyanate concentration was significantly associated with reductions in BOT-2 motor proficiency (p=0.0321), but was not significantly associated in girls and urinary thiocyanate concentration was not associated with KABC-II MPI score for either boys or girls. INTERPRETATION: Motor and cognitive performance continues to be significantly impaired in boys with konzo at 2-year follow-up compared with boys without konzo. Because these impairments are associated in part with exposure to poorly processed cassava as measured by urinary thiocyanate, interventions are urgently needed to ensure improved processing of cassava to detoxify this food source. FUNDING: US National Institutes of Health.


BACKGROUND: Patients diagnosed with inflammatory bowel disease (IBD) during childhood require transfer to an adult gastroenterologist, in Ontario usually just before their 18th birthday. Pediatric onset IBD is a complex phenotype with demonstrated noncompliance risk that may require targeted measures to optimize health care outcomes in the adult care setting. PURPOSE: The purpose of this study was to determine the impact of posttransfer health care setting (academic versus community gastroenterologist) on emergent health resource utilization. METHODS: This was a population-based retrospective cohort study using health care administrative data from Ontario, Canada. A cohort of patients with Pediatric onset IBD was identified and health resource utilization during a 2-year pretransfer period, transfer of care period and 2-year posttransfer period was analyzed. Posttransfer health care setting was defined as academic (i.e., gastroenterologists providing care in a university affiliated tertiary care center) versus community. A third comparator group, loss
to follow-up, was also identified. The primary outcome of this study comprised emergency department utilization. Secondary outcomes included hospitalizations, surgeries, ambulatory visits, endoscopic investigations, and radiological investigations. RESULTS: Overall, there were no significant differences found in emergency department use, ambulatory care visits (aside from the expected drop in the lost to follow-up group), hospitalizations, endoscopic procedures, or radiological procedures between exposure groups. CONCLUSIONS: Posttransfer health care setting does not seem to significantly impact emergent health resource utilization in the posttransfer period.


The One-Leg Stance (OLS) test is a widely adopted tool for the clinical assessment of balance in the elderly and in subjects with neurological disorders. It was previously showed that the ability to control anticipatory postural adjustments (APAs) prior to lifting one leg is significantly impaired by idiopathic Parkinson’s disease (iPD). However, it is not known how APAs are affected by other types of parkinsonism, such as frontal gait disorders (FGD). In this study, an instrumented OLS test based on wearable inertial sensors is proposed to investigate both the initial anticipatory phase and the subsequent unipedal balance. The sensitivity and the validity of the test have been evaluated. Twenty-five subjects with iPD presenting freezing of gait (FOG), 33 with iPD without FOG, 13 with FGD, and 32 healthy elderly controls were recruited. All subjects wore three inertial sensors positioned on the posterior trunk (L4-L5), and on the left and right frontal face of the tibias. Participants were asked to lift a foot and stand on a single leg as long as possible with eyes open, as proposed by the mini-BESTest. Temporal parameters and trunk acceleration were extracted from sensors and compared among groups. The results showed that, regarding the anticipatory phase, the peak of mediolateral trunk acceleration was significantly reduced compared to healthy controls ($p < 0.05$) in subjects with iPD with and without FOG, but not in FGD group ($p = 0.151$). Regarding the balance phase duration, a significant shortening was found in the three parkinsonian groups compared to controls ($p < 0.001$). Moreover, balance was significantly longer ($p < 0.001$) in iPD subjects without FOG compared to subjects with FGD and iPD subjects presenting FOG. Strong correlations between balance duration extracted by sensors and clinical mini-BESTest scores were found ($\rho > 0.74$), demonstrating the method’s validity. Our findings support the validity of the proposed method for assessing the OLS test and its sensitivity in distinguishing among the tested groups. The instrumented test discriminated between healthy controls and people with parkinsonism and among the three groups with parkinsonism. The objective characterization of the initial anticipatory phase represents an interesting improvement compared to most clinical OLS tests.


Given the complexity and ever-changing landscape of health care, the need for new and varied training experiences in systems-level issues is increasingly evident. At Oregon Health & Science University (OHSU), the training program strives to teach interns not only the content and skills of clinical care, but the process of applying these skills in our evolving health care system. This article describes several aspects of our internship program that are designed to contribute to competency in the systems domain. These include didactic and experiential components across a range of settings. It also describes a benchmarks approach to evaluating trainee progress in reaching appropriate milestones in this domain, and outlines challenges facing training programs that are trying to support trainee competency in the systems domain. © 2015 American Psychological Association.

The lack of visualization frameworks to guide interpretation and facilitate discovery is a potential bottleneck for precision medicine, systems genetics and other studies. To address this we have developed an interactive, reproducible, web-based prioritization approach that builds on our earlier work. HitWalker2 is highly flexible and can utilize many data types and prioritization methods based upon available data and desired questions, allowing it to be utilized in a diverse range of studies such as cancer, infectious disease and psychiatric disorders. AVAILABILITY AND IMPLEMENTATION: Source code is freely available at https://github.com/biodev/HitWalker2 and implemented using Python/Django, Neo4j and Javascript (D3.js and jQuery). We support major open source browsers (e.g. Firefox and Chromium/Chrome). CONTACT: wilmotb@ohsu.edu


The adult high-grade B-cell lymphomas sharing molecular features with Burkitt lymphoma (BL) are highly aggressive lymphomas with poor clinical outcome. High-resolution structural and functional genomic analysis of adult Burkitt lymphoma (BL) and high-grade B-cell lymphoma with BL gene-signature (adult-mBL), revealed the MYC-ARF-p53 axis as the primary deregulated pathway. Adult-mBL had either unique or more frequent genomic aberrations (del13q14, del17p, gain8q24 and gain18q21) compared with pediatric-mBL, but shared commonly mutated genes. Mutations in genes promoting the tonic B-cell receptor (BCR)-->PI3K pathway (TCF3 and ID3) did not differ by age, whereas effectors of chronic BCR-->NF-kappaB signaling were associated with adult-mBL. A subset of adult-mBL had BCL2 translocation and mutation, and elevated BCL2 mRNA and protein expression, but had a mutation profile similar to mBL. These double-hit lymphomas may have arisen from a tumor precursor that acquired both BCL2 and MYC translocations and/or KMT2D (MLL2) mutation. Gain/amplification of MIR17HG and its paralogue loci was observed in 50% of adult-mBL. In vitro studies suggested miR-17~92's role in constitutive activation of BCR signaling and sensitivity to ibrutinib. Overall integrative analysis identified an interrelated gene network affected by CN and mutation, leading to disruption of the p53 pathway and the BCR-->PI3K/ or NF-kappaB activation which can be further exploited in vivo by small-molecule inhibitors for effective therapy in adult-mBL.


Follicular lymphoma (FL) is typically an indolent disease, but 30-40% of FL cases transform into an aggressive lymphoma (tFL) with a poor prognosis. To identify the genetic changes that drive this transformation, we sequenced the exomes of 12 cases with paired FL and tFL biopsies and identified 45 recurrently mutated genes in the FL-tFL data set and 39 in the tFL cases. We selected 496 genes of potential importance in transformation and sequenced them in 23 additional tFL cases. Integration of the mutation data with copy-number abnormality (CNA) data provided complementary information. We found recurrent mutations of miR-142, which has not been previously been reported to be mutated in FL/tFL. The genes most frequently mutated in tFL included KMT2D (MLL2), CREBBP, EZH2, BCL2 and MEF2B. Many recurrently mutated genes are involved in epigenetic regulation, the Janus-activated kinase-signal transducer and activator of transcription (STAT) or the nuclear factor-kappaB pathways, immune surveillance and cell cycle regulation or are TFs involved in B-cell development. Of particular interest are mutations and CNAs affecting S1P-activated pathways through S1PR1 or S1PR2, which likely regulate lymphoma cell migration and survival outside of follicles. Our custom gene enrichment panel provides high depth of coverage for the study of clonal evolution or divergence.

**PURPOSE:** To determine best practices for consistent and accurate evaluation of coronal alignment in patients with patellofemoral (PF) instability. **METHODS:** Six reviewers examined 239 knee magnetic resonance images (MRIs) in patients with PF instability and anterior cruciate ligament (ACL) rupture. Measurements included tibial tubercle-to-trochlear groove (TT-TG) distance measured at the most proximal and distal portions of the trochlea, tibial tubercle-to-PCL (TT-PCL) distance, and Dejour classification of trochlear dysplasia. **RESULTS:** Interrater reliability was low for Dejour classification (k = 0.289), but improved to moderate (k = 0.448) when patients were separated into normal/Dejour A and Dejour B/C/D. Interrater reliability was high for proximal and distal TT-TG measurements (interclass correlation coefficients [ICCs] = 0.807 and 0.936, respectively). TT-PCL was moderately reliable (ICC = 0.625), and correlated with TT-TG (r = 0.457, P < .001 proximal and r = 0.451, P < .001 distal). No significant difference was found between the proximal and distal measurements of TT-TG in each patient, though the PF group exhibited higher values than the ACL group (P < .001 for both). TT-PCL was significantly higher for the PF group than the ACL group (P = .015), but this difference lost significance when the group was divided by the TT-PCL cutoff of 24 mm (P = .371). **CONCLUSIONS:** The proximal and distal techniques for measuring the TT-TG distance are similar to each other, and reliable despite level of reviewer training or presence of dysplasia. The TT-PCL distance was predictive of patellofemoral instability. The TT-PCL distance was found to be less reliable than either method of measuring the TT-TG distance. Thus, this study demonstrated TT-TG to be superior to TT-PCL as a measurement of coronal malalignment. Given the variability in Dejour classification in this and other studies, a more reliable classification system for trochlear dysplasia as defined on cross-sectional imaging is warranted. LEVEL OF EVIDENCE: Level III, retrospective clinical trial.


**BACKGROUND:** Ventriculoperitoneal shunt (VPS) placement has been implicated in extraneural metastasis of many primary central nervous system tumors. Reported cases include, but are not limited to, medulloblastoma, germ cell tumor, astrocytoma, oligodendrogioma, lymphoma, ependymoma, melanoma, and choroid plexus tumors. However, a literature review reveals no reported cases of extraneural metastasis of solitary fibrous tumor/hemangiopericytoma (SFT/HPC). **CASE DESCRIPTION:** Here we report the case of a 34-year-old man with recurrent intracranial malignant SFT/HPC who had undergone surgical tumor resection and subsequent placement of a VPS for obstructive hydrocephalus in 2004. Subsequently, the patient presented in 2011 and again in 2013 with abdominal SFT/HPC metastasis likely caused by the presence of the VPS. **CONCLUSION:** The case raises concern regarding placement of a VPS in patients with obstructive hydrocephalus caused by SFT/HPC. To avoid spread of SFT/HPC to the abdomen, we propose that patients with intracranial SFT/HPC and obstructive hydrocephalus be treated primarily by endoscopic third ventriculostomy.


Candida meningitis following neurosurgical procedures is a rare, but potentially devastating complication. The presentation of meningitis can be insidious in immunosuppressed patients and thus can be easily
overlooked. Cerebrospinal fluid studies often resemble bacterial profiles, while cultures can be falsely negative. Candida albicans is the most common species identified in post-surgical Candida meningitis, and delay in diagnosis and treatment can be devastating. The standard induction therapy for Candida meningitis has been amphotericin B combined with flucytosine. A high index of suspicion is needed in any patient with risk factors such as abdominal surgery, bowel perforation, recent broad spectrum antibiotic therapy, intravenous drug use, extremes of age, indwelling catheters, and immunosuppression such as Acquired Immune Deficiency Syndrome (AIDS), malignancy, antineoplastic therapy, and steroid use. Here, we describe three case presentations of patients with giant skull base tumors who developed post-surgical Candida meningitis, each with vastly different clinical courses and outcomes, ranging from benign to catastrophic. We performed a literature review with special focus on common risk factors, Candida species, diagnostic criteria, and treatment.


Uveitis (intraocular inflammation) is a leading cause of vision loss. Although its etiology is largely speculative, it is thought to arise from complex genetic-environmental interactions that break immune tolerance to generate eye-specific autoreactive T cells. Experimental autoimmune uveitis (EAU), induced by immunization with the ocular antigen, interphotoreceptor retinoid binding protein (IRBP), in combination with mycobacteria-containing CFA, has many clinical and histopathological features of human posterior uveitis. Studies in EAU have focused on defining pathogenic CD4+ T cell effector responses, such as those of Th17 cells, but the innate receptor pathways precipitating development of autoreactive, eye-specific T cells remain poorly defined. In this study, we found that fungal-derived antigens possess autoimmune uveitis-promoting function akin to CFA in conventional EAU. The capacity of commensal fungi such as C. albicans or S. cerevisiae to promote IRBP-triggered EAU was mediated by Card9. Since Card9 is an essential signaling molecule of a subgroup of C-type lectin receptors (CLRs) important in host defense, we further evaluated the proximal Card9-activating CLRs. Using single receptor-deficient mice, we identified Dectin-2, but not Mincle or Dectin-1, as a predominant mediator of fungal-promoted uveitis. Conversely, Dectin-2 activation by alpha-mannan sufficiently reproduced the uveitic phenotype of EAU, in a process mediated by the Card9-coupled signaling axis and IL-17 production. Taken together, this report relates the potential of the Dectin-2/Card9-coupled pathway in ocular autoimmunity. Not only does it contribute to understanding of how innate immune receptors orchestrate T cell-mediated autoimmunity, it also reveals a previously unappreciated ability of fungal-derived signals to promote autoimmunity. This article is protected by copyright. All rights reserved.


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.


Lynch syndrome (LS) is a hereditary cancer syndrome caused by a germline mutation in a DNA mismatch repair gene, usually MLH1, MSH2, MSH6, or PMS2. The most common cancers associated with LS are colorectal adenocarcinoma and endometrial carcinoma. Identification of women with LS-associated endometrial cancer is important, as these women and their affected siblings and children are at-risk of developing these same cancers. Germline testing of all endometrial cancer patients is not cost effective, and screening using young age of cancer diagnosis and/or presence of family history of syndrome-associated is underutilized and ineffective. Therefore, most groups now advocate for tumor tissue testing to screen for LS, with germline testing targeted to women with abnormal tissue testing results. Immunohistochemistry for MLH1, MSH2, MSH6, and PMS2 is used in many clinical laboratories for this tumor screening step, as immunohistochemistry is relatively inexpensive and is technically more accessible for smaller clinical labs. PCR-based tissue testing, whereas technically more challenging, does play an important role in the identification of these patients. MLH1 methylation analysis identifies women with tumor MLH1 loss who likely have sporadic endometrial cancer and do not need heightened cancer prevention surveillance. High levels of microsatellite instability have been identified in tumors with retained positive expression of mismatch repair proteins. Somatic sequencing of mismatch repair genes from tumor DNA, whereas not currently available in most clinical laboratories, is helpful in resolution of cases in which germline sequencing fails to identify a mutation in a mismatch repair gene. The tumor tissue testing approach can help to identify most women at-risk for germline mutations in a LS gene, but not all patients will be captured using this approach. Clinical suspicion can still play a pivotal role in accurately identifying a subset of these patients.


Background - Coronary artery calcium (CAC) is an established predictor of future major adverse atherosclerotic cardiovascular events in asymptomatic individuals. However limited data exist as to how CAC compares to functional testing (FT) in estimating prognosis in symptomatic patients. Methods - In the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial, patients with stable chest pain (or dyspnea) and intermediate pre-test probability for obstructive coronary artery disease (CAD) were randomized to FT (exercise electrocardiography, nuclear stress, or stress echocardiography) or anatomic testing. We evaluated those who underwent CAC testing as part of the anatomic evaluation (n=4,209) and compared to results of FT (n=4,602). We stratified CAC and FT results as normal or mildly, moderately or severely abnormal (for CAC: 0, 1-99 Agatston Score [AS], 100-400 AS and >400 AS, respectively; for FT: normal, mild=late positive treadmill, moderate=early positive treadmill or single-vessel ischemia and severe=large ischemic region abnormality). The primary endpoint was all-cause death, myocardial infarction or unstable angina hospitalization over a median follow-up of 26.1 months. Cox regression models were used to calculate hazard ratios and C-statistic to determine predictive and discriminatory value. Results - Overall, the distribution of normal or mildly, moderately or severely abnormal test results was significantly different between FT and CAC (FT = normal 3588 [78.0%], mild 432 [9.4%], moderate 217 [4.7%], severe 365 [7.9%]; CAC = normal 1,457 [34.6%], mild 1340 [31.8%], moderate 772 [18.3%], severe 640 [15.2%], p
Moderate and severe abnormalities in both arms robustly predicted events (moderate: CAC HR 3.14, 95% CI 1.81-5.44 and FT HR 2.65, 95% CI 1.46-4.83; severe: CAC HR 3.56, 95% CI 1.99-6.36 and FT HR 3.88, 95% CI 2.58-5.85). In the CAC arm, the majority of events (n=112/133; 84%) occurred in patients with any positive CAC test (score >0) whereas less than half of events occurred in patients with mild, moderate or severely abnormal FT (n=57/132; 43%) (p<0.001). In contrast, any abnormality on FT was significantly more specific for predicting events (78.6% for FT vs 35.2% for CAC, p<0.001). Overall discriminatory ability in predicting the primary endpoint of mortality, nonfatal myocardial infarction, and unstable angina hospitalization was similar and fair for both CAC and FT (c-statistic, 0.67 vs. 0.64). Coronary computed tomographic angiography provided significantly better prognostic information compared to FT and CAC testing (C-index: 0.72). Conclusion - Among stable outpatients presenting with suspected CAD, most patients experiencing clinical events have measurable CAC at baseline while less than half have any abnormalities on FT. However, an abnormal FT was more specific for cardiovascular events, leading to overall similarly modest discriminatory abilities of both tests. Clinical Trial Registration - URL: https://clinicaltrials.gov; Unique Identifier: NCT01174550.


Signs and symptoms of multiple sclerosis are usually attributed to demyelinating lesions in the spinal cord or cerebral cortex. The hypothalamus is a region that is often overlooked yet controls many important homeostatic functions, including those that are perturbed in multiple sclerosis. In this review we discuss how hypothalamic dysfunction may contribute to signs and symptoms in people with multiple sclerosis. While dysfunction of the hypothalamic-pituitary-adrenal axis is common in multiple sclerosis, the effects and mechanisms of this dysfunction are not well understood. We discuss three hypothalamic mechanisms of fatigue in multiple sclerosis: (1) general hypothalamic-pituitary-adrenal axis hyperactivity, (2) disordered orexin neurotransmission, (3) abnormal cortisol secretion. We then review potential mechanisms of weight dysregulation caused by hypothalamic dysfunction. Lastly, we propose future studies and therapeutics to better understand and treat hypothalamic dysfunction in multiple sclerosis. Hypothalamic dysfunction appears to be common in multiple sclerosis, yet current studies are underpowered and contradictory. Future studies should contain larger sample sizes and standardize hormone and neuropeptide measurements.


Hematopoietic cell transplantation (HCT) is effective in the treatment of inherited marrow failure disorders and other nonmalignant diseases. Conventional myeloablative conditioning regimens have been associated with high transplant-related mortality, particularly in patients with comorbid conditions. Here we report on 14 patients with marrow failure disorders (Shwachman-Diamond syndrome, n = 3; Diamond Blackfan anemia, n = 4; GATA2 deficiency, n = 2; paroxysmal nocturnal hemoglobinuria, n = 4; and an undefined marrow failure disorder, n = 1) who underwent HCT on a prospective, phase II, multicenter clinical trial. Patients were given HLA-matched related (n = 2) or unrelated (n = 12) grafts after conditioning with treosulfan (42 g/m2), fludarabine (150 mg/m2), ± thymoglobulin (n = 11; 6 mg/kg). All patients engrafted. At a median follow-up of 3 years, 13 patients are alive with complete correction of their underlying disease. These results indicate that the combination of treosulfan, fludarabine, and thymoglobulin is effective at establishing donor engraftment with a low toxicity profile and excellent disease-free survival in patients with marrow failure disorders. © 2017 The American Society for Blood and Marrow Transplantation.

The origin of ripples in distortion product otoacoustic emission (DPOAE) amplitude which appear at specific DPOAE frequencies during f1 tone sweeps using fixed high frequency f2 (>20 kHz) in Guinea pigs is investigated. The peaks of the ripples, or local DPOAE amplitude maxima, are separated by approximately half octave intervals and are accompanied by phase oscillations. The local maxima appear at the same frequencies in DPOAEs of different order and velocity responses of the stapes and do not shift with increasing levels of the primaries. A suppressor tone had little effect on the frequencies of the maxima, but partially suppressed DPOAE amplitude when it was placed close to the f2 frequencies. These findings agree with earlier observations that the maxima occur at the same DPOAE frequencies, which are independent of the f2 and the primary ratio, and thus are likely to be associated with DPOAE propagation mechanisms. Furthermore, the separation of the local maxima by approximately half an octave may suggest that the maxima are due to interference of the travelling waves along the basilar membrane at the frequency of the DPOAE. It is suggested that the rippling pattern appears because of interaction between DPOAE reverse travelling waves with standing waves formed in the cochlea. © 2017 Acoustical Society of America.


STUDY OBJECTIVES: Primary insomnia (PI) may increase diabetes risk. We tested the hypothesis that the effects of PI on glucose metabolism could be improved by 2 months of pharmacological treatment. METHODS: Adult men and women meeting clinical criteria for PI were studied (n=20, body mass index 25.1+/−2.7 kg/m2, age 39.7+/−7.9) in a randomized, double-blind, placebo-controlled clinical trial. The study consisted of two 1-day inpatient admissions to a General Clinical Research Center separated by 2 months of at-home treatment with 3 mg eszopiclone or placebo. During inpatient admissions, each subject underwent two intravenous glucose tolerance tests (IVGTTs) pre- and post-treatment. Diet was controlled for micro- and macro-nutrient content and calories on the day prior to pre- and post-treatment IVGTTs. Subjects were randomized following completion of the initial IVGTT to take either placebo or eszopiclone 30 min prior to bedtime at home for 2 months. RESULTS: Two-month eszopiclone treatment did not change insulin sensitivity, glucose tolerance, or any of the sleep measures significantly, compared with placebo. Changes in glycated hemoglobin (HbA1c, clinical measure of glycemic control) were correlated with changes in diary-reported total sleep time in the eszopiclone group (r=0.66, p=0.0360), and in the combined groups’ data (r=0.55, p=0.0125). Changes in polysomnography-measured wake after sleep onset, a hallmark of PI, were positively related to changes in IVGTT-derived glucose effectiveness, or non-insulin-mediated glucose uptake. CONCLUSION: Treatment with 3 mg eszopiclone for 2 months, compared with placebo, did not significantly influence either sleep or measures of diabetes risk in this preliminary study.


OBJECTIVES: To determine if probiotic administration during the first 6 months of life decreases childhood asthma and eczema. METHODS: We conducted a randomized, double-blind controlled trial of Lactobacillus rhamnosus GG (LGG) supplementation on the cumulative incidence of eczema (primary end point) and asthma and rhinitis (secondary end points) in high-risk infants. For the first 6 months of life, intervention infants (n = 92) received a daily dose of 10 billion colony-forming units of LGG and 225 mg of inulin (Amerifit Brands, Cromwell, CT), and control infants (n = 92) received 325 mg of inulin alone. We used survival analysis methods to estimate disease incidences in the presence or absence of LGG and to estimate the efficacy of LGG in delaying or preventing these diseases. RESULTS: Infants were accrued over a 6-year period (median follow-up: 4.6 years; 95% retention rate at 2 years). At 2 years of age, the estimated cumulative incidence of eczema was 30.9% (95% confidence interval [CI], 21.4%-40.4%) in the control arm and 28.7% (95% CI, 19.4%-38.0%) in the LGG arm, for a hazard ratio of 0.95 (95% CI, 0.59-1.53) (log-rank P =
At 5 years of age, the cumulative incidence of asthma was 17.4% (95% CI, 7.6%-27.1%) in the control arm and 9.7% (95% CI, 2.7%-16.6%) in the LGG arm, for a hazard ratio of 0.88 (95% CI, 0.41-1.87) (log-rank P = .25).

CONCLUSIONS: For high-risk infants, early LGG supplementation for the first 6 months of life does not appear to prevent the development of eczema or asthma at 2 years of age.


Ceramides are essential precursors of sphingolipids with a dual role as mediators of apoptotic cell death. Previous work revealed that the ER-resident ceramide phosphoethanolamine (CPE) synthase SMSr/SAMD8 is a suppressor of ceramide-mediated apoptosis in cultured cells. Anti-apoptotic activity of SMSr requires a catalytically active enzyme but also relies on the enzyme’s N-terminal sterile a-motif or SAM domain. Here, we demonstrate that SMSr itself is a target of the apoptotic machinery. Treatment of cells with staurosporine or the death receptor ligand FasL triggers caspase-mediated cleavage of SMSr at a conserved aspartate located downstream of the enzyme’s SAM domain and upstream of its first membrane span. Taking advantage of reconstitution experiments with SMSr produced in a cell-free expression system, specific caspase-inhibitors and gene silencing approaches, we show that SMSr is a novel and specific substrate of caspase-6, a non-conventional effector caspase implicated in Huntington’s and Alzheimer’s diseases. Our findings underscore a role of SMSr as negative regulator of ceramide-induced cell death and, in view of a prominent expression of the enzyme in brain, raise questions regarding its potential involvement in neurodegenerative disorders. © 2017 The Author(s).


To resolve cellular heterogeneity, we developed a combinatorial indexing strategy to profile the transcriptomes of single cells or nuclei, termed sci-RNA-seq (single-cell combinatorial indexing RNA sequencing). We applied sci-RNA-seq to profile nearly 50,000 cells from the nematode Caenorhabditis elegans at the L2 larval stage, which provided >50-fold “shotgun” cellular coverage of its somatic cell composition. From these data, we defined consensus expression profiles for 27 cell types and recovered rare neuronal cell types corresponding to as few as one or two cells in the L2 worm. We integrated these profiles with whole-animals chromatin immunoprecipitation sequencing data to deconvolve the cell type-specific effects of transcription factors. The data generated by sci-RNA-seq constitute a powerful resource for nematode biology and foreshadow similar atlases for other organisms.


OBJECTIVE: To quantify the need for, and interest in, Supported Employment (SE) among recent military Veterans with traumatic brain injury (TBI), and to examine characteristics associated with Veterans’ interest in SE. DESIGN: Stratified random sample of Iraq and Afghanistan War Veterans confirmed to have TBI through the Veterans Health Administration (VHA) screening and evaluation system. SETTING: Community-based via mailed
PARTICIPANTS: We recruited 1,800 Veterans with clinician-confirmed TBI (1,080 mild TBI; 720 moderate/severe TBI) through multiple mailings. Among 1,451 whose surveys were not returned undeliverable, 616 (42%) responded. INTERVENTIONS: Not applicable. MAIN OUTCOME MEASURES: Veterans rated their interest in SE after reading a script describing the program. Additional measures assessed mental health and pain-related comorbidities, employment, financial/housing difficulties, demographics, and military service characteristics. Estimates were weighted to represent the population of Veterans with VHA clinician-confirmed TBI. RESULTS: Unemployment was reported by 45% (95% confidence interval [CI]: 43, 47) of Veterans with TBI. Although 42% (95% CI: 40, 44) reported they would be interested in using SE if it were offered to them, only 12% had heard of SE (95% CI: 11, 14) and <1% had used it. TBI severity and comorbidities were not associated with Veterans’ interest in SE. However, those who were unemployed, looking for work, experiencing financial strain, or at risk for homelessness were more likely to be interested in SE. CONCLUSIONS: Our research highlights an important gap between Veterans’ vocational needs and interests and their use of SE. Systematically identifying and referring those with employment and financial/housing difficulties may help close this gap.


PURPOSE: Behavioral and social science (BSS) competencies are needed to provide quality health care, but psychometrically validated measures to assess these competencies are difficult to find. Moreover, they have not been mapped to existing frameworks, like those from the Liaison Committee on Medical Education (LCME) and Accreditation Council for Graduate Medical Education (ACGME). This systematic review aimed to identify and evaluate the quality of assessment tools used to measure BSS competencies. METHOD: The authors searched the literature published between January 2002 and March 2014 for articles reporting psychometric or other validity/reliability testing, using OVID, CINAHL, PubMed, ERIC, Research and Development Resource Base, SOCIOFILE, and PsycINFO. They reviewed 5,104 potentially relevant titles and abstracts. To guide their review, they mapped BSS competencies to existing LCME and ACGME frameworks. The final included articles fell into three categories: instrument development, which were of the highest quality; educational research, which were of the second highest quality; and curriculum evaluation, which were of lower quality. RESULTS: Of the 114 included articles, 33 (29%) yielded strong evidence supporting tools to assess communication skills, cultural competence, empathy/compassion, behavioral health counseling, professionalism, and teamwork. Sixty-two (54%) articles yielded moderate evidence and 19 (17%) weak evidence. Articles mapped to all LCME standards and ACGME core competencies; the most common was communication skills. CONCLUSIONS: These findings serve as a valuable resource for medical educators and researchers. More rigorous measurement validation and testing and more robust study designs are needed to understand how educational strategies contribute to BSS competency development.


The transition to competency-based medical education (CBME) and adoption of the foundational domains of competence by the Accreditation Council for Graduate Medical Education, Association of American Medical Colleges (AAMC), and American Board of Medical Specialties’ certification and maintenance of certification (MOC) programs provided an unprecedented opportunity for the pediatrics community to create a model of learning and assessment across the continuum. Two frameworks for assessment in CBME have been promoted: (1) entrustable professional activities (EPAs) and (2) milestones that define a developmental trajectory for individual competencies. EPAs are observable and measureable units of work that can be mapped to competencies and milestones critical to performing them safely and effectively. The pediatrics community integrated the two frameworks to create a potential pathway of learning and assessment across the continuum from undergraduate medical education (UME) to graduate medical education (GME) and
from GME to practice. The authors briefly describe the evolution of the Pediatrics Milestone Project and the process for identifying EPAs for the specialty and subspecialties of pediatrics. The method of integrating EPAs with competencies and milestones through a mapping process is discussed, and an example is provided. The authors illustrate the alignment of the AAMC’s Core EPAs for Entering Residency with the general pediatrics EPAs and, in turn, the alignment of the latter with the subspecialty EPAs, thus helping build the bridge between UME and GME. The authors propose how assessment in GME, based on EPAs and milestones, can guide MOC to complete the bridge across the education continuum.


Long-term depression (LTD) between cortical layer 4 spiny stellate cells and layer 2/3 pyramidal cells requires the activation of NMDARs. In young rodents, this form of LTD has been repeatedly reported to require presynaptic NMDARs for its induction. Here we show that at this synapse in the somatosensory cortex of 2- to 3-week-old rats and mice, postsynaptic, not presynaptic NMDARs are required for LTD induction. First, we find no evidence for functional NMDARs in L4 neuron axons using two-photon laser scanning microscopy and two-photon glutamate uncaging. Second, we find that genetic deletion of postsynaptic, but not presynaptic NMDARs prevents LTD induction. Finally, the pharmacology of the NMDAR requirement is consistent with a nonionic signaling mechanism.


Current research in connectomics highlights that self-organized functional networks or “communities” of cortical areas can be detected in the adult brain. This perspective may provide clues to mechanisms of treatment response in psychiatric conditions. Here we examine functional brain community topology based on resting-state fMRI in adult Attention-Deficit/ Hyperactivity Disorder (ADHD; n = 22) and controls (n = 31). We sought to evaluate ADHD patterns in adulthood and their modification by short term stimulant administration. Participants with ADHD were scanned one or two weeks apart, once with medication and once without; comparison participants were scanned at one time-point. Functional connectivity was estimated from these scans and community detection applied to determine cortical network topology. Measures of change in connectivity profile were calculated via a graph measure, termed the Node Dissociation Index (NDI). Compared to controls, several cortical networks had atypical connectivity in adults with ADHD when withholding stimulants, as measured by NDI. In most networks stimulants significantly reduced, but did not eliminate, differences in the distribution of connections between key brain systems relative to the control sample. These findings provide an enriched model of connectivity in ADHD and demonstrate how stimulants may exert functional effects by altering connectivity profiles in the brain. © The Author 2016. Published by Oxford University Press. All rights reserved.


Background: Falls lead to a disproportionate burden of death and disability among older adults despite evidence-based recommendations to screen regularly for fall risk and clinical trials demonstrating the effectiveness of multifactorial interventions to reduce falls. The Centers for Disease Control and Prevention developed STEADI (Stopping Elderly Accidents, Deaths, and Injuries) to assist primary care teams to screen for fall risk and reduce risk of falling in older adults. Purpose of the Study: This paper describes a practical application of STEADI in a large academic internal medicine clinic utilizing the Kotter framework, a tool used to guide clinical practice change. Design and Methods: We describe key steps and decision points in the
implementation of STEADI as they relate to the recommended strategies of the Kotter framework. Strategies include: Creating a sense of urgency, building a guiding coalition, forming a strategic vision and initiative, enlisting volunteers, enabling success by removing barriers, generating short-term wins, sustaining change, and instituting change. Results: Fifty-six patients were screened during pilot testing; 360 patients were screened during the first 3 months of implementation. Key to successful implementation was (a) the development of electronic health record (EHR) tools and workflow to guide clinical practice and (b) the proactive leadership of clinical champions within the practice to identify and respond to barriers.

Implications: Implementing falls prevention in a clinical setting required support and effort across multiple stakeholders. We highlight challenges, successes, and lessons learned that offer guidance for other clinical practices in their falls prevention efforts.


Individuals with serious mental illness face multiple barriers to accessing care and experience disproportionately poor health outcomes. Starting in 2011, New York State undertook a series of major reforms of its Medicaid system designed to address these concerns. In this commentary we review three reforms that aim to change the way New York Medicaid is delivered and experienced, especially for underserved individuals with SMI: Health Homes, Behavioral Health Managed Care, and the Delivery System Reform Incentive Payment Program. We describe the history of these reforms’ and their core themes: coordination and collaboration, cross-sector collaborations to address social determinants of health, prevention and early intervention, and financial reform. We describe the challenges and opportunities these reforms present for improving the health and health care of Medicaid members with SMI, both in New York and as models for change elsewhere. © Meharry Medical College.


This article is a report of the fourth meeting of the Harmonising Outcome Measures for Eczema (HOME) initiative held in Malmo, Sweden on 23-24 April 2015 (HOME IV). The aim of the meeting was to achieve consensus over the preferred outcome instruments for measuring patient-reported symptoms and quality of life for the HOME core outcome set for atopic eczema (AE). Following presentations, which included data from systematic reviews, consensus discussions were held in a mixture of whole group and small group discussions. Small groups were allocated a priori to ensure representation of different stakeholders and countries. Decisions were voted on using electronic keypads. For the patient-reported symptoms, the group agreed by vote that itch, sleep loss, dryness, redness/inflamed skin and irritated skin were all considered essential aspects of AE symptoms. Many instruments for capturing patient-reported symptoms were discussed [including the Patient-Oriented SCOring Atopic Dermatitis_index, Patient-Oriented Eczema Measure (POEM), Self-Administered Eczema Area and Severity Index, Itch Severity Scale, Atopic Dermatitis Quickscore and the Nottingham Eczema Severity Score] and, by consensus, POEM was selected as the preferred instrument to measure patient-reported symptoms. Further work is needed to determine the reliability and measurement error of POEM. Further work is also required to establish the importance of pain/soreness and the importance of collecting information regarding the intensity of symptoms in addition to their frequency. Much of the discussion on quality of life concerned the Dermatology Life Quality Index.
OBJECTIVES: Registry


STUDY OBJECTIVE: Emergency department (ED) crowding and patient boarding are associated with increased mortality and decreased patient satisfaction. This study uses a positive deviance methodology to identify strategies among high-performing, low-performing, and high-performance improving hospitals to reduce ED crowding. METHODS: In this mixed-methods comparative case study, we purposively selected and recruited hospitals that were within the top and bottom 5% of Centers for Medicare & Medicaid Services case-mix-adjusted ED length of stay and boarding times for admitted patients for 2012. We also recruited hospitals that showed the highest performance improvement in metrics between 2012 and 2013. Interviews were conducted with 60 key leaders (physicians, nurses, quality improvement specialists, and administrators). RESULTS: We engaged 4 high-performing, 4 low-performing, and 4 high-performing improving hospitals, matched on hospital characteristics including geographic designation (urban versus rural), region, hospital occupancy, and ED volume. Across all hospitals, ED crowding was recognized as a hospital-wide issue. The strategies for addressing ED crowding varied widely. No specific interventions were associated with performance in length-of-stay metrics. The presence of 4 organizational domains was associated with hospital performance: executive leadership involvement, hospitalwide coordinated strategies, data-driven management, and performance accountability. CONCLUSION: There are organizational characteristics associated with ED decreased length of stay. Specific interventions targeted to reduce ED crowding were more likely to be successfully executed at hospitals with these characteristics. These organizational domains represent identifiable and actionable changes that other hospitals may incorporate to build awareness of ED crowding.


STUDY OBJECTIVE: Emergency department (ED) crowding and patient boarding are associated with increased mortality and decreased patient satisfaction. A need exists to develop Health Insurance Portability and Accountability Act (HIPAA)-compliant registries that comprise integrated electronic health record (EHR) data using prospectively defined variables. An EHR-based standardized patient database—the Registry for Stones of the Kidney and Ureter (ReSKU)—was developed, and herein we describe our implementation outcomes. MATERIALS AND METHODS: Interviews with academic and community endourologists in the United States, Canada, China, and Japan identified demographic, intraoperative, and perioperative variables to populate our registry. Variables were incorporated into a HIPAA-compliant Research Electronic Data Capture database linked to text prompts and registration data within the Epic EHR platform. Specific data collection instruments supporting New patient, Surgery, Postoperative, and Follow-up clinical encounters were created within Epic to facilitate automated data extraction into ReSKU. RESULTS: The number of variables within each instrument includes the following: New patient-60, Surgery-80, Postoperative-64, and Follow-up-64. With manual data entry, the mean times to complete each of the clinic-based instruments were (minutes) as follows: New patient-12.06 +/- 2.30, Postoperative-7.18 +/- 1.02, and Follow-up-8.10 +/- 0.58. These times were significantly reduced with the use of ReSKU structured clinic note templates to the following: New patient-4.09 +/- 1.73, Postoperative-1.41 +/- 0.41, and Follow-up-0.79 +/- 0.38. With automated data extraction from Epic, manual entry is obviated. CONCLUSIONS: ReSKU is a longitudinal prospective nephrolithiasis registry that integrates EHR data, lowering the barriers to performing high quality clinical research and quality outcome assessments in urinary stone disease.


OBJECTIVES: Registry-based clinical research in nephrolithiasis is critical to advancing quality in urinary stone disease management and ultimately reducing stone recurrence. A need exists to develop Health Insurance Portability and Accountability Act (HIPAA)-compliant registries that comprise integrated electronic health record (EHR) data using prospectively defined variables. An EHR-based standardized patient database—the Registry for Stones of the Kidney and Ureter (ReSKU)—was developed, and herein we describe our implementation outcomes. MATERIALS AND METHODS: Interviews with academic and community endourologists in the United States, Canada, China, and Japan identified demographic, intraoperative, and perioperative variables to populate our registry. Variables were incorporated into a HIPAA-compliant Research Electronic Data Capture database linked to text prompts and registration data within the Epic EHR platform. Specific data collection instruments supporting New patient, Surgery, Postoperative, and Follow-up clinical encounters were created within Epic to facilitate automated data extraction into ReSKU. RESULTS: The number of variables within each instrument includes the following: New patient-60, Surgery-80, Postoperative-64, and Follow-up-64. With manual data entry, the mean times to complete each of the clinic-based instruments were (minutes) as follows: New patient-12.06 +/- 2.30, Postoperative-7.18 +/- 1.02, and Follow-up-8.10 +/- 0.58. These times were significantly reduced with the use of ReSKU structured clinic note templates to the following: New patient-4.09 +/- 1.73, Postoperative-1.41 +/- 0.41, and Follow-up-0.79 +/- 0.38. With automated data extraction from Epic, manual entry is obviated. CONCLUSIONS: ReSKU is a longitudinal prospective nephrolithiasis registry that integrates EHR data, lowering the barriers to performing high quality clinical research and quality outcome assessments in urinary stone disease.

and Quality of Life Index for Atopic Dermatitis; however, consensus on a preferred instrument for measuring this domain could not be reached. In summary, POEM is recommended as the HOME core outcome instrument for measuring AE symptoms.


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**OBJECTIVE:** To compare morbidity among small-for-gestational-age (SGA; birth weight less than the 10th percentile for gestational age), appropriate-for-gestational-age (AGA; birth weight 10th to 90th percentile; reference group), and large-for-gestational-age (LGA; birth weight greater than the 90th percentile) neonates in apparently uncomplicated pregnancies at term (37 weeks of gestation or greater). **METHODS:** This secondary analysis, derived from an observational obstetric cohort of 115,502 deliveries, included women with apparently uncomplicated pregnancies of nonanomalous singletons who had confirmatory ultrasound dating no later than the second trimester and who delivered between 37 0/7 and 42 6/7 weeks of gestation. We used two different composite neonatal morbidity outcomes: hypoxic composite neonatal morbidity for SGA and traumatic composite neonatal morbidity for LGA neonates. Log Poisson relative risks (RRs) with 95% CIs adjusted for potential confounding factors (nulliparity, body mass index, insurance status, and neonatal sex) were calculated. **RESULTS:** Among the 63,436 women who met our inclusion criteria, SGA occurred in 7.9% (n=4,983) and LGA in 8.3% (n=5,253). Hypoxic composite neonatal morbidity was significantly higher in SGA (1.1%) compared with AGA (0.7%; adjusted RR 1.44, 95% CI 1.07-1.93) but similar between LGA (0.6%) and AGA (adjusted RR 0.84, 95% CI 0.58-1.22). Traumatic composite neonatal morbidity was significantly higher in LGA (1.9%) than AGA (1.0%; adjusted RR 1.88, 95% CI 1.51-2.34) but similar in SGA (1.3%) compared with AGA (adjusted RR 1.28, 95% CI 0.98-1.67). **CONCLUSION:** Among women with uncomplicated pregnancies, hypoxic composite neonatal morbidity is more common with SGA neonates and traumatic-composite neonatal morbidity is more common with LGA neonates.


AMPA receptors mediate fast excitatory neurotransmission in the mammalian brain and transduce the binding of presynaptically released glutamate to the opening of a transmembrane cation channel. Within the postsynaptic density, however, AMPA receptors coassemble with transmembrane AMPA receptor regulatory proteins (TARPs), yielding a receptor complex with altered gating kinetics, pharmacology, and pore properties. Here, we elucidate structures of the GluA2-TARP gamma2 complex in the presence of the partial agonist kainate or the full agonist quisqualate together with a positive allosteric modulator or with quisqualate alone. We show how TARPs sculpt the ligand-binding domain gating ring, enhancing kainate potency and diminishing the ensemble of desensitized states. TARPs encircle the receptor ion channel, stabilizing M2 helices and pore loops, illustrating how TARPs alter receptor pore properties. Structural and computational analysis suggests the full agonist and modulator complex harbors an ion-permeable channel gate, providing the first view of an activated AMPA receptor.

Tyrosinemia type I (hepatorenal tyrosinemia, HT-1) is an autosomal recessive condition resulting in hepatic failure with comorbidities involving the renal and neurologic systems and long term risks for hepatocellular carcinoma. An effective medical treatment with 2-[[2-nitro-4-trifluoromethylbenzoyl]-1,3-cyclohexanedione (NTBC) exists but requires early identification of affected children for optimal long-term results. Newborn screening (NBS) utilizing blood succinylacetone as the NBS marker is superior to observing tyrosine levels as a way of identifying neonates with HT-1. If identified early and treated appropriately, the majority of affected infants can remain asymptomatic. A clinical management scheme is needed for infants with HT-1 identified by NBS or clinical symptoms. To this end, a group of 11 clinical practitioners, including eight biochemical genetics physicians, two metabolic dietitians nutritionists, and a clinical psychologist, from the United States and Canada, with experience in providing care for patients with HT-1, initiated an evidence- and consensus-based process to establish uniform recommendations for identification and treatment of HT-1. Recommendations were developed from a literature review, practitioner management survey, and nominal group process involving two face-to-face meetings. There was strong consensus in favor of NBS for HT-1, using blood succinylacetone as a marker, followed by diagnostic confirmation and early treatment with NTBC and diet. Consensus recommendations for both immediate and long-term clinical follow-up of positive diagnoses via both newborn screening and clinical symptomatic presentation are provided.


BACKGROUND: The surveys in this study were carried out at the Graduate Medical Education Division at Oregon Health & Science University (OHSU). OHSU implemented two significant wellness initiatives: a wellness program in 2004, and a policy allowing 4 half-days off each academic year to pursue personal or family health care needs in 2010. This study provides a secondary data analysis of five cross-sectional surveys of career satisfaction of resident and fellow trainees. METHODS: All trainees were surveyed five times over a 10-year period using anonymous, cross-sectional web-based survey instruments. Surveys included questions about career satisfaction, perceived stress, sleep hours, burnout, and related factors. RESULTS: This represents 10 years of accumulated responses from over 2,200 residents with results showing continual improvement in their career satisfaction. Response rates ranged from 56% to 72%. During the study period, there was a significant positive change in overall resident career satisfaction, with little change in factors traditionally considered to be predictive of overall career satisfaction such as sleep hours or perceived stress level. In addition, our data support that availability of time for personal tasks could positively impact the overall training experience. CONCLUSION: We postulate that the improvements in satisfaction relate to two major institutional innovations designed to promote resident wellness.


Letermovir, GW275175X (a benzimidazole) and tomeglovir (Bay38-4766) are chemically unrelated human cytomegalovirus (CMV) terminase complex inhibitors that have been tested in human subjects. UL56 gene mutations are the dominant pathway of letermovir resistance, while UL89 and UL56 mutations are known to confer benzimidazole resistance. This study compares the mutations elicited by the three inhibitors during in vitro CMV propagation. GW275175X consistently selected for UL89 D344E, and sometimes UL89 C347S, R351H, or UL56 Q204R. Tomeglovir consistently selected for UL89 V362M, and sometimes UL89 N329S, T350M, H389N, N405D, or UL56 L208M, E407D, H637Q or V639M. Adding to known and novel UL56 mutations, letermovir occasionally selected for UL89 N320H, D344E or M359I. Recombinant phenotyping confirmed that UL89 D344E conferred 9-fold resistance (increased EC50) for GW275175X, and increased the letermovir and tomeglovir EC50 by 1.7 to 2.1-fold for baseline virus and UL56 mutants Q204R, E237D, F261L and M329T. UL89 N320H and M359I conferred <2-fold letermovir resistance but 7-fold resistance for tomeglovir; mutant N320H was also 4-fold resistant to GW275175X. UL89 N329S conferred tomeglovir and letermovir cross-resistance. UL89 T350M conferred resistance to all three inhibitors. UL89 C347S conferred...
27-fold GW275175X resistance. UL89 V362M and H389N conferred 98-fold and 29-fold tomeglovir resistance without cross-resistance. Thus, characteristic UL89 mutations confer substantial resistance to GW275175X and tomeglovir, and are an uncommon accessory pathway of letemovir resistance. Instances of moderate cross-resistance and proximity of the selected UL89 and UL56 mutations suggest targeting of a similar terminase functional locus involving UL56 and UL89 interaction.


Spider silk synthesis is an emerging model for the evolution of tissue-specific gene expression and the role of gene duplication in functional novelty, but its potential has not been fully realized. Accordingly, we quantified transcript (mRNA) abundance in seven silk gland types and three non-silk gland tissues for three cobweb-weaving spider species. Evolutionary analyses based on expression levels of thousands of homologous transcripts and phylogenetic reconstruction of 605 gene families demonstrated conservation of expression for each gland type among species. Despite serial homology of all silk glands, the expression profiles of the glue-forming aggregate glands were divergent from fiber-forming glands. Also surprising was our finding that shifts in gene expression among silk gland types were not necessarily coupled with gene duplication, even though silk-specific genes belong to multi-paralog gene families. Our results challenge widely accepted models of tissue specialization and significantly advance efforts to replicate silk-based high-performance biomaterials.


**OBJECTIVE:** To determine if an extended perioperative course of corticosteroids will improve pain control following transoral robotic surgery (TORS). **STUDY DESIGN:** Randomized, double-blind, placebo-controlled trial. **METHODS:** Patients undergoing TORS for initial treatment of oropharyngeal squamous cell carcinoma received a single intraoperative dose of 10-mg dexamethasone and then were randomized to receive 8-mg dexamethasone every 8 hours, or placebo, for up to 4 days after surgery. Pain, measured by visual analog scale (VAS), was the primary outcome measure. Secondary outcome measures included length of stay, dysphagia assessments, and complications. **RESULTS:** VAS pain scores were similar between steroid and placebo cohorts on postoperative day (POD) 1, 2, and 7 through 21, although they significantly improved in the steroid cohort on POD 3. The steroid cohort also demonstrated a decreased hospital length of stay (median 1 day) and improvement in diet consistency, as measured by the performance status scale on POD 7 through 21. There was no difference in complications between the steroid and placebo cohorts. **CONCLUSION:** Extended perioperative corticosteroids after TORS is safe and may allow earlier improvement in diet consistency and decreased length of hospital stay, although postoperative pain appears minimally affected. **LEVEL OF EVIDENCE:** 1b. *Laryngoscope*, 2017.


Proper neural circuit formation requires the precise regulation of neuronal migration, axon guidance and dendritic arborization. Mutations affecting the function of the transmembrane glycoprotein dystroglycan cause a form
of congenital muscular dystrophy that is frequently associated with neurodevelopmental abnormalities. Despite its importance in brain development, the role for dystroglycan in regulating retinal development remains poorly understood. Using a mouse model of dystroglycanopathy (ISPDL79*) and conditional dystroglycan mutants of both sexes, we show that dystroglycan is critical for the proper migration, axon guidance and dendritic stratification of neurons in the inner retina. Using genetic approaches, we show that dystroglycan functions in neuroepithelial cells as an extracellular scaffold to maintain the integrity of the retinal inner limiting membrane (ILM). Surprisingly, despite the profound disruptions in inner retinal circuit formation, spontaneous retinal activity is preserved. These results highlight the importance of dystroglycan in coordinating multiple aspects of retinal development. SIGNIFICANCE STATEMENT The extracellular environment plays a critical role in coordinating neuronal migration and neurite outgrowth during neural circuit development. The transmembrane glycoprotein dystroglycan functions as a receptor for multiple extracellular matrix proteins, and its dysfunction leads to a form of muscular dystrophy frequently associated with neurodevelopmental defects. Our results demonstrate that dystroglycan is required for maintaining the structural integrity of the inner limiting membrane (ILM) in the developing retina. In the absence of functional dystroglycan, ILM degeneration leads to defective migration, axon guidance and mosaic spacing of neurons, and a loss of multiple neuron types during retinal development. These results demonstrate that disorganization of retinal circuit development is a likely contributor to visual dysfunction in patients with dystroglycanopathy.


BACKGROUND: Congenital cytomegalovirus infections are a leading cause of neurodevelopmental disorders in human and represent a major health care and socio-economical burden. In contrast with this medical importance, the pathophysiological events remain poorly known. Murine models of brain cytomegalovirus infection, mostly neonatal, have brought recent insights into the possible pathogenesis, with convergent evidence for the alteration and possible involvement of brain immune cells. OBJECTIVES AND METHODS: In order to confirm and expand those findings, particularly concerning the early developmental stages following infection of the fetal brain, we have created a model of in utero cytomegalovirus infection in the developing rat brain. Rat cytomegalovirus was injected intraventricularly at embryonic day 15 (E15) and the brains analyzed at various stages until the first postnatal day, using a combination of gene expression analysis, immunohistochemistry and multicolor flow cytometry experiments. RESULTS: Rat cytomegalovirus infection was increasingly seen in various brain areas including the choroid plexi and the ventricular and subventricular areas and was prominently detected in CD45low/int, CD11b+ microglial cells, in CD45high, CD11b+ cells of the myeloid lineage including macrophages, and in CD45+, CD11b- lymphocytes and non-B non-T cells. In parallel, rat cytomegalovirus infection of the developing rat brain rapidly triggered a cascade of pathophysiological events comprising: chemokines upregulation, including CCL2-4, 7 and 12; infiltration by peripheral cells including B-cells and monocytes at E17 and P1, and T-cells at P1; and microglia activation at E17 and P1. CONCLUSION: In line with previous findings in neonatal murine models and in human specimen, our study further suggests that neuroimmune alterations might play critical roles in the early stages following cytomegalovirus infection of the brain in utero. Further studies are now needed to determine which role, whether favorable or detrimental, those putative double-edge swords events actually play.


PDX1+/NKX6-1+ pancreatic progenitors (PPs) give rise to endocrine cells both in vitro and in vivo. This cell population can be successfully differentiated from human pluripotent stem cells (hPSCs) and hold the potential to generate an unlimited supply of beta cells for diabetes treatment. However, the efficiency of PP
generation in vitro is highly variable, negatively impacting reproducibility and validation of in vitro and in vivo studies, and consequently, translation to the clinic. Here, we report the use of a proteomics approach to phenotypically characterize hPSC-derived PPs and distinguish these cells from non-PP populations during differentiation. Our analysis identifies the pancreatic secretory granule membrane major glycoprotein 2 (GP2) as a PP-specific cell surface marker. Remarkably, GP2 is co-expressed with NKX6-1 and PTF1A in human developing pancreata, indicating that it marks the multipotent pancreatic progenitors in vivo. Finally, we show that isolated hPSC-derived GP2+ cells generate beta-like cells (C-PEPTIDE+/NKX6-1+) more efficiently compared to GP2- and unsorted populations, underlining the potential therapeutic applications of GP2. Pancreatic progenitors (PPs) can be derived from human pluripotent stem cells in vitro but efficiency of differentiation varies, making it hard to sort for insulin-producing cells. Here, the authors use a proteomic approach to identify the secretory granule membrane glycoprotein 2 as a marker for PDX1+/NKX6-1+ PPs.


INTRODUCTION: Recently the use of reverse shoulder arthroplasty (RSA) has increased because of a clinical perception of durable functional outcome. However, some patients unexpectedly have a poor recovery of range of motion (ROM) after surgery. Objective factors such as initial diagnosis, pre- and intra-operative ROM, deltoid impairment or arm lengthening have previously been associated with anterior forward flexion (AFF). This study sought to determine if subjective pre-operative factors influence the rate and timing of ROM recovery after RSA. METHODS: Between January 2011 to January 2012, all RSAs performed by a single surgeon were prospectively enrolled in this study. The cohort was divided into two groups based on AFF <90 or >/=90 after surgery. A multivariate analysis was performed to define independent predictive factors of post-operative ROM. Factors assessed included: age, sex, dominant arm, patient activity, body mass index (BMI), pre-operative diagnosis, deltoid status, pain and Constant scores, subjective shoulder value (SSV), simple shoulder test (SST) and radiographic findings. Patients were reviewed at six weeks, and three, six, 12 and 24 months. RESULTS: One hundred and one RSAs were available for analysis. Poor post-operative AFF at six weeks was significantly related to poor pre-operative deltoid strength. Poor post-operative AFF at one-year follow-up was related to surgery of non-dominant arm, pre-operative poor AFF, pre-operative activity, poor subjective shoulder value (SSV), and a low contralateral Constant score. AFF and Constant score improved until six months and then plateaued. In contrast, both internal and external rotation continued to improve beyond six months after surgery. CONCLUSIONS: AFF and Constant scores after RSA plateau at six months after surgery whereas internal and external rotation continue to improve up to two years post operation. Several pre-operative factors including poor pre-operative AFF, surgery on the non-dominant arm, and lower SSV and Constant scores are correlated with post-operative ROM following RSA. Identification of these factors may be useful for counseling on functional expectations as well as customizing rehabilitation plans. LEVEL OF EVIDENCE: Level II, Prospective Cohort Study, Treatment Study.


The rostral raphe pallidus (rRPa) contains sympathetic premotor neurons controlling thermogenesis in brown adipose tissue (BAT). We sought to determine whether a tonic activation of glycineA receptors (GlyAR) in the rRPa contributes to the inhibitory regulation of BAT sympathetic nerve activity (SNA) and of cardiovascular parameters in anesthetized rats. Nanoinjection of the GlyAR antagonist, strychnine (STR), into the rRPa of intact rats increased BAT SNA (peak: +495%), BAT temperature (TBAT, +1.1 degrees C), expired CO2, (+0.4%), core body temperature (TCORE, +0.2 degrees C), mean arterial pressure (MAP, +4 mmHg), and heart rate (HR, +57 beats/min). STR into rRPa in rats with a posterodorsomedial hypothalamus transection produced similar increases in BAT thermogenic and cardiovascular parameters. Glycine nanoinjection into the rRPa evoked a potent inhibition of the cooling-evoked increases in BAT SNA (nadir: -74%), TBAT (-0.2 degrees C), and mean arterial pressure (-18 mmHg).
TCORE (-0.2 degrees C), expired CO2 (-0.2%), MAP (-8 mmHg), and HR (-22 beats/min) but had no effect on the increases in these variables evoked by STR nanoinjection into rRPa. Nanoinjection of GABA into the rRPa inhibited the STR-evoked BAT SNA (nadir: -86%) and reduced the expired CO2 (-0.4%). Blockade of glutamate receptors in rRPa reduced the STR-evoked increases in BAT SNA (nadir: -61%), TBAT (-0.5 degrees C), expired CO2 (-0.3%), MAP (-9 mmHg), and HR (-33 beats/min). We conclude that a tonically active glycinergetic input to the rRPa contributes to the inhibitory regulation of the discharge of BAT sympathetic premotor neurons and of BAT thermogenesis and energy expenditure.


One-electron reduction of [Fe(NO)-(N3PyS)]BF4 (1) leads to the production of the metastable nonheme {FeNO}8 complex, [Fe(NO)(N3PyS)] (3). Complex 3 is a rare example of a high-spin (S = 1) {FeNO}8 and is the first example, to our knowledge, of a mononuclear nonheme {FeNO}8 species that generates N2O. A second, novel route to 3 involves addition of Piloty’s acid, an HNO donor, to an FeII donor. This work provides possible new insights regarding the mechanism of nitric oxide reductases. © 2017 American Chemical Society.


BACKGROUND/OBJECTIVES: The P.A.L.Li.A.T.E. (prognostic assessment of life and limitations after trauma in the elderly) consortium has previously created a prognosis calculator for mortality after geriatric injury based on age, injury severity, and transfusion requirement called the geriatric trauma outcome score (GTOS). Here, we sought to create and validate a prognosis calculator called the geriatric trauma outcome score ii (GTOS II) estimating probability of unfavorable discharge. DESIGN: Retrospective cohort. SETTING: Four geographically diverse Level 1 trauma centers. PARTICIPANTS: Trauma admissions aged 65 to 102 years surviving to discharge from 2000 to 2013. INTERVENTION: None. MEASUREMENTS: Age, injury severity score (ISS), transfusion at 24 hours post-admission, discharge dichotomized as favorable (home/rehabilitation) or unfavorable (skilled nursing/long term acute care/hospice). Training and testing samples were created using the holdout method. A multiple logistic mixed model (GTOS II) was created to estimate the odds of unfavorable disposition then re-specified using the GTOS II as the sole predictor in a logistic mixed model using the testing sample. RESULTS: The final dataset was 16,114 subjects (unfavorable discharge status = 15.4%). Training (n = 8,057) and testing (n = 8,057) samples had similar demographics. The formula based on the training sample was (GTOS II = Age + [0.71 x ISS] + 8.79 [if transfused by 24 hours]). Misclassification rate and AUC were 15.63% and 0.67 for the training sample, respectively, and 15.85% and 0.67 for the testing sample. CONCLUSION: GTOS II estimates the probability of unfavorable discharge in injured elders with moderate accuracy. With the GTOS mortality calculator, it can help in goal setting conversations after geriatric injury.


Current classifications of Chronic Obstructive Pulmonary Disease (COPD) severity are complex and do not grade levels of obstruction. Obstruction is a simpler construct and independent of ethnicity. We constructed an index of obstruction severity based on the FEV1/FVC ratio, with cut-points dividing the Burden of Obstructive Lung Disease (BOLD) study population into four similarly sized strata to those created by the GOLD criteria that uses FEV1. We measured the agreement between classifications and the validity of the FEV1-based
classification in identifying the level of obstruction as defined by the new groupings. We compared the strengths of association of each classification with quality of life (QoL), MRC dyspnoea score and the self-reported exacerbation rate. Agreement between classifications was only fair. FEV1-based criteria for moderate COPD identified only 79% of those with moderate obstruction and misclassified half of the participants with mild obstruction as having more severe COPD. Both scales were equally strongly associated with QoL, exertional dyspnoea and respiratory exacerbations. Severity assessed using the FEV1/FVC ratio is only in moderate agreement with the severity assessed using FEV1 but is equally strongly associated with other outcomes. Severity assessed using the FEV1/FVC ratio is likely to be independent of ethnicity.


BACKGROUND: Periprosthetic hip fractures (PPHFx) are challenging complications that have become increasingly more prevalent. Wide variability exists in the quality and size of prior studies pertaining to hospital stay information. This study used the largest publicly available database in the United States to evaluate perioperative hospital data of PPHFx. METHODS: The Healthcare Cost and Utilization Project-Nationwide Inpatient Sample was used to analyze trends related to the frequency, fracture type, mortality, treatment, patient demographics, time to surgery, length of stay (LOS), and hospital charges associated with PPHFx from 2006-2010. RESULTS: From 2006-2010, average patient age (76.7 years), hospital characteristics, rate of PPHFx, treatment choice, LOS (8.03 days), mortality (2.6%), disposition (78.1% to skilled nursing facility or inpatient rehab), and time to procedure (1.98 days) all remained relatively stable. The southern United States had the highest frequency of PPHFx and females had nearly twice the rate of PPHFx each year at an average of 67%. Despite these consistencies, hospital charges increased by an average of 8.3% per year over the study period ($27,683 over 5 years, P < .0001). CONCLUSION: In the era of containing cost while improving quality of care, this study demonstrates that despite consistent treatment trends of PPHFx, hospital charges are increasing independently. Regardless, surgeons can work to reduce LOS and charge to post acute care facilities to lessen spending. Refining our understanding of these relationships will be fundamental to further improving quality of care and cutting cost associated with these fractures.


BACKGROUND: There is a serious public health need for better understanding of alcohol use disorder disease mechanisms and for improved treatments. At this writing, only three drugs are approved by the Food and Drug Administration as medications to treat alcohol use disorders - disulfiram, naltrexone, and acamprosate. Binge drinking is a form of abusive alcohol drinking defined by the NIAAA as a drinking to blood alcohol levels (BALs)>0.08% during a period of approximately 2h. To model genetic risk for binge-like drinking, we have used selective breeding to create a unique animal model, High Drinking in the Dark (HDID) mice. Behavioral characterization of HDID mice has revealed that HDID mice exhibit behavioral impairment after drinking, withdrawal after a single binge-drinking session, and escalate their intake in response to induction of successive cycles of dependence. Notably, HDID mice do not exhibit altered taste preference or alcohol clearance rates. We therefore asked whether drugs of known clinical relevance could modulate binge-like ethanol drinking in HDID mice, reasoning that this characterization of HDID responses should inform future use of this genetic animal model for screening and development of novel potential therapeutics. METHODS: We tested the efficacy of acamprosate and naltrexone to reduce binge-like drinking in HDID mice. Additionally, we tested the GABAB receptor agonist, baclofen, based on recent pre-clinical and clinical studies demonstrating that it reduces alcohol drinking. We elected not to include disulfiram due to its more limited clinical usage. Mice were tested after acute doses of drugs in the limited-access Drinking in the Dark (DID) paradigm. RESULTS: HDID mice were sensitive to the effects of acamprosate and baclofen, but not
naltrexone. Both drugs reduced binge-like drinking. However, naltrexone failed to reduce drinking in HDID mice. Thus, HDID mice may represent a useful model for screening novel compounds.


Molecular monitoring of chronic myeloid leukemia patients using robust BCR-ABL1 tests standardized to the International Scale (IS) is key to proper disease management, especially when treatment cessation is considered. Most laboratories currently use a time-consuming sample exchange process with reference laboratories for IS calibration. A World Health Organization (WHO) BCR-ABL1 reference panel was developed (MR(1)-MR(4)), but access to the material is limited. In this study, we describe the development of the first cell-based secondary reference panel that is traceable to and faithfully replicates the WHO panel, with an additional MR(4.5) level. The secondary panel was calibrated to IS using digital PCR with ABL1, BCR and GUSB as reference genes and evaluated by 44 laboratories worldwide. Interestingly, we found that >40% of BCR-ABL1 assays showed signs of inadequate optimization such as poor linearity and suboptimal PCR efficiency. Nonetheless, when optimized sample inputs were used, >60% demonstrated satisfactory IS accuracy, precision and/or MR(4.5) sensitivity, and 58% obtained IS conversion factors from the secondary reference concordant with their current values. Correlation analysis indicated no significant alterations in %BCR-ABL1 results caused by different assay configurations. More assays achieved good precision and/or sensitivity than IS accuracy, indicating the need for better IS calibration mechanisms.


Background: There is a pressing workforce shortage and leadership scarcity in palliative care to adequately meet the demands of individuals with serious illness and their families. To address this gap, the Cambia Health Foundation launched its Sojourns Scholars Leadership Program in 2014, an initiative designed to identify, cultivate, and advance the next generation of palliative care leaders. This report intends to summarize the second cohort of Sojourns Scholars’ projects and their reflection on their leadership needs. Objective: This report summarizes the second cohort of sojourns scholars’ project and their reflection on leadership needs. Methods: After providing a written reflection on their own projects, the second cohort participated in a group interview (fireside chat) to elicit their perspectives on barriers and facilitators in providing palliative care, issues facing leadership in palliative care in the United States, and lessons from personal and professional growth as leaders in palliative care. They analyzed the transcript of the group interview using qualitative content analysis methodology. Results: Three themes emerged from descriptions of the scholars’ project experience: challenges in palliative care practice, leadership strategies in palliative care, and three lessons learned to be a leader were identified. Challenges included perceptions of palliative care, payment and policy, and workforce development. Educating and collaborating with other clinicians and influencing policy change are important strategies used to advance palliative care. Time management, leading team effort, and inspiring others are important skills that promote effectiveness as a leader. Discussion: Emerging leaders have a unique view of conceptualizing contemporary palliative care and shaping the future. Conclusions: Providing comprehensive, coordinated care that is high quality, patient and family centered, and readily available depends on strong leadership in palliative care. The Cambia Scholars Program represents a unique opportunity. © 2017 Mary Ann Liebert, Inc.

INTRODUCTION: Few studies have assessed the prevalence and features of axial spondyloarthritis (axSpA) and ankylosing spondylitis in diverse, population-based, community settings. OBJECTIVES: We used computerized diagnoses to estimate the prevalence of axSpA and ankylosing spondylitis in Kaiser Permanente Northern California (KPNC). METHODS: We identified persons aged 18 years or older with 1 or more International Classification of Diseases, Ninth Revision (ICD-9) diagnosis Code 720.X (ankylosing spondylitis and other inflammatory spondylopathies) in clinical encounter data from 1996 through 2009 to estimate the prevalence of axSpA and ankylosing spondylitis. We reviewed medical records to confirm the diagnosis in a random sample and estimated the positive predictive value of computerized data to identify confirmed cases using various case definitions. RESULTS: In the computerized data, 5568 adults had diagnostic codes indicating axSpA. On the basis of our case-finding approach using a single physician diagnosis code for ICD-9 720.X, the point prevalence of these conditions, standardized to the 2000 US Census, was 2.26 per 1000 persons for axSpA and 1.07 per 1000 for ankylosing spondylitis. Less than half of suspected cases saw a rheumatologist. The most specific algorithm for confirmed ankylosing spondylitis required 2 or more computerized diagnoses assigned by a rheumatologist, with 67% sensitivity (95% confidence interval, 64%-69%) and 81% positive predictive value (95% confidence interval, 79%-83%). CONCLUSIONS: Observed prevalence in the KPNC population, compared with national estimates for axSpA and ankylosing spondylitis, suggests there is substantial underrecognition of these conditions in routine clinical practice. However, use of computerized data is able to identify true cases of ankylosing spondylitis, facilitating population-based research.


PURPOSE: To describe the risk and risk factors for ocular hypertension (OHT) in adults with noninfectious uveitis. DESIGN: Retrospective, multicenter, cohort study. PARTICIPANTS: Patients aged >/=18 years with noninfectious uveitis seen between 1979 and 2007 at 5 tertiary uveitis clinics. METHODS: Demographic, ocular, and treatment data were extracted from medical records of uveitis cases. MAIN OUTCOME MEASURES: Prevalent and incident OHT with intraocular pressures (IOPs) of >/=21 mmHg, >/=30 mmHg, and increase of >/=10 mmHg from documented IOP recordings (or use of treatment for OHT). RESULTS: Among 5270 uveitic eyes of 3308 patients followed for OHT, the mean annual incidence rates for OHT >/=21 mmHg and OHT >/=30 mmHg are 14.4% (95% confidence interval [CI], 13.4-15.5) and 5.1% (95% CI, 4.7-5.6) per year, respectively. Statistically significant risk factors for incident OHT >/=30 mmHg included systemic hypertension (adjusted hazard ratio [aHR], 1.29); worse presenting visual acuity (</=20/200 vs. >/=20/40, aHR, 1.47); pars plana vitrectomy (aHR, 1.87); history of OHT in the other eye: IOP >/=21 mmHg (aHR, 2.68), >/=30 mmHg (aHR, 4.86) and prior/current use of IOP-lowering drops or surgery in the other eye (aHR, 4.17); anterior chamber cells: 1+ (aHR, 1.43) and >/=2+ (aHR, 1.59) vs. none; epiretinal membrane (aHR, 1.25); peripheral anterior synechiae (aHR, 1.81); current use of prednisone >7.5 mg/day (aHR, 1.86); periocular corticosteroids in the last 3 months (aHR, 2.23); current topical corticosteroid use [>/=8x/day vs. none] (aHR, 2.58); and prior use of fluocinolone acetonide implants (aHR, 9.75). Bilateral uveitis (aHR, 0.69) and previous hypotony (aHR, 0.43) were associated with statistically significantly lower risk of OHT. CONCLUSIONS: Ocular hypertension is sufficiently common in eyes treated for uveitis that surveillance for OHT is essential at all visits for all cases. Patients with 1 or more of the several risk factors identified are at particularly high risk and must be carefully managed. Modifiable risk factors, such as use of corticosteroids, suggest opportunities to reduce OHT risk within the constraints of the overriding need to control the primary ocular inflammatory disease.

Adolescence is the period of development that begins at puberty and ends in early adulthood. Most commonly, adolescence is divided into three developmental periods: early adolescence (10-14 years of age), late adolescence (15-19 years of age), and young adulthood (20-24 years of age). Adolescence is marked by physical and sexual maturation, social and economic independence, development of identity, acquisition of skills needed to carry out adult relationships and roles, and the capacity for abstract reasoning. Adolescence is characterized by a rapid pace of growth that is second only to that of infancy. Nutrition and the adolescent transition are closely intertwined, since eating patterns and behaviors are influenced by many factors, including peer influences, parental modeling, food availability, food preferences, cost, convenience, personal and cultural beliefs, mass media, and body image. Here, we describe the physiology, metabolism, and nutritional requirements for adolescents and pregnant adolescents, as well as nutrition-related behavior and current trends in adolescent nutrition. We conclude with thoughts on the implications for nutrition interventions and priority areas that would require further investigation.


Providing flavored milk in school lunches is controversial, with conflicting evidence on its impact on nutritional intake versus added sugar consumption and excess weight gain. Nonindustry-sponsored studies using individual-level analyses are needed. Therefore, we conducted this mixed-methods study of flavored milk removal at a rural primary school between May and June 2012. We measured beverage selection/consumption pre- and post-chocolate milk removal and collected observation field notes. We used linear and logistic mixed models to assess beverage waste and identified themes in staff and student reactions. Our analysis of data from 315 unique students and 1,820 beverages choices indicated that average added sugar intake decreased by 2.8 g postremoval, while average reductions in calcium and protein consumption were negligible (12.2 mg and 0.3 g, respectively). Five thematic findings emerged, including concerns expressed by adult staff about student rebellion following removal, which did not come to fruition. Removing flavored milk from school-provided lunches may lower students’ daily added sugar consumption without considerably decreasing calcium and protein intake and may promote healthy weight. © 2017, © The Author(s) 2017.


BACKGROUND: Human endogenous retroviruses (HERVs) comprise approximately 8% of the human genome and while the majority are transcriptionally silent, the most recently integrated HERV, HERV-K (HML-2), remains active. During HIV infection, HERV-K (HML-2) specific mRNA transcripts and viral proteins can be detected. In this study, we aimed to understand the antibody response against HERV-K (HML-2) Gag in the context of HIV-1 infection. RESULTS: We developed an ELISA assay using either recombinant protein or 164 redundant “15mer” HERV-K (HML-2) Gag peptides to test sera for antibody reactivity. We identified a total of eight potential HERV-K (HML-2) Gag immunogenic domains: two on the matrix (peptides 16 and 31), one on p15 (peptide 85), three on the capsid (peptides 81, 97 and 117), one on the nucleocapsid (peptide 137) and one on the QP1 protein (peptide 157). Four epitopes (peptides 16, 31, 85 and 137) were highly immunogenic. No significant differences in antibody responses were found between HIV infected participants (n = 40) and uninfected donors (n = 40) for 6 out of the 8 epitopes tested. The antibody response against nucleocapsid (peptide 137) was significantly lower (p < 0.001), and the response to QP1 (peptide 157) significantly higher (p < 0.05) in HIV-infected adults compared to uninfected individuals. Among those with HIV infection, the
level of response against p15 protein (peptide 85) was significantly lower in untreated individuals controlling HIV ("elite" controllers) compared to untreated non-controllers (P < 0.05) and uninfected donors (P < 0.05). In contrast, the response against the capsid protein (epitopes 81 and 117) was significantly higher in controllers compared to uninfected donors (P < 0.001 and <0.05 respectively) and non-controllers (P < 0.01 and <0.05). Peripheral blood mononuclear cells (PBMCs) from study participants were tested for responses against HERV-K (HML-2) capsid recombinant peptide in gamma interferon (IFN-gamma) enzyme immunospot (Elispot) assays. We found that the HERV-K (HML-2) Gag antibody and T cell response by Elispot were significantly correlated. CONCLUSIONS: HIV elite controllers had a strong cellular and antibody response against HERV-K (HML-2) Gag directed mainly against the Capsid region. Collectively, these data suggest that anti-HERV-K (HML-2) antibodies targeting capsid could have an immunoprotective effect in HIV infection.


OBJECTIVES/HYPOTHESIS: Chronic rhinosinusitis with nasal polyposis (CRSwNP) is a disease process that is driven, in part, by intrinsic mucosal inflammation. Surgery plus continued medical therapy is commonly elected by medically recalcitrant, symptomatic patients. The objective was to evaluate the prevalence of nasal polyp recurrence up to 18 months after endoscopic sinus surgery (ESS) with congruent continuing medical management. STUDY DESIGN: Prospective, multi-center cohort of adult patients undergoing ESS for medically recalcitrant CRSwNP performed between August 2004 and February 2015. METHODS: All patients received baseline nasal endoscopy quantified using Lund-Kennedy grading. All patients included for final analysis provided at least 6 months of postoperative endoscopy examinations. Multivariate analysis was used to identify risk factors for polyp recurrence. RESULTS: Three hundred sixty-three CRSwNP patients having undergone ESS involving polypectomy were enrolled. A total of 244 (67%) participants had graded postoperative endoscopies with average of follow-up of 14.3 +/- 7.0 months. Surgery plus postoperative medical management significantly improved endoscopy total scores at 6 months (P < .001). The recurrence of nasal polyposis 6 months after ESS was 35% (68/197), compared to 38% (48/125) after 12 months, and 40% (52/129) after 18 months. Multivariate analysis identified both prior ESS (odds ratio [OR]: 2.6, 95% confidence interval [CI]: 1.5-4.6; P = .001) and worse preoperative polyposis severity (OR: 1.4, 95% CI: 1.1-1.8; P = .016) as risk factors for recurrent polyposis. CONCLUSIONS: Polyp recurrence is common after ESS with control of polyps up to 18 months found in approximately 60% to 70% of patients. Investigation into both surgical and medical management strategies is warranted to improve upon the observed prevalence of recurrence. LEVEL OF EVIDENCE: 2c. Laryngoscope, 127:550-555, 2017.


OBJECTIVE: Medically refractory chronic rhinosinusitis (CRS) can be managed with appropriate continued medical therapy (CMT) or surgery followed by CMT. Patients who initially elect CMT and do not experience adequate symptom resolution may “cross over” to endoscopic sinus surgery (ESS). Our objective was to identify patient covariates associated with this subset of patients who elect this change in treatment modality. STUDY DESIGN: Retrospective analysis of a prospective, multi-center cohort of adult patients with CRS enrolled between March 2011 and June 2015 in academic, tertiary referral clinics. METHODS: Subjects who initially elected CMT were followed up to 18 months, provided a comprehensive medical history, and completed the 22-item SinoNasal Outcome Test (SNOT-22) at baseline and during 6-month follow-up intervals. Hazard regression modeling was used to identify covariates associated with elective change in treatment modality. RESULTS: One hundred seventy-nine subjects were followed for an average 15.1 (standard deviation +/- 4.6) months. Subjects who elected ESS (55 of 179) had significantly worse average endoscopy scores and reported worse SNOT-22 sleep dysfunction scores at baseline (P <= 0.026). For each single increasing (worsening) point of Lund-Kennedy endoscopy score, the hazard ratio (HR) of crossover increased by...
approximately 6%. Similarly, for every point of worsening in baseline SNOT-22 total score, the hazard of treatment crossover increased by approximately 2%. After covariate adjustment, only baseline SNOT-22 sleep dysfunction scores were associated with an increased risk of treatment crossover (HR = 1.07; 95% confidence interval: 1.02-1.11; P = 0.003). CONCLUSION: Baseline total SNOT-22 and endoscopy scores are associated with treatment crossover, but reported sleep dysfunction is the only significant independent predictor of treatment crossover. LEVEL OF EVIDENCE: 2c. Laryngoscope, 2017.


IL-15 has been implicated as a key regulator of T and NK cell homeostasis in multiple systems; however, its specific role in maintaining peripheral T and NK cell populations relative to other gamma-chain (gammac) cytokines has not been fully defined in primates. In this article, we address this question by determining the effect of IL-15 inhibition with a rhesusized anti-IL-15 mAb on T and NK cell dynamics in rhesus macaques. Strikingly, anti-IL-15 treatment resulted in rapid depletion of NK cells and both CD4(+)- and CD8(+)- effector memory T cells (TEM) in blood and tissues, with little to no effect on naive or central memory T cells. Importantly, whereas depletion of NK cells was nearly complete and maintained as long as anti-IL-15 treatment was given, TEM depletion was countered by the onset of massive TEM proliferation, which almost completely restored circulating TEM numbers. Tissue TEM, however, remained significantly reduced, and most TEM maintained very high turnover throughout anti-IL-15 treatment. In the presence of IL-15 inhibition, TEM became increasingly more sensitive to IL-7 stimulation in vivo, and transcriptional analysis of TEM in IL-15-inhibited monkeys revealed engagement of the JAK/STAT signaling pathway, suggesting alternative gammac cytokine signaling may support TEM homeostasis in the absence of IL-15. Thus, IL-15 plays a major role in peripheral maintenance of NK cells and TEM. However, whereas most NK cell populations collapse in the absence of IL-15, TEM can be maintained in the face of IL-15 inhibition by the activity of other homeostatic regulators, most likely IL-7.


Tooth erosion from an acidic insult may be exacerbated by toothbrushing. The purposes of this study were to develop an in vitro methodology to measure enamel loss after brushing immediately following an acidic episode and to investigate the effect of brushing with an anti-erosive toothpaste. The null hypotheses tested were that tooth erosion after brushing with the toothpaste would not be different from brushing with water and that a 1-hour delay before brushing would not reduce tooth erosion. Forty bovine enamel slabs were embedded, polished, and subjected to baseline profilometry. Specimens were bathed in hydrochloric acid for 10 minutes to simulate stomach acid exposure before post-acid profilometry. Toothbrushing was then simulated with a cross-brushing machine and followed by postbrushing profilometry. Group 1 was brushed with water; group 2 was brushed with a 50:50 toothpasteswater slurry; and groups 3 and 4 were immersed in artificial saliva for 1 hour before brushing with water or the toothpaste slurry, respectively. The depth of enamel loss was analyzed and compared using 1-way analysis of variance and post hoc testing (α = 0.05). Greater enamel loss was measured in groups brushed with toothpaste than in groups brushed with water. One-hour immersion in artificial saliva significantly reduced enamel loss when teeth were brushed with water (group 3; P < 0.05) but not with toothpaste (group 4). This study established a protocol for measuring enamel loss resulting from erosion followed by toothbrush abrasion. The results confirmed the abrasive action of toothpaste on acidsoftened enamel. © 2017 by the Academy of General Dentistry.

The fusion of neurotransmitter-filled vesicles during synaptic transmission is balanced by endocytic membrane retrieval. Despite extensive research, the speed and mechanisms of synaptic vesicle endocytosis have remained controversial. Here, we establish low-noise time-resolved membrane capacitance measurements that allow monitoring changes in surface membrane area elicited by single action potentials and stronger stimuli with high-temporal resolution at physiological temperature in individual bona-fide mature central synapses. We show that single action potentials trigger very rapid endocytosis, retrieving presynaptic membrane with a time constant of 470 ms. This fast endocytosis is independent of clathrin but mediated by dynamin and actin. In contrast, stronger stimuli evoke a slower mode of endocytosis that is clathrin, dynamin, and actin dependent. Furthermore, the speed of endocytosis is highly temperature dependent with a Q10 of approximately 3.5. These results demonstrate that distinct molecular modes of endocytosis with markedly different kinetics operate at central synapses.


BACKGROUND: Little research has been conducted about the quality, benefits, costs, and financial considerations associated with health information technology (HIT), particularly informatics technologies, such as e-prescribing, from the perspective of all its stakeholders. OBJECTIVES: This research effort sought to identify the stakeholders involved in e-prescribing and to identify and rank-order the positives and the negatives from the perspective of the stakeholders to create a framework to assist in the development of incentives and payment mechanisms which result in better managed care. METHODS: The Delphi method was employed by enlisting a panel of experts. They were presented with the results of initial research in an online survey of questions which sought to prioritize the quality, benefit, cost, and financial effects of e-prescribing from the perspective of each stakeholder. From the results of this study, a framework was presented to framework experts. RESULTS: The experts added stakeholders and positives and negatives to the initial lists and rank-ordered the positives and negatives of e-prescribing from the perspective of each stakeholder. The aggregate results were summarized by category of stakeholder. The framework experts evaluated the framework. CONCLUSIONS: Positives and negatives can be rank-ordered from the perspective of each stakeholder. A useful framework was created.


Academic medical centers (AMCs) in the United States built world-class infrastructure to successfully combat disease in the 20th century, which is inadequate for the complexity of sustaining and improving population health. AMCs must now build first-rate 21st-century infrastructure to connect combating disease and promoting health. This infrastructure must acknowledge the bio-psycho-social-environmental factors impacting health and will need to reach far beyond the AMC walls to foster community “laboratories” that support the “science of health,” complementary to those supporting the “science of medicine”; cultivate community “classrooms” to stimulate learning and discovery in the places where people live, work, and play; and strengthen bridges between academic centers and these community laboratories and classrooms to facilitate bidirectional teaching, learning, innovation, and discovery. Private and public entities made deep financial investments that contributed to the AMC disease-centered approach to clinical care, education, and research in the 20th century. Many of these same funders now recognize the need to transform U.S. health care into a system that is accountable for population health and the need for a medical workforce equipped with the skills to measure and improve health. Innovative ideas about communities as centers of learning, the importance of social factors as major determinants of health, and the need for multidisciplinary perspectives to solve complex problems are not new; many are 20th-century ideas still waiting to be fully implemented.
The window of opportunity is now. The authors articulate how AMCs must take bigger and bolder steps to become leaders in population health.


Endometriosis is a relatively common condition in women and some populations of adult female rhesus macaques. However, endometriosis with extensive smooth muscle proliferation, as occurs in endomyometrioma and uterus-like mass (ULM), is rare in women. This report describes a case of endometriosis with extensive smooth muscle metaplasia resembling multiple ULM in a 20-year-old female rhesus macaque. During a protocol-related procedure, a large, smooth, globoid, freely moveable mass was palpated in the midabdomen. Ultrasonography revealed a cystic structure from which dark brown fluid was aspirated. During exploratory laparotomy, an 8-cm spherical mass in the greater omentum and 3 additional masses (diameter, 2 to 5 cm) attached to the omentum were excised. Microscopic examination of the masses revealed numerous foci of ectopic endometrial glands and stroma frequently surrounded by bundles of smooth muscle and fibrous connective tissue. The gross and histologic lesions in this macaque bore many similarities to ULM in women. To our knowledge, this case represents the first report of endometriosis resembling a uterus-like mass in a NHP.


BACKGROUND: The optimal approach for selecting men for bone mineral density (BMD) testing to screen for osteoporosis is uncertain. OBJECTIVE: To compare strategies for selecting older men for screening BMD testing. DESIGN: Prospective cohort study. PARTICIPANTS: A total of 4043 community-dwelling men aged >/=70 years at four US sites. MAIN MEASURES: BMD at the total hip, femoral neck, and lumbar spine using dual-energy x-ray absorptiometry (DXA). Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, and area under the receiver operating curve (AUC) of the Osteoporosis Self-Assessment Tool (OST) and Fracture Risk Assessment Tool (FRAX) without BMD to discriminate between those with and without osteoporosis as defined by World Health Organization (WHO) diagnostic criteria, and between those recommended and not recommended for pharmacologic therapy based on the National Osteoporosis Foundation (NOF) guidelines. KEY RESULTS: Among the cohort, 216 (5.3%) had a BMD T-score </= -2.5 at the femoral neck, total hip, or lumbar spine, and 1184 (29.2%) met criteria for consideration of pharmacologic therapy according to NOF guidelines. The OST had better discrimination (AUC 0.68) than the FRAX (AUC 0.62; p = 0.004) for identifying T-score-defined osteoporosis. Use of an OST threshold of <2 resulted in sensitivity of 0.83 and specificity of 0.36 for the identification of osteoporosis, compared to sensitivity of 0.59 and specificity of 0.59 for the use of FRAX with a cutoff of 9.3% 10-year risk of major osteoporotic fracture. CONCLUSIONS: The OST performs modestly better than the more complex FRAX in selecting older men for BMD testing to screen for osteoporosis; the use of either tool substantially reduces the proportion of men referred for BMD testing compared to universal screening. Of 1000 men aged 70 and older in this community-based cohort, the use of an OST cutoff of <2 to select men for BMD testing would result in 654 men referred for BMD testing, of whom 44 would be identified as having osteoporosis, and nine with osteoporosis would be missed.


BACKGROUND: There is a lack of health promotion programming designed to change the physical activity environment of the group home setting. The Menu-Choice programme assists staff in creating physical
activity goals alongside residents with intellectual disabilities and provides strategies to incorporate activity into the group home schedule. The purpose of this study was to complete a process evaluation of Menu-Choice utilizing qualitative methods. METHODS: Twelve participants, who completed a 10-week pilot intervention (n = 7 staff, mean age 42; n = 5 residents, mean age 52), participated in face-to-face interviews. Participants represented five group home sites involved in the intervention. RESULTS: Meta-themes included: (i) Programme training, (ii) Programme implementation, (iii) Programme physical activity, (iv) Programme barriers, (v) Programme facilitators and (vi) Programme feedback. CONCLUSIONS: Changes in programme training and simplified programme materials are needed to accommodate identified barriers for implementation. The importance of obtaining increased agency support and policy change is highlighted.


Head motion systematically distorts clinical and research MRI data. Motion artifacts have biased findings from many structural and functional brain MRI studies. An effective way to remove motion artifacts is to exclude MRI data frames affected by head motion. However, such post-hoc frame censoring can lead to data loss rates of 50% or more in our pediatric patient cohorts. Hence, many scanner operators collect additional 'buffer data', an expensive practice that, by itself, does not guarantee sufficient high-quality MRI data for a given participant. Therefore, we developed an easy-to-setup, easy-to-use Framewise Integrated Real-time MRI Monitoring (FIRM) software suite that provides scanner operators with head motion analytics in real-time, allowing them to scan each subject until the desired amount of low-movement data has been collected. Our analyses show that using FIRM to identify the ideal scan time for each person can reduce total brain MRI scan times and associated costs by 50% or more.


OBJECTIVE: To estimate the cost and return on investment (ROI) of an intervention targeting work-family conflict (WFC) in the extended care industry. METHODS: Costs to deliver the intervention during a group-randomized controlled trial were estimated, and data on organizational costs-presenteeism, health care costs, voluntary termination, and sick time were collected from interviews and administrative data. Generalized linear models were used to estimate the intervention's impact on organizational costs. Combined, these results produced ROI estimates. A cluster-robust confidence interval (CI) was estimated around the ROI estimate. RESULTS: The per-participant cost of the intervention was $767. The ROI was -1.54 (95% CI: -4.31 to 2.18). The intervention was associated with a $668 reduction in health care costs (P < 0.05). CONCLUSIONS: This paper builds upon and expands prior ROI estimation methods to a new setting.


Germline mutations in the X-linked gene, methyl-CpG-binding protein 2 (MECP2), underlie most cases of Rett syndrome (RTT), an autism spectrum disorder affecting approximately one in 10 000 female live births. The disease is characterized in affected girls by a latent appearance of symptoms between 12 and 18 months of age while boys usually die before the age of two. The nature of the latency is not known, but RTT-like
phenotypes are recapitulated in mouse models, even when MeCP2 is removed at different postnatal stages, including juvenile and adolescent stages. Unexpectedly, here, we show that within a very brief developmental window, between 10 (adolescent) and 15 (adult) weeks after birth, symptom initiation and progression upon removal of MeCP2 in male mice transitions from 3 to 4 months to only several days, followed by lethality. We further show that this accelerated development of RTT phenotype and lethality occur at the transition to adult stage (15 weeks of age) and persists thereafter. Importantly, within this abbreviated time frame of days, the brain acquires dramatic anatomical, cellular and molecular abnormalities, typical of classical RTT. This study reveals a new postnatal developmental stage, which coincides with full-brain maturation, where the structure/function of the brain is extremely sensitive to levels of MeCP2 and loss of MeCP2 leads to precipitous collapse of the neuronal networks and incompatibility with life within days.


Page 18, Acknowledgments, paragraph 1, line 4: The following sentence should appear before the sentence beginning “This work”: "Electron microscopy was performed at the Multiscale Microscopy Core (MMC) with technical support from the Oregon Health & Science University (OHSU)-FEI Living Lab and the OHSU Center for Spatial Systems Biomedicine (OCSSB)". © 2017 American Society for Microbiology.


BACKGROUND: Economic, personnel, and procedural challenges often complicate and interfere with efficient and safe perioperative care of patients with cardiovascular implantable electronic devices (CIEDs). In the context of a process improvement initiative, we created and implemented a comprehensive anesthesiologist-run perioperative CIED service to respond to all routine requests for peripherative CIED consultations at a large academic medical center. This study was designed to determine whether this new care model was associated with improved operating room efficiency, reduced institutional cost, and adequate patient safety. METHODS: We included patients with a CIED and a concurrent cohort of patients with the same eligibility criteria but without a CIED who underwent first-case-of-the-day surgery during the periods between February 1, 2008, and August 17, 2010 (preintervention) and between March 4, 2012, and August 1, 2014 (postintervention). The primary end point was delay in first-case-of-the-day start time. We used multiple linear regression to compare delays in start times during the preintervention and postintervention periods and to adjust for potential confounders. A patient safety database was queried for CIED-related complications. Cost analysis was based on labor minutes saved and was calculated using nationally published administrative estimates. RESULTS: A total of 18,148 first-case surgical procedures were performed in 15,100 patients (preintervention period-7293 patients and postintervention period-7807 patients). Of those, 151 (2.1%) patients had a CIED in the preintervention period, and 146 (1.9%) had a CIED in the postintervention period. After adjustment for imbalances in baseline characteristics (age, American Society of Anesthesiologists physical status, and surgical specialty), the difference in mean first-case start delay between the postintervention and preintervention periods in the cohort of patients with a CIED was -16.7 minutes (95% confidence interval [CI],
The difference in mean delay between the postintervention and preintervention periods in the cohort without a CIED was 4.7 minutes (95% CI, 5.4 to 3.9). There were 3 CIED-related adverse events during the preintervention period and none during the postintervention period. Based on reduction in first-case start delay, the intervention was associated with cost savings (estimated institutional savings $14,102 annually, or $94.06 per CIED patient), with a return on investment ratio of 2.18 over the course of the postintervention period. CONCLUSIONS: Based on our experience, specially trained anesthesiologists can provide efficient and safe perioperative care for patients with CIEDs. Other centers may consider implementing a similar strategy as our specialty adopts the perioperative surgical home model.


BACKGROUND: Collagen VI is a ubiquitously-expressed macromolecule that forms unique microfibrillar assemblies in the extracellular matrix. Mutations in the COL6A1, COL6A2 and COL6A3 genes result in congenital muscular dystrophy, arguing that collagen is critical for skeletal muscle development and function. Antibodies against collagen VI are important clinical and diagnostic tools in muscular dystrophy. They are used to confirm genetic findings by detecting abnormalities in the distribution, organization and overall levels of collagen VI in cells and tissues isolated from patients. METHODS: Many antibodies have been raised against tissue-purified collagen VI and individual collagen VI chains, however few have been properly validated for sensitivity and chain specificity. To address this deficiency, we compared the ability of 23 commercially-available antibodies to detect extracellular collagen VI by immunohistochemistry on frozen tissue sections. To determine chain specificity, immunoblot analyses were conducted on cell lysates isolated from cells transfected with cDNAs for each individual chain and cells expressing all three chains together. RESULTS: Our analyses identified 15 antibodies that recognized tissue collagen VI by immunohistochemistry at varying intensities and 20 that successfully detected collagen VI by immunoblotting. Three antibodies failed to recognize collagen VI by either method under the conditions tested. All chain-specific antibodies that worked by immunoblotting specifically recognized their correct chain, and no other chains. CONCLUSIONS: This series of side-by-side comparisons reveal at least two antibodies specific for each chain that work well for immunohistochemistry on frozen sections. This validation study expands the repertoire of antibodies available for muscular dystrophy studies caused by defects in collagen VI.


INTRODUCTION: Chronic wounds are increasing in prevalence and are a costly problem for the US healthcare system and throughout the world. Typically outcomes studies in the field of wound care have been limited to small clinical trials, comparative effectiveness cohorts and attempts to extrapolate results from claims data-bases. As a result, outcomes in real world clinical settings may differ from these published studies. OBJECTIVES: This study presents a modified intent-to-treat framework for measuring wound outcomes and measures the consistency of population based outcomes across two distinct settings. METHODS: In this retrospective observational analysis, we describe the largest to date, cohort of patient wound outcomes derived from 626 hospital based clinics and one academic tertiary care clinic. We present the results of a modified intent-to-treat analysis of wound outcomes as well as demographic and descriptive data. After applying the exclusion criteria, the final analytic sample includes the outcomes from 667,291 wounds in the national sample and 1,788 wounds in the academic sample. RESULTS: We found a consistent modified intent to treat healing rate of 74.6% from the 626 clinics and 77.6% in the academic center. We recommend that a standard modified intent to treat healing rate be used to report wound outcomes to allow for consistency and comparability in measurement across providers, payers and healthcare systems. This article is protected by copyright. All rights reserved.

Introduction: Despite widespread use of exogenous synthetic oxytocin during the birth process, few studies have examined the effect of this drug on breastfeeding. Based on neuroscience research, endogenous oxytocin may be altered or manipulated by exogenous administration or by blocking normal function of the hormone or receptor. Women commonly cite insufficient milk production as their reason for early supplementation, jeopardizing breastfeeding goals. Researchers need to consider the role of birth-related medications and interventions on the production of milk. This article examines the literature on the role of exogenous oxytocin on breastfeeding in humans. Methods: Using the method described by Whittemore and Knafl, this integrative review of literature included broad search criteria within the PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane, and Scopus databases. Studies published in English associating a breastfeeding outcome in relation to oxytocin use during the birth process were included. Twenty-six studies from 1978 to 2015 met the criteria. Results: Studies were analyzed according to the purpose of the research, measures and methods used, results, and confounding variables. The 26 studies reported 34 measures of breastfeeding. Outcomes included initiation and duration of breastfeeding, infant behavior, and physiologic markers of lactation. Timing of administration of oxytocin varied. Some studies reported on low-risk birth, while others included higher-risk experiences. Fifty percent of the results (17 of 34 measures) demonstrated an association between exogenous oxytocin and less optimal breastfeeding outcomes, while 8 of 34 measures (23%) reported no association. The remaining 9 measures (26%) had mixed findings. Breastfeeding intentions, parity, birth setting, obstetric risk, and indications for oxytocin use were inconsistently controlled among the studies. Discussion: Research on breastfeeding and lactation following exogenous oxytocin exposure is limited by few studies and heterogeneous methods. Despite the limitations, researchers and clinicians may benefit from awareness of this body of literature. Continued investigation is recommended given the prevalence of oxytocin use in clinical practice. © 2017 by the American College of Nurse-Midwives


Introduction: Maternity care providers administer oxytocin prophylactically to prevent postpartum hemorrhage (PPH). Prophylactic oxytocin is generally considered effective and safe and is promoted by national organizations for standardized use. In this article, the evidence supporting prophylactic oxytocin administration for women undergoing spontaneous labor and birth compared with women whose labors included administration of exogenous oxytocin for induction or augmentation is explored. Methods: Using data from randomized controlled trials included in 2 recent Cochrane meta-analyses papers, only studies with women in spontaneous labor were selected for inclusion (N = 4 studies). Outcomes of immediate postpartum bleeding volumes (≥ 500 mL or 1000 mL), risk for blood transfusion, and risk for administration of more uterotonic medication were pooled from these 4 studies. Focused random effects meta-analyses were used. Results: Compared to women without prophylactic oxytocin, women who received prophylactic oxytocin had a lower risk of having a 500 mL or higher blood loss. However, prophylactic oxytocin did not lower risk of PPH (≥ 1000 mL), blood transfusion, or need for additional uterotonic treatment. Discussion: Prophylactic oxytocin may not confer the same benefits to women undergoing spontaneous labor and birth compared to women laboring with oxytocin infusion. Reasons for this difference are explored from a pharmacologic perspective. In addition, the value of prophylactic oxytocin given recent changes in the definition of PPH from greater than or equal to 500 mL to 1000 mL or more after birth is discussed. Finally, gaps in research on adverse effects of prophylactic oxytocin are presented. More research is needed on reducing risk of PPH for women in spontaneous labor. © 2017 by the American College of Nurse-Midwives

Transcriptomic studies are important tools for understanding the development and function of the different cell types that make up complex tissues. Zebrafish (Danio rerio) is a valuable organism for modeling key aspects of vertebrate development, cell biology, and human disease. However, the small size of individual larvae and relative scarcity of certain cell types in zebrafish can hamper efforts to collect enough pure material for cell type-specific transcriptomic studies. Thus, there is a need in the zebrafish field for spatially and temporally resolved gene expression assays. This chapter will discuss the general principles behind the TU-tagging method to isolate cell type-specific RNAs and provide guidance in designing and executing TU-tagging experiments in zebrafish.


OBJECTIVE: This study evaluated the effects of filler type and the addition of thio-urethane oligomers on light-transmission, polymerization kinetics and depth of cure of resin composites. METHODS: BisGMA:UDMA:TEGMA (5:3:2wt%) were mixed with 0 (control) or 20wt% thio-urethane. Fillers with various sizes and refractive indices were included and refractive index (RI) measured. Unfilled resins were used as controls. The RIs of materials were measured before and after polymerization. The irradiance reaching the bottom of 3-mm thick specimens was measured during the polymerization. Degree of conversion to a depth of 5mm was mapped. An optical bench was used to simultaneously follow conversion and light transmission. RESULTS: The addition of thio-urethane increased the RI for all composites. As expected, RI also increased with conversion for all materials. The one exception was for the material filled with OX-50, in which the RI of the composite decreased with conversion. In this case, the irradiance at the bottom of the 3mm specimen was also the lowest among all groups. The addition of thio-urethanes had only minimal effect on light transmission within a filler type, but led to increased conversion in depth for all groups. The filler type itself had a greater effect on light transmission, and that correlated well with the degree of conversion. SIGNIFICANCE: The effect of the thio-urethane addition on degree of conversion in depth was dependent on filler type. The additive can be tailored to improve the RI match with the filler to optimize light transmission in dental composites.


Objective: 1) to determine the moment during the redox polymerization reaction of dual cure cements at which to photo-activate the material in order to reduce the polymerization stress, and 2) to evaluate possible synergistic effects between adding chain transfer agents and delayed photo-activation. Methods: The two pastes of an experimental dual-cure material were mixed, and the polymerization kinetics of the redox phase was followed. The moment when the material reached its maximum rate of redox polymerization (MRRP) of cement was determined. The degree of conversion (DC) and maximum rates of polymerization (Rmax) were assessed for materials where: the photoactivation immediately followed material mixing, at MRRP, 1min before and 1min after MRRP. Thio-urethane (TU) additives were synthesized and added to the cement (20% wt), which was then cured under the same conditions. The polymerization kinetics was evaluated for both cements photo-activated immediately or at MRRP, followed by measurements of polymerization stress, flexural strength (FS) and elastic modulus (EM). Knoop hardness was measured before and after ethanol storage. Results: Photo-activating the cement at or after MRRP reduced the Rmax and the polymerization stress. Addition of TU promoted additional and more significant reduction, while not affecting the Rmax. Greater hardness loss was observed for cements with TU, but the final hardness was similar for all experimental conditions. Addition of TU slightly reduced the EM and did not affect the FS. Conclusion: Delayed photo-activation and addition of TU significantly reduce the polymerization stress of dual-cured cements. © 2017 Elsevier Ltd.
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 critical synthesis of the EPA literature, to serve as a guide for UME faculty development efforts. This model includes four dimensions for Core EPA faculty development: (1) observation skills in authentic settings (workplace-based assessments), (2) coaching and feedback skills, (3) self-assessment and reflection skills, and (4) peer guidance skills developed through a community of practice. These dimensions form a conceptual foundation for meaningful faculty participation in entrustment decision making. The authors also differentiate between the UME learning environment and the graduate medical education learning environment to highlight distinct challenges and opportunities for faculty development in UME settings. They conclude with recommendations and research questions for future Core EPA faculty development efforts.


Recent advances in multiplex immunohistochemistry techniques allow for quantitative, spatial identification of multiple immune parameters for enhanced diagnostic and prognostic insight. However, applying such techniques to murine fixed tissues, particularly sensitive epitopes, such as CD4, CD8alpha, and CD19, has been difficult. We compared different fixation protocols and Ag-retrieval techniques and validated the use of multiplex immunohistochemistry for detection of CD3(+)CD4(+) and CD3(+)CD8(+) T cell subsets in murine spleen and tumor. This allows for enumeration of these T cell subsets within immune environments, as well as the study of their spatial distribution.


KEY POINTS: STE20 (Sterile 20)/SPS-1 related proline/alanine-rich kinase (SPAK) and oxidative stress-response kinase-1 (OSR1) phosphorylate and activate the renal Na(+) -K(+) -2Cl(-) cotransporter 2 (NKCC2) and Na(+)-Cl(-) cotransporter (NCC). Mouse models suggest that OSR1 mainly activates NKCC2-mediated sodium transport along the thick ascending limb, while SPAK mainly activates NCC along the distal convoluted tubule, but the kinases may compensate for each other. We hypothesized that disruption of both kinases would lead to polyuria and severe salt-wasting, and generated SPAK/OSR1 double knockout mice to test this. Despite a lack of SPAK and OSR1, phosphorylated NKCC2 abundance was still high, suggesting the existence of an alternative activating kinase. Compensatory changes in SPAK/OSR1-independent phosphorylation sites on both NKCC2 and NCC and changes in sodium transport along the collecting duct were also observed. Potassium restriction revealed that SPAK and OSR1 play essential roles in the emerging model that NCC activation is central to sensing changes in plasma [K(+)]. ABSTRACT: STE20 (Sterile 20)/SPS-1 related proline/alanine-rich kinase (SPAK) and oxidative stress-response kinase-1 (OSR1) activate the renal cation cotransporters Na(+)-K(+) -2Cl(-) cotransporter (NKCC2) and Na(+)-Cl(-) cotransporter (NCC) via
phosphorylation. Knockout mouse models suggest that OSR1 mainly activates NKCC2, while SPAK mainly activates NCC, with possible cross-compensation. We tested the hypothesis that disrupting both kinases causes severe polyuria and salt-wasting by generating SPAK/OSR1 double knockout (DKO) mice. DKO mice displayed lower systolic blood pressure compared with SPAK knockout (SPAK-KO) mice, but displayed no severe phenotype even after dietary salt restriction. Phosphorylation of NKCC2 at SPAK/OSR1-dependent sites was lower than in SPAK-KO mice, but still significantly greater than in wild type mice. In the renal medulla, there was significant phosphorylation of NKCC2 at SPAK/OSR1-dependent sites despite a complete absence of SPAK and OSR1, suggesting the existence of an alternative activating kinase. The distal convoluted tubule has been proposed to sense plasma [K(+)], with NCC activation serving as the primary effector pathway that modulates K(+) secretion, by metering sodium delivery to the collecting duct. Abundance of phosphorylated NCC (pNCC) is dramatically lower in SPAK-KO mice than in wild type mice, and the additional disruption of OSR1 further reduced pNCC. SPAK-KO and kidney-specific OSR1 single knockout mice maintained plasma [K(+)] following dietary potassium restriction, but DKO mice developed severe hypokalaemia. Unlike mice lacking SPAK or OSR1 alone, DKO mice displayed an inability to phosphorylate NCC under these conditions. These data suggest that SPAK and OSR1 are essential components of the effector pathway that maintains plasma [K(+)].


Metallochaperones are a diverse family of trafficking molecules that provide metal ions to protein targets for use as cofactors. The copper chaperone for superoxide dismutase (Cc1) activates immature copper-zinc superoxide dismutase (Sod1) by delivering copper and facilitating the oxidation of the Sod1 intramolecular disulfide bond. Here, we present structural, spectroscopic, and cell-based data supporting a novel copper-induced mechanism for Sod1 activation. Cc1 binding exposes an electropositive cavity and proposed "entry site" for copper ion delivery on immature Sod1. Copper-mediated sulfenylation leads to a sulfenic acid intermediate that eventually resolves to form the Sod1 disulfide bond with concomitant release of copper into the Sod1 active site. Sod1 is the predominant disulfide bond-requiring enzyme in the cytoplasm, and this copper-induced mechanism of disulfide bond formation obviates the need for a thiol/disulfide oxidoreductase in that compartment.


BACKGROUND: Growing evidence suggests that concussion increases the risk of lower extremity (LE) musculoskeletal injury. However, it is unclear to how the effect of concussion on LE injury risk may be influenced by previous injuries. This study sought to examine the association between concussion, previous LE injuries, and the risk of LE injury to the same previously injured limb (ipsilateral) or the opposite limb (contralateral). METHODS: This retrospective study examined medical records from 110 concussed athletes and 110 matched controls for LE
injuries in the 365 days before and after the concussion event. The effect of concussion on time to injury was assessed with a Cox proportional hazard model after adjusting for injury history. Fine and Gray subdistribution models assessed the cumulative risk of ipsilateral and contralateral injury by group. RESULTS: Concussion was associated with an increased instantaneous relative risk of LE injury when adjusting for LE injury history [hazard ratio (HR) = 1.67, 95% confidence interval (CI) = 1.11-2.53], agreeing with previous results. Among individuals who had a history of LE injuries before the concussion event, a nonsignificant yet moderate effect of concussion on the instantaneous relative risk of ipsilateral injuries was found after adjusting for the competing risk of contralateral injuries and censored values (HR = 1.85, 95% CI = 0.76-4.46). CONCLUSIONS: This study provides independent confirmation of previous studies, reporting an association between concussion and LE injury risk. Furthermore, this study suggests that future large-scale studies should consider the competing risk of ipsilateral, contralateral, and new injuries in populations with an injury history.


In this paper we investigate how to correctly estimate the state of a linear system in a discrete time setting, when the communication between sensors and/or actuators with the controller is corrupted by sparse attacks. We give conditions for the system to be resilient against malicious packet drops without assuming that the attacker follows any specific probabilistic model. The performance of the proposed algorithm is demonstrated through numerical simulations, where a flexible payload is transported by a group of Unmanned Aerial Vehicles (UAVs). © 2017 American Automatic Control Council (AACC).


Preovulatory granulosa cells express the low-molecular-mass MAP2D variant of microtubule-associated protein 2 (MAP2). Activation of the luteinizing hormone choriogonadotropin receptor by human chorionic gonadotropin (hCG) promotes dephosphorylation of MAP2D on Thr256 and Thr259. We sought to evaluate the association of MAP2D with the cytoskeleton, and the effect of hCG on this association. MAP2D partially colocalized, as assessed by confocal immunofluorescence microscopy, with the vimentin intermediate filament and microtubule cytoskeletons in naive cells. In vitro binding studies showed that MAP2D bound directly to vimentin and beta-tubulin. Phosphorylation of recombinant MAP2D on Thr256 and Thr259, which mimics the phosphorylation status of MAP2D in naive cells, reduces binding of MAP2D to vimentin and tubulin by two- and three-fold, respectively. PKA-dependent phosphorylation of vimentin (Ser32 and Ser38) promoted binding of vimentin to MAP2D and increased contraction of granulosa cells with reorganization of vimentin filaments and MAP2D from the periphery into a thickened layer surrounding the nucleus and into prominent cellular extensions. Chemical disruption of vimentin filament organization increased progesterone production. Taken together, these results suggest that hCG-stimulated dephosphorylation of MAP2D at Thr256 and Thr259, phosphorylation of vimentin at Ser38 and Ser72, and the resulting enhanced binding of MAP2D to vimentin might contribute to the progesterone synthetic response required for ovulation.


BACKGROUND: Minority groups are affected by significant disparities in kidney transplantation (KT) in Veterans Affairs (VA) and non-VA transplant centers. However, prior VA studies have been limited to retrospective, secondary database analyses that focused on multiple stages of the KT process simultaneously. Our goal was to determine whether disparities during the evaluation period for KT exist in the VA as has been found in non-
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...


OBJECTIVE: To determine the overall long-term effectiveness of treatment with epidural corticosteroid injections for lumbar central spinal stenosis and the effect of repeat injections, including crossover injections, on outcomes through 12 months. DESIGN: Multicenter, double-blind, randomized controlled trial comparing epidural injections of corticosteroid plus lidocaine versus lidocaine alone. SETTING: Sixteen clinical sites.

PARTICIPANTS: Participants with imaging-confirmed lumbar central spinal stenosis (N=400).

INTERVENTIONS: Participants were randomized to receive either epidural injections with corticosteroid plus lidocaine or lidocaine alone with the option of blinded crossover after 6 weeks to receive the alternate treatment. Participants could receive 1 to 2 injections from 0 to 6 weeks and up to 2 injections from 6 to 12 weeks. After 12 weeks, participants received usual care. MAIN OUTCOME MEASURES: Primary outcomes were the Roland-Morris Disability Questionnaire (RDQ) (range, 0-24, where higher scores indicate greater disability) and leg pain intensity (range, 0 [no pain] to 10 [pain as bad as you can imagine]). Secondary outcomes included opioid use, spine surgery, and crossover rates. RESULTS: At 12 months, both treatment groups maintained initial observed improvements, with no significant differences between groups on the RDQ (adjusted mean difference, -0.4; 95% confidence interval [CI], -1.6 to 0.9; P=.55), leg pain (adjusted mean difference, 0.1; 95% CI, -0.5 to 0.7; P=.75), opioid use (corticosteroid plus lidocaine: 41.4% vs lidocaine alone: 36.3%; P=.41), or spine surgery (corticosteroid plus lidocaine: 16.8% vs lidocaine alone: 11.8%; P=.22). Fewer participants randomized to corticosteroid plus lidocaine (30%, n=60) versus lidocaine alone (45%, n=90) crossed over after 6 weeks (P=.003). Among participants who crossed over at 6 weeks, the 6- to 12-week RDQ change did not differ between the 2 randomized treatment groups (adjusted mean difference, -1.0; 95% CI, -2.6 to 0.7; P=.24). In both groups, participants crossing over at 6 weeks had worse 12-month trajectories compared with participants who did not choose to crossover. CONCLUSIONS: For lumbar spinal stenosis symptoms, epidural injections of corticosteroid plus lidocaine offered no benefits from 6 weeks to 12 months beyond that of injections of lidocaine alone in terms of self-reported pain and function or reduction in use of opioids and spine surgery. In patients with improved pain and function 6 weeks after initial injection, these outcomes were maintained at 12 months. However, the trajectories of pain and function outcomes after 3 weeks did not differ by injectate type. Repeated injections of either type offered no additional long-term benefit if injections in the first 6 weeks did not improve pain.


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 cocultures of bone marrow stromal cells. Patient-derived xenografts retained the original pattern of mutations found in the matched patient material. Stromal coculture did not prevent leukemia cell cycle activity, but 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 patients with refractory relapses, individual patterns of marked drug resistance and exceptional responses to new agents of immediate clinical relevance were detected. The BCL2-inhibitor venetoclax was highly active below 10 nM in B-cell precursor ALL (BCP-ALL) subsets, including MLL-AF4 and TCF3-HLF ALL, and in some T-cell ALLs (T-ALLs), predicting in vivo activity as a single agent and in combination with dexamethasone and vincristine. Unexpected sensitivity to dasatinib with half maximal inhibitory concentration values below 20 nM was detected in 2 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 on the basis of drug profiling information and achieved a 5-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 to develop drug repurposing strategies for patients with urgent medical needs.


OBJECTIVE: To examine rehabilitation therapy utilization for Parkinson disease (PD). METHODS: We identified 174,643 Medicare beneficiaries with a diagnosis of PD in 2007 and followed them through 2009. The main outcome measures were annual receipt of physical therapy (PT), occupational therapy (OT), or speech therapy (ST). RESULTS: Outpatient rehabilitation fee-for-service use was low. In 2007, only 14.2% of individuals with PD had claims for PT or OT, and 14.6% for ST. Asian Americans were the highest users of PT/OT (18.4%) and ST (18.4%), followed by Caucasians (PT/OT 14.4%, ST 14.8%). African Americans had the lowest utilization (PT/OT 7.8%, ST 8.2%). Using logistic regression models that accounted for repeated measures, we found that African American patients (adjusted odds ratio [AOR] 0.63 for PT/OT, AOR 0.63 for ST) and Hispanic patients (AOR 0.97 for PT/OT, AOR 0.91 for ST) were less likely to have received therapies compared to Caucasian patients. Patients with PD with at least one neurologist visit per year were 43% more likely to have a claim for PT evaluation as compared to patients without neurologist care (AOR 1.43, 1.30-1.48), and this relationship was similar for OT evaluation, PT/OT treatment, and ST. Geographically, Western states had the greatest use of rehabilitation therapies, but provider supply did not correlate with utilization. CONCLUSIONS: This claims-based analysis suggests that rehabilitation therapy utilization among older patients with PD in the United States is lower than reported for countries with comparable health care infrastructure. Neurologist care is associated with rehabilitation therapy use; provider supply is not.


Japanese communication relies heavily on nonverbal cues and context. The purpose of this study was to examine the impact of video-mediated communication (VMC) on communication satisfaction and marital relationships in young couples separated during the perinatal period as they honor the Japanese tradition of Satogaeri Bunben. Couples were assigned to the VMC treatment group (n = 14) or control group (n = 13). A mixed-methods approach to data collection and analysis was used. Longitudinal quantitative analysis from the Primary Communication Inventory and Intimate Bond Measure revealed significant differences between the Husband groups. Primary Communication Inventory and Intimate Bond Measure were strongly correlated regardless of group. Qualitative analysis of participant diaries revealed the addition of visual cues helped create a sense of "virtual co-presence," which was both positive and negative. In conclusion, VMC appears to
improve communication in the separated Japanese perinatal couples, especially through the addition of visual cues provided with VMC.


The gallbladder and cystic duct (GBCs) are parts of the extrahepatic biliary tree and share a common developmental origin with the ventral pancreas. Here, we report on the very first genetic reprogramming of patient-derived human GBCs to beta-like cells for potential autologous cell replacement therapy for type 1 diabetes. We developed a robust method for large-scale expansion of human GBCs ex vivo. GBCs were reprogrammed into insulin-producing pancreatic beta-like cells by a combined adenoviral-mediated expression of hallmark pancreatic endocrine transcription factors PDX1, MAFA, NEUROG3, and PAX6 and differentiation culture in vitro. The reprogrammed GBCs (rGBCs) strongly induced the production of insulin and pancreatic endocrine genes and these responded to glucose stimulation in vitro. rGBCs also expressed an islet-specific surface marker, which was used to enrich for the most highly reprogrammed cells. More importantly, global mRNA and microRNA expression profiles and protein immunostaining indicated that rGBCs adopted an overall beta-like state and these rGBCs engrafted in immunodeficient mice. Furthermore, comparative global expression analyses identified putative regulators of human biliary to beta cell fate conversion. In summary, we have developed, for the first time, a reliable and robust genetic reprogramming and culture expansion of primary human GBCs-derived from multiple unrelated donors-into pancreatic beta-like cells ex vivo, thus showing that human gallbladder is a potentially rich source of reprogrammable cells for autologous cell therapy in diabetes.


Modern drug discovery has embraced in vitro platforms that enable investigation of large numbers of compounds within tractable timeframes and for feasible costs. These endeavors have been greatly aided in recent years by advances in molecular and cell-based methods such as gene delivery and editing technology, advanced imaging, robotics, and quantitative analysis. As such, the examination of phenotypic impacts of novel molecules may only be limited by the size of the compound collection. Innate immune signaling processes in mammalian cells are especially amenable to high-throughput screening platforms since the cellular responses elicited by their activation often result in high level transcription that can be harnessed in the form of bioluminescent or fluorescent signal. In addition, targeted activation of innate immune pathways represents a valuable therapeutic strategy applicable to multiple chronic and acute human diseases. Herein, we describe the optimization and utilization of a high-throughput screening method using human reporter cells reactive to stimulation of the type I interferon response. Importantly, the principles and methods described can be applied to adherent reporter cells of diverse derivation and innate signaling pathway readouts.


The purpose of this study was to demonstrate the feasibility of using a commercial two-dimensional (2D) detector array with an inherent detector spacing of 5 mm to achieve submillimeter accuracy in localizing the radiation isocenter. This was accomplished by delivering the Vernier “dose” caliper to a 2D detector array where the nominal scale was the 2D detector array and the non-nominal Vernier scale was the radiation dose strips produced by the high-definition (HD) multileaf collimators (MLCs) of the linear accelerator. Because the HD MLC sequence was similar to the picket fence test, we called this procedure the Vernier picket fence (VPF) test. We confirmed the accuracy of the VPF test by offsetting the HD MLC bank by known increments and
comparing the known offset with the VPF test result. The VPF test was able to determine the known offset within 0.02 mm. We also cross-validated the accuracy of the VPF test in an evaluation of couch hysteresis. This was done by using both the VPF test and the ExacTrac optical tracking system to evaluate the couch position. We showed that the VPF test was in agreement with the ExacTrac optical tracking system within a root-mean-square value of 0.07 mm for both the lateral and longitudinal directions. In conclusion, we demonstrated the VPF test can determine the offset between a 2D detector array and the radiation isocenter with submillimeter accuracy. Until now, no method to locate the radiation isocenter using a 2D detector array has been able to achieve such accuracy.


A rate-limiting aspect of transgenic mouse models of mammary adenocarcinoma is that primary tumor burden in mammary tissue typically defines study end-points. Thus, studies focused on elucidating mechanisms of late-stage de novo metastasis are compromised, as are studies examining efficacy of anti-cancer therapies targeting mediators of metastasis in the adjuvant setting. Numerous murine mammary cancer models have been developed via targeted expression of dominant oncoproteins to mammary epithelial cells yielding models variably mimicking histopathologic and transcriptome-defined breast cancer subtypes common in women1. While much has been learned regarding the biology of mammary carcinogenesis with these models, their utility in identifying molecules regulating growth of late-stage metastasis are compromised as mice are typically euthanized at earlier time points due to significant primary tumor burden. Moreover, since a significant percentage of women diagnosed with breast cancer receive adjuvant therapy after surgical resection of primary tumors and prior to presence of detectable metastatic disease, preclinical models of de novo metastasis are urgently needed as platforms to evaluate new therapies aimed at targeting metastatic foci. To address these deficiencies, we developed a murine model of de novo mammary cancer metastasis, wherein primary mammary tumors are surgically resected, and metastatic foci subsequently develop over a 115 day post-surgical period. This long latency provides a tractable model to identify functionally significant regulators of metastatic progression in mice lacking primary tumor, as well as a model to evaluate preclinical therapeutic efficacy of agents aimed at blocking functionally significant molecules aiding metastatic tumor survival and growth.


OBJECTIVES/HYPOTHESIS: Idiopathic subglottic stenosis (iSGS) is a rare and potentially life-threatening disease marked by recurrent and progressive airway obstruction frequently requiring repeated surgery to stabilize the airway. Unknown etiology and low disease prevalence have limited the ability to characterize the natural history of iSGS and resulted in variability in surgical management. It is uncertain how this variation relates to clinical outcomes. STUDY DESIGN: Medical record abstraction. METHODS: Utilizing an international, multi-institutional collaborative, we collected retrospective data on patient characteristics, treatment, and clinical outcomes. We investigated variation between and within open and endoscopic treatment approaches and assessed therapeutic outcomes; specifically, disease recurrence and need for tracheostomy at last follow-up. RESULTS: Strikingly, 479 iSGS patients across 10 participating centers were nearly exclusively female (98%, 95% confidence interval [CI], 96.1-99.6), Caucasian (95%, 95% CI, 92.2-98.8), and otherwise healthy (mean age-adjusted Charlson Comorbidity Index 1.5; 95% CI, 1.44-1.69). The patients presented at a mean age of 50 years (95% CI, 48.8-51.1). A total of 80.2% were managed endoscopically, whereas 19.8% underwent open
reconstruction. Endoscopic surgery had a significantly higher rate of disease recurrence than the open approach (chi(2) = 4.09, P = 0.043). Tracheostomy was avoided in 97% of patients irrespective of surgical approach (95% CI, 94.5-99.8). Interestingly, there were outliers in rates of disease recurrence between centers using similar treatment approaches. CONCLUSION: Idiopathic subglottic stenosis patients are surprisingly homogeneous. The heterogeneity of treatment approaches and the observed outliers in disease recurrence rates between centers raises the potential for improved clinical outcomes through a detailed understanding of the processes of care. LEVEL OF EVIDENCE: 4. Laryngoscope, 126:1390-1396, 2016.


Molecular networks governing responses to targeted therapies in cancer cells are complex dynamic systems that demonstrate nonintuitive behaviors. 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 a reverse-engineered Bayesian network model, 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 revealed novel regulators of G1-S transition, IER2, TRIB1, TRIM27. Experimental validation of model predictions confirmed 10 of 12 predicted genes to have a role in G1-S progression. Further analysis showed that TRIB1 regulated the cyclin D1 promoter via NFκB and AP-1 sites and sensitized cells to TRAIL-induced apoptosis. In clinical specimens of breast cancer, TRIB1 levels correlated with expression of NFκB and its target genes (IL8, CSF2), and TRIB1 copy number and expression were predictive of clinical outcome. Together, our results establish a critical role of TRIB1 in cell cycle and survival that is mediated via the modulation of NFκB signaling. Cancer Res; 77(7); 1575-85. (c)2017 AACR.


BACKGROUND: In non-small cell lung cancer (NSCLC), platelet-derived growth factor receptor (PDGFR) mediates angiogenesis, tissue invasion, and tumor interstitial pressure. Olaratumab (IMC-3G3) is a fully human anti-PDGFRalpha monoclonal antibody. This Phase II study assessed safety and efficacy of olaratumab+paclitaxel/carboplatin (P/C) versus P/C alone for previously untreated advanced NSCLC. MATERIALS AND METHODS: Patients received up to six 21-day cycles of P 200mg/m2 and C AUC 6 (day 1)+/-olaratumab 15mg/kg (days 1 and 8). Primary endpoint was PFS. Olaratumab was continued in the olaratumab+P/C arm until disease progression. RESULTS: 131 patients were: 67 with olaratumab+P/C and 64 with P/C; 74% had nonsquamous NSCLC. Median PFS was similar between olaratumab+P/C and P/C (4.4 months each) (HR 1.29; 95% CI [0.86-1.93]; p=0.21). Median OS was similar between olaratumab+P/C (11.8 months) and P/C (11.5 months) (HR 1.04; 95% CI [0.68-1.57]; p=0.87). Both arms had similar toxicity profiles. All evaluable cases were PDGFR-negative by immunohistochemistry. Tumor stroma PDGFR expression was evaluable in 23/131 patients, of which 78% were positive. CONCLUSIONS: The addition of olaratumab to P/C did not result in significant prolongation of PFS or OS in advanced NSCLC. Olaratumab studies in other patient populations, including soft tissue sarcoma (NCT02783599), pancreatic cancer (NCT03086369), and pediatric malignancies (NCT02677116) are underway.

Purpose: To define the phenotype of C2orf71 associated retinopathy and to present novel mutations in this gene.

Methods: A retrospective multicenter study of patients with retinopathy and identified C2orf71 mutations was performed. Ocular function (visual acuity, visual fields, electroretinogram [ERG] responses); retinal morphology (fundus, optical coherence tomography); and underlying mutations were analyzed. Results: Thirteen patients from 11 families, who were aged 7 to 63 years (mean: 32.1 years) at their first examination with presumed compound heterozygous (6/13 patients) or homozygous (7/13 patients) C2orf71 mutations were identified. Eight of the mutations were novel. Truncation mutations were responsible in all cases. Nyctalopia was observed in less than 50% of patients. Visual acuity ranged from 20/20 to light perception. Severe visual loss was associated with atrophic maculopathy. Full-field ERG responses showed severe progressive cone-rod or rod-cone dysfunction. Typical fundus changes were progressive symmetrical retinopathy with an early mild maculopathy and patchy circular midperipheral RPE atrophy. Normal retinal lamination was preserved despite early disruption of the ellipsoid zone and RPE irregularities. Outer retinal tubulations were associated with better-preserved visual acuity. Conclusions: On the basis of our multicenter analysis, C2orf71 might represent a more frequently mutated gene in autosomal recessive retinitis pigmentosa in some populations. The phenotype analysis over a wide age range showed a variable and progressive retinal degeneration with early onset maculopathy and a better visual potential before the age of 30 years.


The combination of molecular pathogen diagnostics and the biomarker procalcitonin (PCT) are changing the use of antimicrobials in patients admitted to critical care units with severe community-acquired pneumonia, possible septic shock, or other clinical syndromes. An elevated serum PCT level is good supportive evidence of a bacterial pneumonia, whereas a low serum PCT level virtually eliminates an etiologic role for bacteria even if the culture for a potential bacterial pathogen is positive. Serum PCT levels can be increased in any shocklike state; a low PCT level eliminates invasive bacterial infection as an etiology in more than 90% of patients.


The article to which this erratum refers was published in Am J Ind Med. 2017; 60: 635-643 (10.1002/ajim.22728). The following statement should have been included under "DISCLOSURE (AUTHOR)" Oregon Health and Science University (OHSU) and Dr. Kent Anger have a significant financial interest in Northwest Education Training and Assessment (or NwETA), a company that may have a commercial interest in the results of this research and technology. This potential individual and institutional conflict of interest has been reviewed and managed by OHSU. © 2017 Wiley Periodicals, Inc.

Introduction: The majority of patients with non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL) present with comorbidities. Many of them are poor candidates for intensive chemo-immunotherapy regimens, such as FCR (fludarabine, cyclophosphamide, rituximab). Still, most clinical trials aim to enroll ‘fit’ patients, who poorly represent the community oncology population. Areas covered: In the past decade, bendamustine hydrochloride, a cytotoxic agent with structural similarities to both alkylating agents and purine analogs, has received widespread use in therapy of NHL and CLL, and has demonstrated a relatively favorable toxicity profile. However, bendamustine has not been well studied in patients with hematologic malignancies who have comorbidities. Here we review the clinical data on use of bendamustine in older and unfit patients with NHL and CLL, and analyze whether there is an optimal dose of bendamustine in patients who have significant comorbidities, including renal dysfunction. Expert commentary: Reduced intensity regimens of bendamustine are effective in CLL patients with comorbidities and renal dysfunction. Even with the introduction of targeted therapies, bendamustine will likely continue to be an important therapeutic option in patients with comorbidities because of its tolerability, efficacy and cost. © 2017 Informa UK Limited, trading as Taylor & Francis Group.


BACKGROUND: The purpose of this study was to compare long-term functional and quality of life (QOL) outcomes after total laryngectomy with primary closure and those who underwent reconstruction with noncircumferential radial free forearm tissue transfer (RFFTT). METHODS: Sixty-seven patients were identified by chart review and underwent long-term follow-up using QOL surveys and standardized interviews. RESULTS: The RFFTT group had significantly higher rates of chemotherapy, gastric tube (G-tube) at surgery, and postoperative stricture. At follow-up, most patients (88%) had a tracheoesophageal prosthesis (TEP) and were using it as their primary communication method. Diet and swallowing outcomes were comparable and no one had a G-tube. Device life and TEP complications did not differ significantly. Only voice-related QOL differed significantly between the RFFTT group and those who had undergone total laryngectomy without adjuvant treatment. CONCLUSION: Despite more extensive treatment, the reconstructed group achieved comparable outcomes to those who had undergone total laryngectomy with adjuvant treatment.


Contemporary research suggests that the mammalian brain is a complex system, implying that damage to even a single functional area could have widespread consequences across the system. To test this hypothesis, we pharmacogenetically inactivated the rhesus monkey amygdala, a subcortical region with distributed and well-defined cortical connectivity. We then examined the impact of that perturbation on global network organization using resting-state functional connectivity MRI. Amygdala inactivation disrupted amygdalocortical communication and distributed corticocortical coupling across multiple functional brain systems. Altered coupling was explained using a graph-based analysis of experimentally established structural connectivity to simulate disconnection of the amygdala. Communication capacity via monosynaptic and polysynaptic pathways, in aggregate, largely accounted for the correlational structure of endogenous brain activity and many of the non-local changes that resulted from amygdala inactivation. These results highlight the structural basis of distributed neural activity and suggest a strategy for linking focal neuropathology to remote neurophysiological changes.

Growth factors alter cellular behavior through shared signaling cascades, raising the question of how specificity is achieved. Here, we have determined how growth factor actions are encoded into Akt signaling dynamics by real-time tracking of a fluorescent sensor. In individual cells, Akt activity was encoded in an analog pattern, with similar latencies (approximately 2 min) and half-maximal peak response times (range of 5-8 min). Yet, different growth factors promoted dose-dependent and heterogeneous changes in signaling dynamics. Insulin treatment caused sustained Akt activity, whereas EGF or PDGF-AA promoted transient signaling; PDGF-BB produced sustained responses at higher concentrations, but short-term effects at low doses, actions that were independent of the PDGF-alpha receptor. Transient responses to EGF were caused by negative feedback at the receptor level, as a second treatment yielded minimal responses, whereas parallel exposure to IGF-I caused full Akt activation. Small-molecule inhibitors reduced PDGF-BB signaling to transient responses, but only decreased the magnitude of IGF-I actions. Our observations reveal distinctions among growth factors that use shared components, and allow us to capture the consequences of receptor-specific regulatory mechanisms on Akt signaling.


AIM: This article describes progress the Oregon Consortium for Nursing Education has made toward addressing the academic progression goals provided by the 2011 Institute of Medicine's Future of Nursing: Leading Change, Advancing Health report. BACKGROUND: The history of the consortium's development is described, emphasizing the creation of an efficient and sustainable organization infrastructure that supports a shared curriculum provided through a community college/university partnership. METHOD: Data and analysis describing progress and challenges related to supporting a shared curriculum and increasing access and affordability for nursing education across the state are presented. RESULTS: We identified four crucial attributes of maintaining collaborative community that have been cultivated to assure the consortium continues to make progress toward reaching the Institute of Medicine's Future of Nursing goals. CONCLUSION: Oregon Consortium for Nursing Education provides important lessons learned for other statewide consortiums to consider when developing plans for sustainability.


Chronic Myeloid Leukemia (CML) is largely caused by the Philadelphia (Ph) chromosome carrying the Break point Cluster Region-Abelson (BCR-ABL) oncogene. Imatinib is a BCR-ABL-targeted therapy and considered the standard of care in CML management. Resistance to imatinib therapy often develops because of mutations in the BCR-ABL kinase domain. In this study, we evaluated PBA2, a novel BCR-ABL inhibitor, for its anti-cancer activity against BCR-ABL expressing BaF3 cells. PBA2 shows potent activity against wild-type and T315I mutated BaF3 cells as compared with imatinib. PBA2 inhibited the phosphorylation of BCR-ABL and its downstream signaling in BaF3/WT and BaF3/T315I cells. PBA2 inhibited the mRNA expression of BCR-ABL in BaF3/WT and BaF3/T315I cells. Mechanistically, PBA2 increased the cell population in sub G1 phase of the cell cycle, induced apoptosis and elevated ROS production in both BaF3/WT and BaF3/T315I cells. Taken together, our results indicate that PBA2 exhibits anti-proliferative effects and inhibits the imatinib-resistant T315I BCR-ABL mutation. PBA2 may be a novel drug candidate for overcoming the resistance to imatinib in CML patients.

The nervous system and cardiovascular system develop in concert and are functionally interconnected in both health and disease. This white paper focuses on the cellular and molecular mechanisms that underlie neural-cardiac interactions during development, during normal physiological function in the mature system, and during pathological remodelling in cardiovascular disease. The content on each subject was contributed by experts, and we hope that this will provide a useful resource for newcomers to neurocardiology as well as aficionados.


Background. Patient engagement throughout research is a way to generate more relevant patient-important research questions, methods and results with the ultimate aim of facilitating translation of research into practice. Tokenism is defined as the practice of making perfunctory or symbolic efforts to engage communities or patients. Objective. We wanted to explore how tokenism might influence engaging patients in research to help researchers work towards more genuine engagement. Methods. The Community Clinician Advisory Group and Patient and Clinician Engagement program held a workshop at the 2015 North American Primary Care Research Group meeting titled ‘How Do We Move beyond Tokenism in Patient Engagement?’ Patients, clinicians and academic researchers contributed examples of genuine and token engagement characteristics based on personal experience and knowledge. Data were iteratively collated and categorized into domains and items. Results. Examples of genuine and token engagement were categorized into three domains: Methods/Structure of engagement, Intent and Relationship building. Members with experience in patient-engaged research projects felt that longitudinal engagement was a key element to effectively translating research into local community and practice. Conclusions. The group (i) highly valued genuine intent and relationship building as elements to combat tokenism; (ii) noted that early genuine attempts at engagement may superficially resemble tokenism as researchers build enduring and trusting relationships with patient/community partners and (iii) emphasized the importance of seeking and utilizing patient experiences throughout research. These observations may contribute to more formal methods to help researchers (and reviewers) evaluate where engagement processes sit along the ‘genuine-token’ continuum. © The Author 2017. Published by Oxford University Press.


The properties of cervical mucus vary in response to both natural and artificial hormonal changes. During ovulatory cycles, cervical mucus becomes increasingly fluid and favorable to sperm penetration as estradiol levels increase. Following ovulation, as estradiol levels decrease and progesterone increases, the mucus increases in viscosity and becomes impenetrable to sperm. Cervical mucus thickening also occurs in response to synthetic progestins administered by various routes, and this is commonly believed to represent the essential contraceptive mechanism of progestin-only methods that do not block ovulation. However, only limited experimental evidence supports a direct contraceptive effect of progestogens on cervical mucus, with even less known about the cellular processes involved and timing of this response. Methodologic limitations associated with clinical assessments of cervical mucus complicate our understanding of contraceptive treatment effects. The evaluation of timing of progestogen-induced changes in cervical mucus must account for natural variation in the hormonal milieu during ovulatory cycles. Key pathways involved in cervical mucus production with potential as novel nonhormonal contraceptive targets have been identified. More research is needed to clarify the role of cervical mucus in current hormonal contraceptives and to support the development of novel nonhormonal cervix-based methods.

PURPOSE/OBJECTIVES: To explore family caregivers’ perspectives of caring for patients with terminal hepatocellular carcinoma (HCC) as patients approached the end of life. RESEARCH APPROACH: Longitudinal, qualitative descriptive design. SETTING: Oregon Health and Science University in Portland and Veterans Affairs Portland Health Care System in Oregon. PARTICIPANTS: 13 family caregivers with a mean age of 56 years (range = 22-68 years). The majority of family caregivers were female (n = 10) and identified as White (n = 11). METHODOLOGIC APPROACH: Interview data were collected from family caregivers once a month for as many as six months, for a total of 39 interviews. Data were analyzed using conventional content analysis. FINDINGS: Five core categories and nine subcategories were identified. From the time of the terminal diagnosis to the end of life, family caregivers felt unprepared, uncertain, and in need of information. They struggled with whether symptoms were HCC- or cirrhosis-related. INTERPRETATION: Nurses can support family caregivers by eliciting their knowledge and concerns, and attending to symptom presentation and interpretation and to treatment challenges. Understanding challenges caregivers experience is crucial for developing interventions that address their desire for information, support, and help along the HCC disease trajectory. IMPLICATIONS FOR NURSING: Nurses play a critical role in preparing caregivers to understand the importance of pain assessment and management and early referral to palliative care.


OBJECTIVE: The objective of this study was to explore the types of patient safety events that take place during pediatric out-of-hospital cardiac arrest resuscitation. METHODS: Retrospective medical record review from a single large urban EMS system of EMS-treated pediatric (<18 years of age) out-of-hospital cardiac arrests (OHCA) occurring between 2008 and 2011. A chart review tool was developed for this project and each chart was reviewed by a multidisciplinary review panel. Safety events were identified in the following clinical domains: resuscitation; assessment, impression/diagnosis, and clinical decision making; airway/breathing; fluids and medications; procedures; equipment; environment; and system. RESULTS: From a total of 497 critical transports during the study period, we identified 35 OHCA cases (7%). A total of 87% of OHCA cases had a safety event identified. Epinephrine overdoses were identified in 31% of the OHCA cases, most of which were 10-fold overdoses. Other medication errors included failure to administer epinephrine when indicated and administration of atropine when not indicated. In 20% of OHCA cases, 3 or more intubation attempts were not successful. Lack of end-tidal CO2 use for tube confirmation was also common. The most common arrest algorithm errors were placing an advanced airway too early (before administration of epinephrine) and giving a medication not included in the algorithm, primarily atropine, both occurring in almost 1/3 of cases. CONCLUSIONS: Safety events were common during pediatric OHCA resuscitation especially in the domains of medications, airway/breathing, and arrest algorithms.


OBJECTIVE: To compare odds of survival to hospital discharge among pediatric out-of-hospital cardiac arrest (OHCA) patients receiving either bag-valve-mask ventilation (BVM), supraglottic airway (SGA) or endotracheal intubation (ETI), after adjusting for the propensity to receive a given airway intervention. METHODS: Retrospective cohort study using the Cardiac Arrest Registry to Enhance Survival (CARES) database from January 1 201-December 31, 2015. The CARES registry includes data on cardiac arrests from 17 statewide registries and approximately 55 additional US cities. We included patients less than 18 years of age who suffered a non-traumatic OHCA and received a resuscitation attempt by Emergency Medical Services (EMS). The key exposure was the airway management strategy (BVM, ETI, or SGA). The primary outcome was survival to hospital discharge. RESULTS: Of the 3793 OHCA cases included from 405 EMS agencies, 1724 cases were analyzed after limiting the analysis to EMS agencies that used all 3 devices. Of the 1724, 781
(45.3%) were treated with BVM only, 727 (42.2%) ETI, and 215 (12.5%) SGA. Overall, 20.7% had ROSC and 10.9% survived to hospital discharge. After using a propensity score analysis, the odds ratio for survival to hospital discharge for ETI compared to BVM was 0.39 (95% CI 0.26-0.59) and for SGA compared to BVM was 0.32 (95% CI 0.12-0.84). These relationships were robust to the sensitivity analyses including complete case, EMS-agency matched, and age-stratified. CONCLUSIONS: BVM was associated with higher survival to hospital discharge compared to ETI and SGA. A large randomized clinical trial is needed to confirm these findings.


Treatments for high-risk essential thrombocytemia (ET) address thrombocytosis, disease-related symptoms, as well as risks of thrombosis, hemorrhage, transformation to myelofibrosis and leukemia. Patients resistant/intolerant to hydroxycarbamide (HC) have a poor outlook. MAJIC (ISRCTN61925716) is a randomized phase II trial of ruxolitinib (JAK1/2 inhibitor) vs Best Available Therapy (BAT) in ET and polycythemia vera (PV) patients resistant or intolerant to HC. Here findings of MAJIC-ET are reported, where the modified intention-to-treat population included 58 & 52 patients randomized to receive ruxolitinib or BAT respectively. There was no evidence of improvement in complete response within 1 year reported in 27 (46.6%) patients treated with ruxolitinib vs 23 (44.2%) with BAT (P=.40). At 2 years rates of thrombosis, hemorrhage and transformation were not significantly different, however some disease-related symptoms improved in patients receiving ruxolitinib relative to BAT. Molecular responses were uncommon; there were two complete molecular responses (CMR) and one partial molecular response (PMR) in CALR positive ruxolitinib-treated patients. Transformation to myelofibrosis occurred in one CMR patient, presumably due to the emergence of a different clone raising questions about the relevance of CMR in ET patients. Grade 3&4 anemia occurred in 19% & 0% of ruxolitinib vs 0% (both grades) BAT arm, grade 3&4 thrombocytopenia in 5.2% & 1.7% of ruxolitinib vs 0% (both grades) of BAT treated patients. Rates of discontinuation or treatment switching did not differ between the two trial arms. The MAJIC-ET trial suggests that ruxolitinib is not superior to current second-line treatments for ET.


Multiple sclerosis (MS) is a disabling, chronic disease that imposes a significant economic burden on patients and the US healthcare system. The largest cost component for individuals with MS are prescription drugs, specifically disease-modifying therapies (DMTs). Despite an increase in the number and diversity of DMTs over the past 10 years, acquisition costs for all DMTs have escalated dramatically at rates substantially higher than medical inflation. Currently, costs for most DMTs exceed $70,000 a year. Recent cost-effectiveness studies suggest the cost for nearly all DMTs exceeds generally accepted thresholds for what is considered a good value in the USA, even after factoring expected rebates. The high cost of DMTs is symptomatic of systemic dysfunction in the pharmaceutical market. Strategies aimed at reigning in high-cost medications include proposals ranging from increasing pricing transparency to allowing Medicare to negotiate directly with manufacturers. Because the economics of pharmaceuticals are inherently complex, a diversity of approaches will be required.

Importance: After identification of activating mutations of the KIT gene in gastrointestinal stromal tumor (GIST)—the most common sarcoma of the gastrointestinal tract—a phase 2 study demonstrated efficacy of imatinib mesylate in patients with metastatic GIST harboring a KIT exon 11 mutation. Initial results of long-term follow-up have found a survival benefit in this subgroup of patients. Objective: To assess the long-term survival of patients with GIST who were treated in SWOG study S0033 and to present new molecular data regarding treatment outcomes. Design, Setting, and Participants: In this follow-up of randomized clinical trial participants (from December 15, 2000, to September 1, 2001), patients were required to have advanced GIST that was not surgically curable. Postprotocol data collection occurred from August 29, 2011, to July 15, 2015. Using modern sequencing technologies, 20 cases originally classified as having wild-type tumors underwent reanalysis. This intergroup study was coordinated by SWOG, a cooperative group member within the National Clinical Trials Network, with participation by member/affiliate institutions. This follow-up was not planned as part of the initial study. Interventions: Patients were randomized to 1 of 2 dose levels of imatinib mesylate, including 400 mg once daily (400 mg/d) vs 400 mg twice daily (800 mg/d), and were treated until disease progression or unacceptable toxic effects of the drug occurred. Main Outcomes and Measures: The primary end point was overall survival. Updated survival data were correlated with clinical and molecular factors, and patterns of postprotocol therapies were enumerated and described in long-term survivors.

Results: Of 695 eligible patients (376 men [54.1%]; 319 women [45.9%]; mean [SD] age, 60.1 [14.0] years), 189 survived 8 years or longer, including 95 in the 400-mg/d dose arm and 94 in the 800-mg/d arm. The 10-year estimate of overall survival was 23% (95% CI, 20%-26%). Among 142 long-term survivors, imatinib was the sole therapy administered in 69 (48.6%), with additional systemic agents administered to 54 patients (38.0%). Resequencing studies of 20 cases originally classified as KIT/PDGFRA wild-type GIST revealed that 17 (85.0%) harbored a pathogenic mutation, most commonly a mutation of a subunit of the succinate dehydrogenase complex. Conclusions and Relevance: A subset of patients with metastatic GIST experiences durable, long-term overall survival with imatinib treatment. Although this study provides guidance for management of GIST harboring the most common KIT and PDGFRA mutations, optimal management of other genotypic subtypes remains unclear. Trial Registration: clinicaltrials.gov Identifier: NCT00009906.


Estuarine turbidity maxima (ETM) function as hotspots of microbial activity and diversity in estuaries, yet, little is known about the temporal and spatial variability in ETM bacterial community composition. To determine which environmental factors affect ETM bacterial populations in the Columbia River estuary, we analyzed ETM bacterial community composition (Sanger sequencing and amplicon pyrosequencing of 16S rRNA gene) and bulk heterotrophic production (3 H-leucine incorporation rates). We collected water 20 times to cover five ETM events and obtained 42 samples characterized by different salinities, turbidities, seasons, coastal regimes (upwelling vs. downwelling), locations, and particle size. Spring and summer populations were distinct. All May samples had similar bacterial community composition despite having different salinities (1-24 PSU), but summer non-ETM bacteria separated into marine, freshwater, and brackish assemblages. Summer ETM bacterial communities varied depending on coastal upwelling or downwelling conditions and on the sampling site location with respect to tidal intrusion during the previous neap tide. In contrast to ETM, whole (>0.2 mum) and free-living (0.2-3 mum) assemblages of non-ETM waters were similar to each other, indicating that particle-attached (>3 mum) non-ETM bacteria do not develop a distinct community. Brackish water type (ETM or non-ETM) is thus a major factor affecting particle-attached bacterial communities. Heterotrophic production was higher in particle-attached than free-living fractions in all brackish waters collected throughout the water column during the rise to decline of turbidity through an ETM event (i.e., ETM-impacted waters). However, free-living communities showed higher productivity prior to or after an ETM event (i.e., non-ETM-impacted waters). This study has thus found that Columbia River ETM bacterial communities vary based on seasons, salinity, sampling location, and particle size, with the existence of three particle types characterized by different bacterial communities in ETM, ETM-impacted, and non-ETM-impacted brackish waters. Taxonomic analysis suggests that ETM key biological function is to remineralize organic matter.

BACKGROUND: Women are at substantially greater risk for anterior cruciate ligament (ACL) injuries than are men.

PURPOSE: To conduct a systematic review and meta-analysis of the literature to clarify the effect of the menstrual cycle and contraceptives on the laxity of and noncontact injuries to the ACL.

STUDY DESIGN: Systematic review; Level of evidence, 4.

METHODS: Searches were conducted using MEDLINE (1946-August 2016), the Cochrane Library Database, clinical trial registries, and related reference lists. Search terms included athletic injuries, knee injuries, ligaments, joint instability, menstrual cycle, ovulation, hormones, and contraceptives. Investigators independently dually abstracted and reviewed study details and quality using predefined criteria and evaluated overall strength of evidence using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) criteria.

RESULTS: Twenty-one studies totaling 68,758 participants were included: 5 on the menstrual cycle and ACL injury, 7 on hormonal contraceptives and ACL injury, as well as 13 on menstrual cycle and ligament laxity. Four of 5 studies of women not using hormonal contraception indicated that the luteal phase was the least associated with ACL injuries. The 2 largest and highest quality studies on hormonal contraceptives suggested that hormonal contraceptives may be protective against ACL injury. Six of 12 studies on ACL laxity provided quantitative data for meta-analysis, finding significantly increased laxity during the ovulatory phase compared with the follicular phase.

CONCLUSION: The literature suggests an association between hormonal fluctuations and ACL injury. Recent studies have suggested that oral contraceptives may offer up to a 20% reduction in risk of injury. The literature on ACL injuries and the menstrual cycle has more than doubled over the past decade, permitting quantitative analysis for the first time. However, the overall strength of this evidence is low. Promising potential directions for future research include long-term observational studies with ongoing hormonal assays and large interventional trials of follicular suppression, including newer hormonal methods.


Emerging evidence suggests that exogenous protein/amino acid supplementation has the potential to improve the recovery of critically ill patients. After a careful review of the published evidence, experts have concluded that critically ill patients should receive up to 2.0-2.5 g/kg/d of protein. Despite this, however, recent review of current International Nutrition Survey data suggests that protein in critically ill patients is underprescribed and grossly underdelivered. Furthermore, the survey suggests that most of protein administration comes from enteral nutrition (EN) despite the availability of products and protocols that enhance the delivery of protein/amino acids in the intensive care unit (ICU) setting. While future research clarifies the dose, timing, and composition for exogenous protein administration, as well as identification of patients who will benefit the most, ongoing process improvement initiatives should target a concerted effort to increase protein intake in the critically ill. This assertion follows from the notion that current patients are possibly being harmed while we wait for confirmatory evidence. Further research should also develop better tools to enable bedside practitioners to monitor optimal or adequate protein intake for individual patients. Finally, exploring the effect of combining adequate protein delivery with early mobility and/or resistance exercise in the ICU setting has the greatest potential for improving the functional outcomes of survivors of critical illness and warrants further study.

Cutaneous small-vessel vasculitis (CSVV) is an infrequent manifestation of pediatric inflammatory bowel disease (IBD). We report two cases of CSVV associated with ulcerative colitis, review the literature, and discuss the diagnostic evaluation of children who present with CSVV and abdominal pain. After excluding more common causes of CSVV and abdominal pain in children, including immunoglobulin A vasculitis (previously Henoch-Schönlein purpura), infectious colitis, and drug-induced vasculitis, alternative diagnoses such as CSVV secondary to IBD or systemic vasculitis with gastrointestinal involvement must be considered. © 2017 Wiley Periodicals, Inc.


Cutaneous small-vessel vasculitis (CSVV) is an infrequent manifestation of pediatric inflammatory bowel disease (IBD). We report two cases of CSVV associated with ulcerative colitis, review the literature, and discuss the diagnostic evaluation of children who present with CSVV and abdominal pain. After excluding more common causes of CSVV and abdominal pain in children, including immunoglobulin A vasculitis (previously Henoch-Schönlein purpura), infectious colitis, and drug-induced vasculitis, alternative diagnoses such as CSVV secondary to IBD or systemic vasculitis with gastrointestinal involvement must be considered.


The precise value of the normal adult protein requirement has long been debated. For many reasons—none of them being the difficulty of carrying out long-term nutrition experiments in free-living people—uncertainty is likely to persist indefinitely. By contrast, the controlled environment of the intensive care unit and relatively short trajectory of many critical illnesses make it feasible to use hard clinical outcome trials to determine protein requirements for critically ill patients in well-defined clinical situations. This article suggests how the physiological principles that underlie our understanding of normal protein requirements can be incorporated into the design of such clinical trials. The main focus is on 3 principles: (1) the rate of body nitrogen loss roughly predicts an individual’s minimum protein requirement and is thus essential to measure to identify individual patients and clinical situations in which the minimum protein requirement is importantly increased, (2) existing muscle mass sets an upper limit on the rate at which amino acids can be mobilized from muscle for transfer to central proteins and sites of injury and is thus important to monitor to identify patients who are at greatest risk of protein deficiency-related adverse outcomes, and (3) negative energy balance increases the dietary protein requirement, so calorie-deprived patients—whether obese or not—should be enrolled in hard clinical outcome trials that compare the current practice of “permissive underfeeding” (underprovision of all nutrients, including protein) with hypocaloric nutrition supplemented by a suitably generous amount of protein.


BACKGROUND: Optimal management of patients with stable chest pain relies on the prognostic information provided by noninvasive cardiovascular testing, but there are limited data from randomized trials comparing anatomic with functional testing. METHODS: In the PROMISE trial (Prospective Multicenter Imaging Study for Evaluation of Chest Pain), patients with stable chest pain and intermediate pretest probability for obstructive coronary artery disease (CAD) were randomly assigned to functional testing (exercise electrocardiography, nuclear stress, or stress echocardiography) or coronary computed tomography angiography (CTA). Site-
based diagnostic test reports were classified as normal or mildly, moderately, or severely abnormal. The primary end point was death, myocardial infarction, or unstable angina hospitalizations over a median follow-up of 26.1 months. RESULTS: Both the prevalence of normal test results and incidence rate of events in these patients were significantly lower among 4500 patients randomly assigned to CTA in comparison with 4602 patients randomly assigned to functional testing (33.4% versus 78.0%, and 0.9% versus 2.1%, respectively; both P<0.001). In CTA, 54.0% of events (n=74/137) occurred in patients with nonobstructive CAD (1%-69% stenosis). Prevalence of obstructive CAD and myocardial ischemia was low (11.9% versus 12.7%, respectively), with both findings having similar prognostic value (hazard ratio, 3.74; 95% confidence interval [CI], 2.60-5.39; and 3.47; 95% CI, 2.42-4.99). When test findings were stratified as mildly, moderately, or severely abnormal, hazard ratios for events in comparison with normal tests increased proportionally for CTA (2.94, 7.67, 10.13; all P<0.001) but not for corresponding functional testing categories (0.94 [P=0.87], 2.65 [P=0.001], 3.88 [P<0.001]). The discriminatory ability of CTA in predicting events was significantly better than functional testing (c-index, 0.72; 95% CI, 0.68-0.76 versus 0.64; 95% CI, 0.59-0.69; P=0.04). If 2714 patients with at least an intermediate Framingham Risk Score (>10%) who had a normal functional test were reclassified as being mildly abnormal, the discriminatory capacity improved to 0.69 (95% CI, 0.64-0.74).

CONCLUSIONS: Coronary CTA, by identifying patients at risk because of nonobstructive CAD, provides better prognostic information than functional testing in contemporary patients who have stable chest pain with a low burden of obstructive CAD, myocardial ischemia, and events. CLINICAL TRIAL REGISTRATION: URL: http://www.clinicaltrials.gov. Unique identifier: NCT01174550.


The integration of mental health services in primary care settings has expanded rapidly in recent years with psychologists being at the forefront of efforts to promote healthy behaviors, reduce disease, and care for behavioral, emotional, and developmental needs to promote overall health and well-being for children and families (Asarnow, Kolko, Miranda, & Kazak, 2017; Stancin & Perrin, 2014). While there are many psychologists working in pediatric primary care (PPC), little is known about the specific activities that these psychologists engage in, the training they receive, or funding mechanisms that support their work. This study sought to address this gap in the literature through a survey of psychologists working in PPC. An anonymous online survey was disseminated to members of professional organizations and listservs who were identified as having interest in PPC. Psychologists (N=65) currently practicing in PPC completed the survey by reporting on clinical roles and practices, professional training, practice settings, and funding supports in PPC settings. Results indicate that psychologists assume a number of roles in PPC including providing individual and family therapy, conducting screenings for child mental health concerns, and providing consultation to medical colleagues. Many psychologists also provide supervision and offer educational opportunities for those in related fields, such as medicine and social work. Engagement in research activities was identified as a secondary activity. It was reported that a number of clinical activities were not billed for on a regular basis. Additional areas of research will be discussed along with implications for clinical services in PPC. © 2017 American Psychological Association.


BACKGROUND: Earlier use of in-hospital plasma, platelets, and red blood cells (RBCs) has improved survival in trauma patients with severe hemorrhage. Retrospective studies have associated improved early survival with prehospital blood product transfusion (PHT). We hypothesized that PHT of plasma and/or RBCs would result in improved survival after injury in patients transported by helicopter. METHODS: Adult trauma patients transported by helicopter from the scene to nine Level 1 trauma centers were prospectively observed from January to November 2015. Five helicopter systems had plasma and/or RBCs, whereas the other four helicopter systems used only crystalloid resuscitation. All patients meeting predetermined high-risk criteria were analyzed. Patients receiving PHT were compared with patients not receiving PHT. Our primary analysis compared mortality at 3 hours, 24 hours, and 30 days, using logistic regression to adjust for confounders and site heterogeneity to model patients who were matched on propensity scores. RESULTS: Twenty-five thousand one hundred eighteen trauma patients were admitted, 2,341 (9%) were transported by helicopter, of which 1,058 (45%) met the highest-risk criteria. Five hundred eighty-five of 1,058 patients were flown on helicopters carrying blood products. In the systems with blood available, prehospital median systolic blood pressure (125 vs 128) and Glasgow Coma Scale (7 vs 14) was significantly lower, whereas median Injury Severity Score was significantly higher (21 vs 14). Unadjusted mortality was significantly higher in the systems with blood products available, at 3 hours (8.4% vs 3.6%), 24 hours (12.6% vs 8.9%), and 30 days (19.3% vs 13.3%). Twenty-four percent of eligible patients received a PHT. A median of 1 unit of RBCs and plasma were transfused prehospital. Of patients receiving PHT, 24% received only plasma, 7% received only RBCs, and 69% received both. In the propensity score matching analysis (n = 109), PHT was not significantly associated with mortality at any time point, although only 10% of the high-risk sample were able to be matched. CONCLUSION: Because of the unexpected imbalance in systolic blood pressure, Glasgow Coma Scale, and Injury Severity Score between systems with and without blood products on helicopters, matching was limited, and the results of this study are inconclusive. With few units transfused to each patient and small outcome differences between groups, it is likely large, multicenter, randomized studies will be required to detect survival differences in this important population. LEVEL OF EVIDENCE: Level II.


It is unclear. Pseudoephedrine causes an average increase of 1.2 mm Hg in systolic blood pressure (BP) in patients with controlled hypertension. However, the studies are not adequately powered to provide evidence about whether this rise in systolic BP is linked to patient-oriented outcomes (strength of recommendation: C, multiple randomized controlled trials supporting disease-oriented evidence). Significant variations in BP are defined differently among studies. In addition, we do not have data on chronic use of oral decongestants; the longest time on medication in these trials was 4 weeks.


BACKGROUND: In the CALGB (Alliance) 100104 study, lenalidomide versus placebo after autologous stem-cell transplantation (ASCT) was investigated for patients with newly diagnosed myeloma. That study showed improved time to progression and overall survival and an increase in second primary malignancies for lenalidomide at a median follow-up of 34 months. Here we report an updated intention-to-treat analysis of
Vestibular information is known to be important for postural stability on tilting surfaces, but the relative importance of vestibular loss was most unstable within a critical tilt velocity range of 2 to 8 deg/s. Subjects with vestibular deficiency lost their balance in more than 90% of trials during the 4 deg/s condition, but never fell during slower tilts (0.25-1 deg/s) and fell only very rarely during faster tilts (16-32 deg/s). At the critical velocity of 1 deg/s and in follow-up.


Using electronic health record data, we examined longitudinal changes in community health center (CHC) visit rates from 2013 through 2014 in Medicaid expansion versus nonexpansion states. Visits from 219 CHCs in 5 expansion states and 4 nonexpansion states were included. Rates were computed using generalized estimating equation Poisson models. Rates increased in expansion state CHCs for new patient, preventive, and limited-service visits (14%, 41%, and 23%, respectively, P < .01 for all), whereas these rates remained unchanged in nonexpansion states. One year after ACA Medicaid expansions, CHCs in expansion states saw an influx of new patients and provided increased preventive services.
range in which falls occurred, the body center of mass stayed aligned with respect to the surface, onset of ankle dorsiflexion was delayed, and there was delayed or absent gastrocnemius inhibition, suggesting that subjects were attempting to actively align their upper bodies with respect to the moving surface instead of to gravity. Vestibular information may be critical for stability at velocities of 2 to 8 deg/s because postural sway above 2 deg/s may be too fast to elicit stabilizing responses through the graviceptive somatosensory system, and postural sway below 8 deg/s may be too slow for somatosensory-triggered responses or passive stabilization from trunk inertia.


BACKGROUND: COPD prevalence is highly variable and geographical altitude has been linked to it, yet with conflicting results. We aimed to investigate this association, considering well known risk factors. METHODS: A pooled analysis of individual data from the PREPOCOL-PLATINO-BOLD-EPI-SCAN studies was used to disentangle the population effect of geographical altitude on COPD prevalence. Post-bronchodilator FEV1/FVC below the lower limit of normal defined airflow limitation consistent with COPD. High altitude was defined as >1500 m above sea level. Undiagnosed COPD was considered when participants had airflow limitation but did not report a prior diagnosis of COPD. RESULTS: Among 30,874 participants aged 56.1 +/- 11.3 years from 44 sites worldwide, 55.8% were women, 49.6% never-smokers, and 12.9% (3978 subjects) were residing above 1500 m. COPD prevalence was significantly lower in participants living at high altitude with a prevalence of 8.5% compared to 9.9%, respectively (p < 0.005). However, known risk factors were significantly less frequent at high altitude. Hence, in the adjusted multivariate analysis, altitude itself had no significant influence on COPD prevalence. Living at high altitude, however, was associated with a significantly increased risk of undiagnosed COPD. Furthermore, subjects with airflow limitation living at high altitude reported significantly less respiratory symptoms compared to subjects residing at lower altitude. CONCLUSION: Living at high altitude is not associated with a difference in COPD prevalence after accounting for individual risk factors. However, high altitude itself was associated with an increased risk of undiagnosed COPD.


Methamphetamine (MA) abuse has been linked to violence, risk-taking behaviors, decreased sexual inhibition, and criminal activity. It is important to understand mechanisms underlying these drug effects for prevention and treatment of MA-associated social problems. Previous studies have demonstrated that experimenter-administered amphetamine inhibits pair bonding and increases aggression in monogamous prairie voles. It is not currently known whether similar effects on social behaviors would be obtained under conditions during which the drug is voluntarily (actively) administered. The current study investigated whether MA drinking affects pair bonding and what neurocircuits are engaged. In Experiment 1, we exposed male and female voles to 4 days each of 20 and 40 mg/L MA under a continuous 2-bottle choice (2BC) procedure. Animals were housed either singly or in mesh-divided cages with a social partner. Voles consumed MA in a drinking solution, but MA drinking was not affected by either sex or housing condition. In Experiment 2, we investigated whether MA drinking disrupts social bonding by measuring aggression and partner preference formation following three consecutive days of 18-hour/day access to 100 mg/L MA in a 2BC procedure. Although aggression toward a novel opposite-sex animal was not affected by MA exposure, partner preference was inhibited in MA drinking animals. Experiment 3 examined whether alterations in hypothalamic neuropeptides provide a potential explanation for the inhibition of partner preference observed in Experiment 2. MA drinking led to significant decreases in oxytocin, but not vasopressin, in the paraventricular nucleus of the hypothalamus. These experiments are the first investigation into how voluntary pre-exposure to MA affects the development of social attachment in a socially monogamous species and identify potential neural circuits involved in these effects.

This paper focuses on securely estimating the state of a nonlinear dynamical system from a set of corrupted measurements. In particular, we consider a wide class of nonlinear systems, and propose a technique which enables us to perform secure state estimation for such nonlinear systems. We then provide guarantees on the achievable state estimation error against arbitrary corruptions, and analytically characterize the number of errors that can be perfectly corrected by a decoder. To illustrate how the proposed nonlinear estimation approach can be applied to practical systems, we focus on secure estimation for the wide area control of an interconnected power system under cyber-physical attacks and communication failures, and propose a secure estimator for the power system. Finally, we numerically show that the proposed secure estimation algorithm enables us to reconstruct the attack signals accurately. © 2017 American Automatic Control Council (AACC).


The International Protein Summit in 2016 brought experts in clinical nutrition and protein metabolism together from around the globe to determine the impact of high-dose protein administration on clinical outcomes and address barriers to its delivery in the critically ill patient. It has been suggested that high doses of protein in the range of 1.2-2.5 g/kg/d may be required in the setting of the intensive care unit (ICU) to optimize nutrition therapy and reduce mortality. While incapable of blunting the catabolic response, protein doses in this range may be needed to best stimulate new protein synthesis and preserve muscle mass. Quality of protein (determined by source, content and ratio of amino acids, and digestibility) affects nutrient sensing pathways such as the mammalian target of rapamycin. Achieving protein goals the first week following admission to the ICU should take precedence over meeting energy goals. High-protein hypocaloric (providing 80%-90% of caloric requirements) feeding may evolve as the best strategy during the initial phase of critical illness to avoid overfeeding, improve insulin sensitivity, and maintain body protein homeostasis, especially in the patient at high nutrition risk. This article provides a set of recommendations based on assessment of the current literature to guide healthcare professionals in clinical practice at this time, as well as a list of potential topics to guide investigators for purposes of research in the future.


BACKGROUND: Astronauts are exposed to $^{56}$Fe ions that may pose a significant health hazard during and following prolonged missions in deep space. We showed previously that object recognition requiring the hippocampus, a structure critical for cognitive function, is affected in 2-month-old mice irradiated with $^{56}$Fe ions. Here we examined object recognition in 6-month-old mice irradiated with $^{56}$Fe ions, a biological age more relevant to the typical ages of astronauts. Moreover, because the mechanisms mediating the detrimental effects of $^{56}$Fe ions on hippocampal function are unclear, we examined changes in hippocampal networks involved in synaptic plasticity and memory, gene expression, and epigenetic changes in cytosine methylation ($5$mC) and hydroxymethylation ($5$hmC) that could accompany changes in gene expression. We assessed the effects of whole body $^{56}$Fe ion irradiation at early (2 weeks) and late (20 weeks) time points on hippocampus-dependent memory and hippocampal network stability, and whether these effects are associated with epigenetic changes in hippocampal DNA methylation (both $5$mC and $5$hmC) and gene expression. RESULTS: At the two-week time point, object recognition and network stability were impaired following irradiation at the 0.1 and 0.4 Gy dose, but not following irradiation at the 0.2 Gy dose. No
Impairments in object recognition or network stability were seen at the 20-week time point at any irradiation dose used. Consistent with this pattern, the significance of pathways for gene categories for 5hmC was lower, though not eliminated, at the 20-week time point compared to the 2-week time point. Similarly, significant changes were observed for 5mC gene pathways at the 2-week time point, but no significant gene categories were observed at the 20-week time point. Only the 5hmC changes tracked with gene expression changes. CONCLUSIONS: Dose- and time-dependent epigenomic remodeling in the hippocampus following 56Fe ion exposure correlates with behavioral changes.


Current guidelines for hypercholesterolemia treatment emphasize lifestyle modification and lipid-modifying therapy to reduce the risk for cardiovascular disease. Statins are the primary class of agents used for the treatment of hypercholesterolemia. Although statins are effective for many patients, they fail to achieve optimal reduction in lipids for some patients, including those who have or are at high risk for cardiovascular disease. The PCSK9 gene was identified in the past decade as a potential therapeutic target for the management of patients with hypercholesterolemia. Pharmacologic interventions to decrease PCSK9 levels are in development, with the most promising approach using monoclonal antibodies that bind to PCSK9 in the plasma. Two monoclonal antibodies, alirocumab and evolocumab, have recently been approved for the treatment of hypercholesterolemia, and a third one, bococizumab, is in phase 3 clinical development. All 3 agents achieve significant reductions in levels of low-density lipoprotein cholesterol, as well as reductions in non-high-density lipoprotein cholesterol, apolipoprotein B, and lipoprotein(a). Long-term outcome trials are under way to determine the sustained efficacy, safety, and tolerability of PCSK9 inhibitors and whether this novel class of agents decreases the risk for major cardiovascular events in patients on lipid-modifying therapy. Available data suggest that PCSK9 inhibitors provide a robust reduction in atherogenic cholesterol levels with a good safety profile, especially for patients who fail to obtain an optimal clinical response to statin therapy, those who are statin intolerant or have contraindications to statin therapy, and those with familial hypercholesterolemia.


**PURPOSE:** Recent research has found unrealistic optimism (UO) among patient-subjects in early-phase oncology trials. Our aim was to investigate the cognitive and motivational factors that evoke this bias in this context. We expected perceptions of control to be a strong correlate of unrealistic optimism. METHODS: A study of patient-subjects enrolled in early-phase oncology trials was conducted at two sites in the USA. Respondents completed questionnaires designed to assess unrealistic optimism and several risk attribute variables that have been found to evoke the bias in other contexts. RESULTS: One hundred and seventy-one patient-subjects agreed to be interviewed for our study. Significant levels of perceived controllability were found with respect to all nine research-related questions. Perceptions of control were found to predict unrealistic optimism. Two other risk attribute variables, awareness of indicators (p=0.024) and mental image (p=0.022), were correlated with unrealistic optimism. However, in multivariate regression analysis, awareness and mental image dropped out of the model and perceived controllability was the only factor independently associated with unrealistic optimism (p<0.0001). CONCLUSION: Patient-subjects reported that they can, at least partially, control the benefits they receive from participating in an early-phase oncology trial. This sense of control may underlie unrealistic optimism about benefiting personally from trial participation. Effective interventions to counteract unrealistic optimism may need to address the psychological factors that give rise to distorted risk/benefit processing.
Recent advances in light microscopy permit visualization of the behavior of individual molecules within dense macromolecular ensembles in live cells. It is now conceptually possible to relate the dynamic organization of molecular machinery to cellular function. However, inherent heterogeneities, as well as disparities between spatial and temporal scales, pose substantial challenges in deriving such a relationship. New approaches are required to link discrete single-molecule behavior with continuous cellular-level processes. Here we combined intercalated molecular and cellular imaging with a computational framework to detect reproducible transient changes in the behavior of individual molecules that are linked to cellular behaviors. Applying our approach to integrin transmembrane receptors revealed a spatial density gradient underlying characteristic molecular density increases and mobility decreases, indicating the subsequent onset of local protrusive activity. Integrin mutants further revealed that these density and mobility transients are separable and depend on different binding domains within the integrin cytoplasmic tail. Our approach provides a generalizable paradigm for dissecting dynamic spatiotemporal molecular behaviors linked to local cellular events.


Introduction Early initiation of thromboprophylaxis is highly desired in pelvic fracture patients, but it is often delayed due to the fear of hemorrhage. Aim of our study was to assess the safety of early initiation of venous thromboprophylaxis in patients with pelvic trauma managed nonoperatively. Methods Three-year (2010-2012) retrospective study of trauma patients with pelvic fractures who were managed nonoperatively and received thromboprophylaxis with low-molecular-weight heparin (LMWH). Patients were stratified in two groups based on the timing of initiation of prophylaxis; early (initiation within first 24 h) and late (after 24 h). Primary outcome measures included decrease in hemoglobin (Hb) levels, number of packed red blood cell (pRBC) units transfused, and the need for hemorrhage control (operative or angioembolization) after initiation of prophylaxis. Regression analysis was performed. Results 255 patients were included (158 in early and 97 in late group). Mean ± standard deviation age was 48.2 ± 23.3 y, and 50.6% were male. After adjusting for confounders, there was no difference between the two groups in the decrease in Hb levels (b = 0.087, 95% confidence interval [CI] = −0.253 to 1.025; P = 0.23) or pRBC units transfused (b = −0.005, 95% CI = −0.366 to 0.364; P = 0.75). One patient required hemorrhage control postprophylaxis and belonged to the late group. Subanalysis of patients with signs of bleeding (n = 52) showed no difference between the two groups in the decrease in Hb levels or pRBC units transfused. Patients who received LMWH after 24 h had a higher incidence of symptomatic deep venous thrombosis and a longer hospital length of stay. Conclusions Early initiation of thromboprophylaxis with LMWH in patients with pelvic fractures managed nonoperatively is safe and decreases the risk of symptomatic deep venous thrombosis. © 2017 Elsevier Inc.


**PURPOSE:** To compare the effect of elevated intraocular pressure (IOP) on retinal capillary filling in elderly vs adult rats using optical coherence tomography angiography (OCTA). METHODS: The IOP of elderly (24-month-old, N=12) and adult (6-8-month-old, N=10) Brown Norway rats was elevated in 10mmHg increments from 10 to 100mmHg. At each IOP level, 3D OCT data were captured using an optical microangiography (OMAG) scanning protocol and then post-processed to obtain both structural and vascular images. Mean arterial blood pressure (MAP), respiratory rate, pulse and blood oxygen saturation were monitored non-invasively throughout each experiment. Ocular perfusion pressure (OPP) was calculated as the difference between MAP...
for each animal and IOP at each level. The capillary filling index (CFI), defined as the ratio of area occupied by functional capillary vessels to the total scan area but excluding relatively large vessels of >30mum, was calculated at each IOP level and analyzed using the OCTA angiograms. Relative CFI vs IOP was plotted for the group means. CFI vs OPP was plotted for every animal in each group and data from all animals were combined in a CFI vs OPP scatter plot comparing the two groups. RESULTS: The MAP in adult animals was 108+/-5mmHg (mean+/−SD), whereas this value in the elderly was 99+/-5mmHg. All other physiologic parameters for both age groups were uniform and stable. In elderly animals, significant reduction of the CFI was first noted at IOP 40mmHg, as opposed to 60mmHg in adult animals. Individual assessment of CFI as a function of OPP for adult animals revealed a consistent plateau until OPP reached between 40 and 60mmHg. Elderly individuals demonstrated greater variability, with many showing a beginning of gradual deterioration of CFI at an OPP as high as 80mmHg. Overall comparison of CFI vs OPP between the two groups was not statistically significant. CONCLUSIONS: Compared to adults, some, but not all, elderly animals demonstrate a more rapid deterioration of CFI vs OPP. This suggests a reduced autoregulatory capacity that may contribute to increased glaucoma susceptibility in some older individuals. This variability must be considered when studying the relationship between IOP, ocular perfusion and glaucoma in elderly models.


Melanoma is usually apparent on the skin and readily detected by trained medical providers using a routine total body skin examination, yet this malignancy is responsible for the majority of skin cancer-related deaths. Currently, there is no national consensus on skin cancer screening in the USA, but dermatologists and primary care providers are routinely confronted with making the decision about when to recommend total body skin examinations and at what interval. The objectives of this paper are: to propose rational, risk-based, data-driven guidelines commensurate with the US Preventive Services Task Force screening guidelines for other disorders; to compare our proposed guidelines to recommendations made by other national and international organizations; and to review the US Preventive Services Task Force’s 2016 Draft Recommendation Statement on skin cancer screening.


BACKGROUND: Self-management interventions are considered effective in patients with COPD, but trials have shown inconsistent results and it is unknown which patients benefit most. This study aimed to summarize the evidence on effectiveness of self-management interventions and identify subgroups of COPD patients who benefit most. METHODS: Randomized trials of self-management interventions between 1985 and 2013 were identified through a systematic literature search. Individual patient data of selected studies were requested from principal investigators and analyzed in an individual patient data meta-analysis using generalized mixed effects models. RESULTS: Fourteen trials representing 3,282 patients were included. Self-management interventions improved health-related quality of life at 12 months (standardized mean difference 0.08, 95% confidence interval [CI] 0.00-0.16) and time to first respiratory-related hospitalization (hazard ratio 0.79, 95% CI 0.66-0.94) and all-cause hospitalization (hazard ratio 0.80, 95% CI 0.69-0.90), but had no effect on mortality. Prespecified subgroup analyses showed that interventions were more effective in males (6-month COPD-related hospitalization: interaction P=0.006), patients with severe lung function (6-month all-cause hospitalization: interaction P=0.016), moderate self-efficacy (12-month COPD-related hospitalization: interaction P=0.036), and high body mass index (6-month COPD-related hospitalization: interaction P=0.028 and 6-month mortality: interaction P=0.026). In none of these subgroups, a consistent effect was shown on all relevant outcomes. CONCLUSION: Self-management interventions exert positive effects in patients with
COPD on respiratory-related and all-cause hospitalizations and modest effects on 12-month health-related quality of life, supporting the implementation of self-management strategies in clinical practice. Benefits seem similar across the subgroups studied and limiting self-management interventions to specific patient subgroups cannot be recommended.


PURPOSE: Education leaders at the 2012 Academic Emergency Medicine Consensus Conference on education research proposed that dedicated postgraduate education scholarship fellowships (ESFs) might provide an effective model for developing future faculty as scholars. A formal needs assessment was performed to understand the training gap and inform the development of ESFs. METHOD: A mixed-methods needs assessment was conducted of four emergency medicine national stakeholder groups in 2013: department chairs; faculty education/research leaders; existing education fellowship directors; and current education fellows/graduates. Descriptive statistics were reported for quantitative data. Qualitative data from semistructured interviews and free-text responses were analyzed using a thematic approach. RESULTS: Participants were 11/15 (73%) education fellowship directors, 13/20 (65%) fellows/graduates, 106/239 (44%) faculty education/research leaders, and a convenience sample of 26 department chairs. Department chairs expected new education faculty to design didactics (85%) and teach clinically (96%). Faculty education/research leaders thought new faculty were inadequately prepared for job tasks (83.7%) and that ESFs would improve the overall quality of education research (91.1%). Fellowship directors noted that ESFs provide skills, mentorship, and protected time for graduates to become productive academicians. Current fellows/graduates reported pursuing an ESF to develop skills in teaching and research methodology. CONCLUSIONS: Stakeholder groups uniformly perceived a need for training in education theory, clinical teaching, and education research. These findings support dedicated, deliberate training in these areas. Establishment of a structure for scholarly pursuits prior to assuming a full-time position will effectively prepare new faculty. These findings may inform the development, implementation, and curricula of ESFs.


The importance of context in regulation of gene expression is now an accepted principle; yet the mechanism by which the microenvironment communicates with the nucleus and chromatin in healthy tissues is poorly understood. A functional role for nuclear and cytoskeletal architecture is suggested by the phenotypic differences observed between epithelial and mesenchymal cells. Capitalizing on recent advances in cryogenic techniques, volume electron microscopy and super-resolution light microscopy, we studied human mammary epithelial cells in three-dimensional (3D) cultures forming growth-arrested acini. Intriguingly, we found deep nuclear invaginations and tunnels traversing the nucleus, encasing cytoskeletal actin and/or intermediate filaments, which connect to the outer nuclear envelope. The cytoskeleton is also connected both to other cells through desmosome adhesion complexes and to the extracellular matrix through hemidesmosomes. This finding supports a physical and/or mechanical link from the desmosomes and hemidesmosomes to the nucleus, which had previously been hypothesized but now is visualized for the first time. These unique structures, including the nuclear invaginations and the cytoskeletal connectivity to the cell nucleus, are consistent with a dynamic reciprocity between the nucleus and the outside of epithelial cells and tissues.
Hydrogen peroxide (H2O2) is a highly relevant metabolite in many biological processes, including the oral microbiome. To study this metabolite, we developed a 25 μm diameter, highly sensitive, nonenzymatic H2O2 sensor with a detection limit of 250 nM and a broad linear range of 250 nM to 7 mM. The sensor used the synergistic activity of the catalytically active Pt nanoparticles on a high surface area multiwalled carbon nanotube and conducting ionic liquid matrix to achieve high sensitivity (2.4 ± 0.24 mA cm⁻² mM⁻¹) for H2O2 oxidation. The unique composite allowed us to miniaturize the sensor and couple it with a Pt electrode (25 μm diameter each) for use as a dual scanning electrochemical microscopy probe. We could detect 65 ± 10 μM H2O2 produced by Streptococcus gordonii (Sg) in a simulated biofilm at 50 μm above its surface in the presence of 1 mM glucose and artificial saliva solution (pH 7.2 at 37 °C). Because of its high stability and low detection limit, the sensor showed a promising chemical image of H2O2 produced by Sg biofilms. We were also able to detect 30 μM H2O2 at 50 μm above the biofilm in the presence of the H2O2-decomposing salivary lactoperoxidase and thiocyanate, which would not otherwise be possible using an existing H2O2 assay. Thus, this sensor can potentially find applications in the study of other important biological processes in a complex matrix where circumstances demand a low detection limit in a compact space. © 2017 American Chemical Society.

UNLABELLED: Cerebellar granule cell GABAA receptor responses to alcohol vary as a function of alcohol consumption phenotype, representing a potential neural mechanism for genetic predilection for alcohol abuse (Kaplan et al., 2013; Mohr et al., 2013). However, there are numerous molecular targets of alcohol in the cerebellum, and it is not known how they interact to affect cerebellar processing during consumption of socially relevant amounts of alcohol. Importantly, direct evidence for a causative role of the cerebellum in alcohol consumption phenotype is lacking. Here we determined that concentrations of alcohol that would be achieved in the blood after consumption of 1–2 standard units (9 mm) suppresses transmission through the cerebellar cortex in low, but not high, alcohol consuming rodent genotypes (DBA/2J and C57BL/6J mice, respectively). This genotype-selective suppression is mediated exclusively by enhancement of granule cell GABAA receptor currents, which only occurs in DBA/2J mice. Simulating the DBA/2J cellular phenotype in C57BL/6J mice by infusing the GABAA receptor agonist, 4,5,6,7-tetrahydroisoxazolo-[5,4-c]pyridine-3-ol hydrochloride, into cerebellar lobules IV–VI, in vivo, significantly reduced their alcohol consumption and blood alcohol concentrations achieved. 4,5,6,7-Tetrahydroisoxazolo-[5,4-c]pyridine-3-ol hydrochloride infusions also significantly decreased sucrose consumption, but they did not affect consumption of water or general locomotion. Thus, genetic differences in cerebellar response to alcohol contribute to alcohol consumption phenotype, and targeting the cerebellar GABAA receptor system may be a clinically viable therapeutic strategy for reducing excessive alcohol consumption. SIGNIFICANCE STATEMENT: Alcohol abuse is a leading cause of preventable death and illness; and although alcohol use disorders are 50%–60% genetically determined, the cellular and molecular mechanisms of such genetic influences are largely unknown. Here we demonstrate that genetic differences in cerebellar granule cell GABAA receptor responses to recreational concentrations of alcohol are the primary determinant of alcohol’s impact on cerebellar processing and that pharmacologically modifying such responses alters alcohol consumption. These data highlight the cerebellum as an important neuroanatomical region in alcohol consumption phenotype and as a target for pharmacological treatment of alcohol use disorders. The results also add to the growing list of cognitive/emotional roles of the cerebellum in psychiatric disease and drug abuse.

The role of cognitive mechanisms in the clinical course of neurodevelopmental disorders is poorly understood. Attention Deficit Hyperactivity Disorder (ADHD) is emblematic in that numerous alterations in cognitive development are apparent, yet how they relate to changes in symptom expression with age is unclear. To resolve the role of cognitive mechanisms in ADHD, a developmental perspective that takes into account expected within-group heterogeneity is needed. **METHOD:** The current study uses an accelerated longitudinal design and latent trajectory growth mixture models in a sample of children ages 7-13 years carefully characterized as with (n = 437) and without (n = 297) ADHD to (a) identify heterogeneous developmental trajectories for response inhibition, visual spatial working memory maintenance, and delayed reward discounting and (b) to assess the relationships between these cognitive trajectories and ADHD symptom change. **RESULTS:** Best-fitting models indicated multiple trajectory classes in both the ADHD and typically developing samples, as well as distinct relationships between each cognitive process and ADHD symptom change. Developmental change in response inhibition and delayed reward discounting were unrelated to ADHD symptom change, while individual differences in the rate of visual spatial working memory maintenance improvement predicted symptom remission in ADHD. **CONCLUSION:** Characterizing heterogeneity in cognitive development will be crucial for clarifying mechanisms of symptom persistence and recovery. Results here suggest working memory maintenance may be uniquely related to ADHD symptom improvement. (PsycINFO Database Record)


Chronic graft-versus-host disease (cGVHD) remains one of the most significant long-term complications after allogeneic blood and marrow transplantation. Diagnostic biomarkers for cGVHD are needed for early diagnosis and may guide identification of prognostic markers. No cGVHD biomarker has yet been validated for use in clinical practice. We evaluated both previously known markers and performed discovery-based analysis for cGVHD biomarkers in a 2 independent test sets (total of 36 cases }\leq\text{1 month from diagnosis and 31 time-matched controls with no cGVHD}). On the basis of these results, 11 markers were selected and evaluated in 2 independent replication cohorts (total of 134 cGVHD cases and 154 controls). cGVHD cases and controls were evaluated for several clinical covariates, and their impact on biomarkers was identified by univariate analysis. The 2 replications sets were relatively disparate in the biomarkers they replicated. Only sBAFF and, most consistently, CXCL10 were identified as significant in both replication sets. Other markers identified as significant in only 1 replication set included intercellular adhesion molecule 1 (ICAM-1), anti-LG3, aminopeptidase N, CXCL9, endothelin-1, and gelsolin. Multivariate analysis found that all covariates evaluated affected interpretation of the biomarkers. CXCL10 had an increased significance in combination with anti-LG3 and CXCL9, or inversely with CXCR3(+)CD56(bright) natural killer (NK) cells. There was significant heterogeneity of cGVHD biomarkers in a large comprehensive evaluation of cGVHD biomarkers impacted by several covariates. Only CXCL10 strongly correlated in both replication sets. Future analyses for plasma cGVHD biomarkers will need to be performed on very large patient groups with consideration of multiple covariates.

An explosion of knowledge and technology is revolutionizing medicine and patient care. Novel testing must be brought to the clinic with safety and accuracy, but also in a timely and cost-effective manner, so that patients can benefit and laboratories can offer testing consistent with current guidelines. Under the oversight provided by the Clinical Laboratory Improvement Amendments, laboratories have been able to develop and optimize laboratory procedures for use in-house. Quality improvement programs, interlaboratory comparisons, and the ability of laboratories to adjust assays as needed to improve results, utilize new sample types, or incorporate new mutations, information, or technologies are positive aspects of Clinical Laboratory Improvement Amendments oversight of laboratory-developed procedures. Laboratories have a long history of successful service to patients operating under Clinical Laboratory Improvement Amendments. A series of detailed clinical examples illustrating the quality and positive impact of laboratory-developed procedures on patient care is provided. These examples also demonstrate how Clinical Laboratory Improvement Amendments oversight ensures accurate, reliable, and reproducible testing in clinical laboratories.

Background Intrauterine infection is a significant cause of early preterm birth. We have developed a fetal-neonatal model in the rhesus macaque to determine the impact of chronic intrauterine infection with Ureaplasma parvum on early neonatal reflexes and brain development. Methods Time-mated, pregnant rhesus macaques were randomized to be inoculated with U. parvum (serovar 1; 10^5 c.f.u.) or control media at ~120 days’ gestational age (dGA). Neonates were delivered by elective hysterotomy at 135-147 dGA (term=167d), stabilized, and cared for in our nonhuman primate neonatal intensive care unit. Neonatal reflex behaviors were assessed from birth, and fetal and postnatal brain magnetic resonance imaging (MRI) was performed. Results A total of 13 preterm and 5 term macaque infants were included in the study. Ten preterm infants survived to 6 months of age. U. parvum-infected preterm neonates required more intensive respiratory support than did control infants. MRI studies suggested a potential perturbation of brain growth and white matter maturation with exposure to intra-amniotic infection. Conclusion We have demonstrated the feasibility of longitudinal fetal-neonatal studies in the preterm rhesus macaque after chronic intrauterine infection. Future studies will examine long-term neurobehavioral outcomes, cognitive development, neuropathology, and in vivo brain imaging to determine the safety of antenatal antibiotic treatment for intrauterine infection. © 2017 International Pediatric Research Foundation, Inc.
categorized according to GC response. Of them, 39% of the subjects responded to low dose (\(<=10 \text{ mg}\) prednisone, 9% did not respond to GC, and the remainder (52%) had variable responses to GC. The HES subtype diagnosis was the best predictor of response to GC with myeloid forms and lymphocytic variants of HES being the least responsive to GC. CONCLUSIONS: In a large cohort of well-characterized subjects with HES, the odds of response to GC was predicted by HES subtype. Using this model, clinicians may more readily proceed to second-line agents in subjects with confirmed lymphocytic or myeloid forms of HES.


PURPOSE: To correlate angiogenic cytokines in the aqueous humour with total retinal blood flow in subjects with type 2 diabetes with non-proliferative diabetic retinopathy (NPDR). METHODS: A total of 17 controls and 16 NPDR patients were recruited into the study. Aqueous humour was collected at the start of cataract surgery to assess the concentration of 14 angiogenic cytokines. Aqueous humour was analysed using the suspension array method. Six images were acquired to assess total retinal blood flow (TRBF) using the prototype RTVue Doppler Fourier domain optical coherence tomography (Doppler FD-OCT) (Optovue, Inc., Fremont, CA) using a double circular scan protocol, 1 month postsurgery. At the same visit, forearm blood was collected to determine glycosylated haemoglobin (A1c). RESULTS: Transforming growth factor beta (TGF-beta1, TGF-beta2) and PLGF were increased while FGF-1 was reduced in NPDR compared to controls (Bonferroni corrected, \(p < 0.003\) for all). Total retinal blood flow (TRBF) was significantly reduced in the NPDR group compared to controls (33.1 +/- 9.9 versus 43.3 +/- 5.3 \(\text{mul/min}\), \(p = 0.002\)). Aqueous FGF-1 significantly correlated with TRBF in the NPDR group \((r = 0.71, p = 0.01; r^2 = 0.51)\). In a multiple regression analysis, A1c was found to be a significant predictor of aqueous TGF-beta1 and FGF-1 \((p = 0.018\) and \(p = 0.020\), respectively). CONCLUSION: Aqueous angiogenic cytokines (TGF-beta1, TGF-beta2 and PLGF) were elevated in conjunction with a reduction in TRBF in patients with NPDR compared to controls. Non-invasive measurement of TRBF may be useful for predicting aqueous FGF-1 levels and severity of vasculopathy in DR.


When the University of Washington, School of Nursing determined that its post-BSN-DNP degree program, with multiple specialty tracks and programs of study, was not sustainable, the curriculum was re-envisioned. The revised program is consistent with the American Association of Colleges of Nursing (AACN) Essentials of Doctoral Education for Advanced Nursing Practice and the national Licensure Accreditation, Certification, and Education (LACE) model. The re-envisioned program was conceptualized as a single degree in which students preparing for any specialty would have the same number of required credits with the majority of courses (DNP core) required for all students. Two major pathways, 1) advanced practice registered nursing and 2) advanced systems and population health were identified. The model allows for specialties to be added or discontinued without major disruption to the core curriculum. The consolidated curriculum reduced instructional costs to the school by approximately 26% and reduced and made more equitable the tuition costs for the majority of students. The revised consolidated program is innovative, maintains quality, attracts students, and aligns with resources. This article discusses how we achieved revision and consolidation of a post-BSN DNP program with multiple specialty tracks that is innovative, high quality, sustainable, and replicable by other schools of nursing.

OBJECTIVES: The purpose of this study was to investigate temperature rise in the composite and dentin of a class I cavity in extracted human molars under different restoration conditions, including the use of different composite types, layering methods, and curing lights. METHODS: Open occlusal cavities were prepared on 28 extracted human molars. A conventional (Filtek Z250) and a bulk-fill (Filtek Bulk Fill Posterior; BFP) composite were used to restore the preparations. BFP was incrementally layered or bulk-filled. Bulk-filled BFP was cured with two different lights, the Elipar S10 and the BeLite. Each layer was illuminated for 20s, while thermograms of the specimens were recorded for 100s using an infrared thermal camera. Temperature changes on the composite and dentin surfaces were obtained at points of interest (POI) pertaining to successive incremental distances of 0.75mm from the top of the cavity to the pulp. The polymerization kinetics of each composite was determined using photo-differential scanning calorimetry. RESULTS: The greatest temperature rise was observed 0.75mm apical from the top of the cavity. All groups showed over 6 degrees C maximum temperature rise (DeltaTmax) at the pulpal side of the dentin. Upon curing, Z250 reached DeltaT=5 degrees C faster than BFP; however, DeltaTmax of the two composites were comparable at any POI. Bulk filling showed greater DeltaTmax than incremental filling at 0.75mm apical from the top and in the middle of the cavity. The Elipar S10 light generated faster temperature changes in the curing composite at all recorded positions throughout the depth of the cavity and greater DeltaTmax in all POIs compared to BeLite. SIGNIFICANCE: Real-time thermographic analysis demonstrated that the composite type and layering method did not influence the temperature rise at the pulpal side of dentin during composite restoration of an occlusal preparation in a tooth. The amount and initial rate of temperature increase was most affected by the radiant exposure of the light curing unit. Within the limitations of this in vitro study, when irradiation time is constant, a curing light with higher radiant power can induce relatively high thermal transfer, thereby increasing the risk of pulpal damage.

BACKGROUND: Skeletal-related events (SREs) are common complications of bone metastatic castration-resistant prostate cancer (mCRPC). To the authors’ knowledge, there are limited data regarding which factors predict SREs. The authors identified risk factors for SREs in men with bone mCRPC using characteristics commonly available in the medical record. METHODS: Data from 454 patients with nonmetastatic CRPC were identified from 2 Veteran Affairs Medical Centers from 2000 through 2013. Among these men, 233 (51%) developed bone metastases during follow-up and represented the study cohort. First occurrence of an SRE was abstracted from the medical records. A stepwise multivariable Cox model was used to select the strongest predictors of time to SRE. RESULTS: The median age of the patients at the time of diagnosis of bone mCRPC was 75 years (interquartile range, 68-81 years), and there were 153 nonblack patients (66%). During follow-up (median, 7.8 months [interquartile range, 2.9-18.3 months]), 88 patients (38%) had an SRE. On univariable analysis, more recent year of metastasis (hazard ratio [HR], 0.91), prostate-specific antigen doubling time of >/=9 months versus <9 months (HR, 0.50), and bone pain (HR, 3.34) were all found to be associated with SRE risk. On multivariable analysis, year of metastasis (HR, 0.93), biopsy Gleason score of 7 versus </=6 (HR, 1.74), radiotherapy as the primary localized treatment versus none (HR, 2.33), and bone pain (HR, 3.64) were associated with SRE risk. The area under the curve for a multivariable model based upon these risk factors was 0.744. CONCLUSIONS: The authors identified several significant predictors of SREs among men with mCRPC. In particular, men with bone pain are at high risk of an SRE. If confirmed, future trials should focus on prolonging life and reducing SRE risk in patients with mCRPC with bone pain. Cancer 2017;123:1528-1535. (c) 2017 American Cancer Society.

Background and Aims: The risks of missed findings after inadequate bowel preparation are not fully characterized in a diverse cohort. We aimed to evaluate the likelihood of missed polyps after an inadequate preparation as assessed by using the Boston Bowel Preparation Scale (BBPS). Methods: In this observational study of prospectively collected data within a large, national, endoscopic consortium, we identified patients aged 50 to 75 years who underwent average-risk screening colonoscopy (C1) followed by a second colonoscopy for any indication within 3 years (C2). We determined the polyp detection rates (PDRs) and advanced PDRs during C2 stratified by C1 BBPS scores. Results: Among segment pairs without polyps at C1 (N = 601), those with inadequate C1 BBPS segment scores had a higher PDR at C2 (10%) compared with those with adequate bowel preparation at C1 (5%; P = .04). Among segment pairs with polyps at C1 (N = 154), segments with inadequate bowel preparation scores at C1 had higher advanced PDRs at C2 (20%) compared with those with adequate bowel preparation scores at C1 (4%; P = .03). In multivariable analysis, the presence of advanced polyps at C1 (adjusted odds ratio [OR] 3.5; 95% confidence intervals [CIs], 1.1-10.8) but not inadequate BBPS scores at C1 (adjusted OR 1.8; 95% CI, 0.6-5.1) was associated with a significantly increased risk of advanced polyps at C2. Conclusions: Inadequate BBPS segment scores generally are associated with higher rates of polyps and advanced polyps at subsequent colonoscopy within a short timeframe. The presence of advanced polyps as well as inadequate BBPS segment scores can inform the risk of missed polyps and help triage which patients warrant a timely repeat colonoscopy. © 2017 American Society for Gastrointestinal Endoscopy.


Purpose Optimal assessment methods and criteria for reporting hearing outcomes in children who receive treatment with cisplatin are uncertain. The objectives of our study were to compare different ototoxicity classification systems, to evaluate the feasibility of including otoacoustic emissions and extended high frequency audiometry, and to evaluate a central review mechanism for audiologic results for cisplatin-treated children in the cooperative group setting. Patients and Methods Eligible participants were 1 to 30 years, with planned cisplatin-containing treatment. Hearing evaluations were conducted at baseline, before each cisplatin cycle, and at the end of therapy. Audiologic results were assessed and graded by the testing audiologist and by two central review audiologists using the American Speech-Language-Hearing Association Ototoxicity Criteria (ASHA), Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE), and Brock Ototoxicity Grades (Brock). One central reviewer also used the Society for Industrial and Organizational Psychology Ototoxicity Scale (SIOP). Results At the end of treatment, the prevalence of any degree of ototoxicity ranged from 40% to 56%, and severe ototoxicity ranged from 7% to 22%. Compared with CTCAE, SIOP detected significantly more ototoxicity ( P = .004), whereas Brock criteria detected significantly fewer patients with any or severe ototoxicity ( P < .001 for both). SIOP detected ototoxicity earlier than did the other scales. Agreement between the central reviewers and the institutional audiologist was almost perfect for ASHA and Brock, whereas the poorest agreement occurred with CTCAE. Conclusion The SIOP scale may be superior to ASHA, Brock, and CTCAE scales for classifying ototoxicity in pediatric patients who were treated with cisplatin. Future studies should evaluate inter-rater reliability of the SIOP scale.


SM is a fundamental component of mammalian cell membranes that contributes to mechanical stability, signaling, and sorting. Its production involves the transfer of phosphocholine from phosphatidylcholine onto ceramide, a reaction catalyzed by SM synthase (SMS) 1 in the Golgi and SMS2 at the plasma membrane. Mammalian cells also synthesize trace amounts of the SM analog ceramide phosphoethanolamine (CPE), but the physiological relevance of CPE production is unclear. Previous work revealed that SMS2 is a bifunctional enzyme producing both SM and CPE, whereas a closely related enzyme, sphingomyelin synthase-related protein (SMSr)/SAMD8, acts as a monofunctional CPE synthase in the endoplasmatic reticulum. Using domain swapping and site-directed mutagenesis on enzymes expressed in defined lipid environments, we here identified structural determinants that mediate head group selectivity of SMS family members. Notably, a single residue adjacent to the catalytic histidine in the third exoplasmic loop profoundly influenced enzyme specificity, with glutamic acid permitting SMS-catalyzed CPE production and aspartic acid confining the enzyme to produce SM. An exchange of exoplasmic residues with SMSr proved sufficient to convert SMS1 into a bulk CPE synthase. This allowed us to establish mammalian cells that produce CPE rather than SM as the principal phosphosphingolipid and provide a model of the molecular interactions that impart catalytic specificity among SMS enzymes.


The diagnosis of primary scalp alopecia remains one of the most challenging fields in dermatopathology. In this review, we would like to connect the established classification of primary alopecia into scarring (cicatricial) and non-scarring (non-cicatricial) with current concepts. We introduce a simplified pathway for the diagnosis of the most common causes of alopecia, including a discussion of tissue processing techniques and use of immunohistochemistry.


INTRODUCTION: The purpose of this study was to examine the epidemiology of primary and revision total hip arthroplasty (THA) in teaching and nonteaching hospitals. METHODS: The Healthcare Cost and Utilization Project Nationwide Inpatient Sample was queried from 2006 to 2010 to identify primary and revision THAs at teaching and nonteaching hospitals. RESULTS: A total of 1,336,396 primary and 223,520 revision procedures were identified. Forty-six percent of all primary and 54% of all revision procedures were performed at teaching hospitals. Teaching hospitals performed 17% of their THAs as revisions; nonteaching hospitals performed 12% as revisions. For primary and revision THAs, teaching hospitals had fewer patients aged >65 years, fewer Medicare patients, similar gender rates, more nonwhite patients, and more patients in the highest income quartile compared with nonteaching hospitals. Costs, length of stay, and Charlson Comorbidity Index scores were similar; however, the mortality rate was lower at teaching hospitals. CONCLUSIONS: This study found small but significant differences in key epidemiologic and outcome variables in examining primary and revision THA at teaching and nonteaching hospitals. LEVEL OF EVIDENCE: Level III.


BACKGROUND: Unicuspid aortic valve (UAV) is a rare disorder, often difficult to distinguish from bicuspid aortic valve (BAV). BAV and UAV share valve pathology such as the presence of a raphe, leaflet fusion, aortic stenosis, aortic regurgitation, and/or ascending aortic dilatation, but a comprehensive echocardiographic comparison
of patients with UAV and BAV has not been previously performed. METHODS: We investigated UAV and BAV patients at an early stage of disease included in GenTAC, a national registry of genetically related aortic aneurysms and associated cardiac conditions. Clinical and echocardiographic data from the GenTAC Registry were compared between 17 patients with UAV and 17 matched-controls with BAV. RESULTS: Baseline characteristics including demographics, clinical findings including family history of BAV and aortic aneurysm/coarctation, and echocardiographic variables were similar between BAV and UAV patients; aortic stenosis was more common and more severe in patients with UAV. This was evidenced by higher mean and peak gradient, smaller aortic valve area, and more advanced valvular degeneration (all P < .05). There were no significant differences in aortic dimensions, with a similar pattern of enlargement of the ascending aorta. CONCLUSIONS: The similar baseline characteristics with more accelerated aortic valve degeneration and stenosis suggest that UAV represents an extreme in the spectrum of BAV syndromes. Therefore, it is reasonable to consider application of recommendations for the management of patients with BAV to those with the rarer UAV.


Nutritional deficiencies, decreased bone mineral density, and dumping syndrome are just some of the challenges these patients face. Here’s how to optimize their care.


Hypertrophic cardiomyopathy (HCM) is the most common monogenetic hereditary heart disease. With advances in cardiac imaging and genetics, an increasing number of patients with HCM are being identified. However, the condition remains underrecognized, largely because its clinical manifestations are unpredictable and vary among individuals even within the same family. The presentation ranges from sudden cardiac death to a completely benign course with no morbidity or impact on longevity. The overall prognosis of HCM is excellent, but it is this unpredictability that makes the diagnosis and management challenging, requiring a multifaceted approach.


Translating the genetic and epigenetic heterogeneity underlying human cancers into therapeutic strategies is an ongoing challenge. Large-scale sequencing efforts have uncovered a spectrum of mutations in many hematologic malignancies, including acute myeloid leukemia (AML), suggesting that combinations of agents will be required to treat these diseases effectively. Combinatorial approaches will also be critical for combating the emergence of genetically heterogeneous subclones, rescue signals in the microenvironment, and tumor-intrinsic feedback pathways that all contribute to disease relapse. To identify novel and effective drug combinations, we performed ex vivo sensitivity profiling of 122 primary patient samples from a variety of hematologic malignancies against a panel of 48 drug combinations. The combinations were designed as drug pairs that target nonoverlapping biological pathways and comprise drugs from different classes, preferably with Food and Drug Administration approval. A combination ratio (CR) was derived for each drug
pair, and CRs were evaluated with respect to diagnostic categories as well as against genetic, cytogenetic, and cellular phenotypes of specimens from the two largest disease categories: AML and chronic lymphocytic leukemia (CLL). Nearly all tested combinations involving a BCL2 inhibitor showed additional benefit in patients with myeloid malignancies, whereas select combinations involving PI3K, CSF1R, or bromodomain inhibitors showed preferential benefit in lymphoid malignancies. Expanded analyses of patients with AML and CLL revealed specific patterns of ex vivo drug combination efficacy that were associated with select genetic, cytogenetic, and phenotypic disease subsets, warranting further evaluation. These findings highlight the heuristic value of an integrated functional genomic approach to the identification of novel treatment strategies for hematologic malignancies.


BACKGROUND: Atrial arrhythmias are the most common complication encountered in the growing and aging population with congenital heart disease. OBJECTIVES: This study sought to assess the types and patterns of atrial arrhythmias, associated factors, and age-related trends. METHODS: A multicenter cohort study enrolled 482 patients with congenital heart disease and atrial arrhythmias, age 32.0 +/- 18.0 years, 45.2% female, from 12 North American centers. Qualifying arrhythmias were classified by a blinded adjudicating committee. RESULTS: The most common presenting arrhythmia was intra-atrial re-entrant tachycardia (IART) (61.6%), followed by atrial fibrillation (28.8%), and focal atrial tachycardia (9.5%). The proportion of arrhythmias due to IART increased with congenital heart disease complexity from 47.2% to 62.1% to 67.0% in patients with simple, moderate, and complex defects, respectively (p = 0.0013). Atrial fibrillation increased with age to surpass IART as the most common arrhythmia in those >/=50 years of age (51.2% vs. 44.2%; p < 0.0001). Older age (odds ratio [OR]: 1.024 per year; 95% confidence interval [CI]: 1.010 to 1.039; p = 0.001) and hypertension (OR: 2.00; 95% CI: 1.08 to 3.71; p = 0.029) were independently associated with atrial fibrillation. During a mean follow-up of 11.3 +/- 9.4 years, the predominant arrhythmia pattern was paroxysmal in 62.3%, persistent in 28.2%, and permanent in 9.5%. Permanent atrial arrhythmias increased with age from 3.1% to 22.6% in patients <20 years to >/=50 years, respectively (p < 0.0001). CONCLUSIONS: IART is the most common presenting atrial arrhythmia in patients with congenital heart disease, with a predominantly paroxysmal pattern. However, atrial fibrillation increases in prevalence and atrial arrhythmias progressively become permanent as the population ages.


PURPOSE: To determine the location of the subscapularis split during arthroscopic Latarjet created by an inside-out technique passing a switching stick from the posterior portal across the glenohumeral joint. METHODS: An inside-out technique was used to arthroscopically create a subscapularis split in 20 fresh-frozen human cadaveric shoulders. The distance between the exit point of the switching stick and the upper border of the subscapularis and the anterior circumflex vessels was measured arthroscopically and after open dissection. RESULTS: Twelve splits were in the upper third of the subscapularis, 3 were at the junction of the upper third and the middle third, and 5 were in the middle third. None were at the junction between the middle and lower third as desired. CONCLUSIONS: Using the inside-out method during arthroscopic Latarjet may produce a high subscapularis split if it is performed from with a switching stick that is inserted through the posterior approach, and passed across the glenohumeral joint at the level of the inferior glenoid. CLINICAL RELEVANCE: This study analyzed the relative risk of high subscapularis split during the arthroscopic Latarjet procedure.
Recent evidence suggests that athletes are at a higher risk of lower body injuries in the months and years following a concussion. However, little is known about how people modify their movements post-concussion. This study examined kinematics during a jump cut motion in young adults with a concussion history (n=9; 4 males, 5 females). Kinematic differences during a jump cut maneuver between individuals with and without a concussion history. International Journal of Psychophysiology. doi:10.1016/j.ijpsycho.2017.08.003


OBJECTIVES/HYPOTHESIS: Assess the reliability of a Sleep Endoscopy Rating Scale (SERS) and its relationship with pediatric obstructive sleep apnea (OSA) severity. STUDY DESIGN: Retrospective case series of pediatric patients who underwent drug-induced sleep endoscopy (DISE) at the time of surgery for OSA from January 1, 2013 to May 1, 2014. METHODS: Three blinded otolaryngologists scored obstruction on DISE recordings as absent (0), partial (+1), or complete (+2) at six anatomic levels: nasal airway, nasopharynx, velopharynx, oropharynx, hypopharynx, and arytenoids. Ratings were summed for a SERS total score (range, 0-12). Reliability was calculated using a kappa statistic with linear weighting. SERS ratings and obstructive apnea-hypopnea index (OAHI) were compared using Spearman correlation. A receiver operating characteristic (ROC) analysis determined the ability of the SERS total score to predict severe OSA (OAHI >10). RESULTS: Thirty-nine patients were included (mean age, 8.3 +/- 5.1 years; 36% obese; mean OAHI, 19.1 +/- 23.7). Intrarater and inter-rater reliability was substantial-to-excellent (kappa = 0.61-0.83) and fair-to-substantial (kappa = 0.33-0.76), respectively. Ratings correlated best with OAHI for the oropharynx (r = 0.54, P = .02), hypopharynx (r = 0.48, P = .04), and SERS total score (r = 0.75, P = .002). In ROC analysis, a SERS total score >/=6 demonstrated sensitivity/specificity of 81.8%/87.5%, respectively, and correctly classified 84% of patients. CONCLUSIONS: The SERS can be applied reliably in children undergoing DISE for OSA. Ratings of the oropharynx, hypopharynx, and SERS total score demonstrated significant correlation with OSA severity. A SERS total score >/=6 was an accurate predictor of severe OSA. LEVEL OF EVIDENCE: 4. Laryngoscope, 126:1492-1498, 2016.


We sought to determine if symptomatic cardiogenic limb emboli have a random distribution or if there are demographic or echocardiographic factors that predict site of embolization, limb salvage and mortality. Upper (UE) and lower extremity (LE) emboli were evaluated over a 16-year period (1996-2012). Demographic (age, gender, smoking, medical comorbidities) and echocardiographic data were analyzed to determine predictors of embolic site. All symptomatic patients underwent surgical revascularization. Limb salvage and mortality were compared with Kaplan-Meier analysis. A total of 161 patients with symptomatic cardiogenic emboli were identified: 56 UE and 105 LE. The female-to-male ratio for UE emboli (70%;30%) was significantly higher than for LE emboli (47%;53%; p=0.008). No other demographic factors were statistically different. Upper extremity patients were more likely to have atrial fibrillation (50% vs 29.8%, p=0.028), while LE patients had a higher percentage of aortic or mitral valvular disease or intracardiac thrombus (71.4% vs 52.5%, p=0.038). The 30-day limb salvage was higher for UE compared to LE (100% vs 88%, p=0.008). There was a trend toward higher 30-day mortality in the LE group (14% vs 5%, p=0.11). Survival at 1, 3, and 5 years were similar (UE: 62.2%, 44.2%, 35.3%; LE: 69.1%, 47.5%, 30.3%; p=ns). Upper extremity emboli are more frequent in women and patients with atrial fibrillation. Lower extremity emboli are more frequent in the presence of valvular disease or intracardiac thrombus, and are associated with increased 30-day limb loss and mortality. These findings suggest gender- and cardiac-specific differences in patterns of blood flow leading to preferential sites of peripheral embolization.
females; 3.1 years post-injury) and 10 controls (6 males, 4 females). Peak center of mass and peak knee angles during the landing phase of a jump-cut maneuver were evaluated. Participants with a concussion history demonstrated decreased knee varus (left: Mconc = -0.5 +/- 1 degrees, Mctrl = 3.6 +/- 1 degrees; right: Mconc = 5.1 +/- 1.2 degrees, Mctrl = 7.8 +/- 1.12 degrees) and external rotation (left: Mconc = 2.5 +/- 1.6 degrees, Mctrl = 13.0 +/- 1.5 degrees; right: Mconc = 7.7 +/- 1.6 degrees, Mctrl = 12.8 +/- 1.5 degrees) regardless of whether the cut was oriented towards the left or right. The kinematic patterns demonstrated in individuals with a concussion history may be suggestive of increased knee injury risk. This study adds to the growing body of literature linking orthopedic injury in those no longer displaying the acute signs and symptoms of concussion.


PURPOSE: Survival for children and young adults with high-risk B-acute lymphoblastic leukemia has improved significantly, but 20% to 25% of patients are not cured. Children's Oncology Group study AALL0232 tested two interventions to improve survival. PATIENTS AND METHODS: Between January 2004 and January 2011, AALL0232 enrolled 3,154 participants 1 to 30 years old with newly diagnosed high-risk B-acute lymphoblastic leukemia. By using a 2 x 2 factorial design, 2,914 participants were randomly assigned to receive dexamethasone (14 days) versus prednisone (28 days) during induction and high-dose methotrexate versus Capizzi escalating-dose methotrexate plus pegasparagase during interim maintenance 1. RESULTS: Planned interim monitoring showed the superiority of the high-dose methotrexate regimens, which exceeded the predefined boundary and led to cessation of enrollment in January 2011. At that time, participants randomly assigned to high-dose methotrexate during interim maintenance 1 versus those randomly assigned to Capizzi methotrexate had a 5-year event-free survival (EFS) of 82% versus 75.4% (P = .006). Mature final data showed 5-year EFS rates of 79.6% for high-dose methotrexate and 75.2% for Capizzi methotrexate (P = .008). High-dose methotrexate decreased both marrow and CNS recurrences. Patients 1 to 9 years old who received dexamethasone and high-dose methotrexate had a superior outcome compared with those who received the other three regimens (5-year EFS, 91.2% v 83.2%, 80.8%, and 82.1%; P = .015). Older participants derived no benefit from dexamethasone during induction and experienced excess rates of osteonecrosis. CONCLUSION: High-dose methotrexate is superior to Capizzi methotrexate for the treatment of high-risk B-acute lymphoblastic leukemia, with no increase in acute toxicity. Dexamethasone given during induction benefited younger children but provided no benefit and was associated with a higher risk of osteonecrosis among participants 10 years and older.


The nonclassical HLA molecule MHC-related protein 1 (MR1) presents metabolites of the vitamin B synthesis pathways to mucosal-associated invariant T (MAIT) cells and other MR1-restricted T cells. This new class of Ags represents a variation on the classical paradigm of self/non-self discrimination because these T cells are activated through their TCR by small organic compounds generated during microbial vitamin B2 synthesis. Beyond the fundamental significance, the invariant nature of MR1 across the human population is a tantalizing feature for the potential development of universal immune therapeutic and diagnostic tools. However, many aspects of MR1 Ag presentation and MR1-restricted T cell biology remain unknown, and the ubiquitous expression of MR1 across tissues and cell lines can be a confounding factor for experimental purposes. In this study, we report the development of a novel CRISPR/Cas9 genome editing lentiviral system and its use to efficiently disrupt MR1 expression in A549, THP-1, and K562 cell lines. We generated isogenic MR1(-/-) clonal derivatives of the A549 lung carcinoma and THP-1 monocytic cell lines and used these to
study T cell responses to intracellular pathogens. We confirmed that MAIT cell clones were unable to respond to MR1(-/-) clones infected with bacteria whereas Ag presentation by classical and other nonclassical HLAs was unaffected. This system represents a robust and efficient method to disrupt the expression of MR1 and should facilitate investigations into the processing and presentation of MR1 Ags as well as into the biology of MAIT cells.


Most melanocytic tumors can be characterized as a benign nevus or a melanoma by a trained pathologist using traditional histopathological methods. However, a minority demonstrates ambiguous features and continues to be a diagnostic challenge. Genetic expression profiling (GEP) assays have been developed in an effort to resolve this dilemma. These assays measure mRNA levels of specified genes using reverse transcription quantitative polymerase chain reaction technology. The development of GEP assays, methodology, challenges associated with GEP validation and testing, and the suitability of a currently available GEP test for clinical use are reviewed. © 2017 The Authors.


PURPOSE: To examine medical student attitudes toward cost-conscious care and whether regional health care intensity is associated with reported exposure to physician role-modeling behaviors related to cost-conscious care. METHOD: Students at 10 U.S. medical schools were surveyed in 2015. Thirty-five items assessed attitudes toward, perceived barriers to and consequences of, and observed physician role-modeling behaviors related to cost-conscious care (using scales for cost-conscious and potentially wasteful behaviors; Cronbach alphas of 0.82 and 0.81, respectively). Regional health care intensity was measured using Dartmouth Atlas End-of-Life Chronic Illness Care data: ratio of physician visits per decedent compared with the U.S. average, ratio of specialty to primary care physician visits per decedent, and hospital care intensity index. RESULTS: Of 5,992 students invited, 3,395 (57%) responded. Ninety percent (2,640/2,932) agreed physicians have a responsibility to contain costs. However, 48% (1,1416/2,960) thought ordering a test is easier than explaining why it is unnecessary, and 58% (1,685/2,928) agreed ordering fewer tests will increase the risk of malpractice litigation. In adjusted linear regression analyses, students in higher-health-care-intensity regions reported observing significantly fewer cost-conscious role-modeling behaviors: For each one-unit increase in the three health care intensity measures, scores on the 21-point cost-conscious role-modeling scale decreased by 4.4 (SE 0.7), 3.2 (0.6), and 3.9 (0.6) points, respectively (all P < .001).

CONCLUSIONS: Medical students endorse barriers to cost-conscious care and encounter conflicting role-modeling behaviors, which are related to regional health care intensity. Enhancing role modeling in the learning environment may help prepare future physicians to address health care costs.


Defects in the RNA-binding protein, TDP-43, are known to cause a variety of neurodegenerative disease including amyotrophic lateral sclerosis (ALS) and frontotemporal lobar dementia (FTLD). A variety of experimental systems have shown that neurons are sensitive to TDP-43 expression levels, yet the specific functional defects resulting from TDP-43 dysregulation have not been well described. Using the Drosophila TDP-43 orthologue TBPH, we previously showed that TBPH null animals display locomotion defects as third instar larvae. Furthermore, loss of TBPH caused a reduction in cacophony, a type II voltage-gated calcium channel, expression and that genetically restoring cacophony in motor neurons in TBPH mutant animals was sufficient
to rescue the locomotion defects. In the present study, we examined the relative contributions of NMJ physiology and the motor program to the locomotion defects and identified subsets of neurons that require cacophony expression to rescue the defects. At the NMJ, we showed mEPP amplitudes and frequency require TBPH. Cacophony expression in motor neurons rescued mEPP frequency but not mEPP amplitude. We also showed that TBPH mutants displayed reduced motor neuron bursting and coordination during crawling and restoring cacophony selectively in two pairs of cells located in the brain, the AVM001b/2b neurons, also rescued the locomotion and motor defects, but not the defects in NMJ physiology. These results suggest that the behavioral defects associated with loss of TBPH throughout the nervous system can be associated with defects in a small number of genes in a limited number of central neurons, rather than peripheral defects.

**SIGNIFICANCE STATEMENT**

TDP-43 dysfunction is a common feature in neurodegenerative diseases including ALS, FTLD, and Alzheimer’s disease. Loss and gain of function models have shown neurons are sensitive to TDP-43 expression levels, but the specific defects caused by TDP-43 loss of function have not been described in detail. A Drosophila loss-of-function model displays pronounced locomotion defects that can be reversed by restoring the expression levels of a voltage-gated calcium channel, cacophony. We show these defects can be rescued by expression of cacophony in motor neurons and by expression in two pairs of neurons in the brain. These data suggest that loss of TDP-43 can disrupt the central circuitry of the CNS, opening up identification of alternative therapeutic targets for TDP-43 proteinopathies.


**BACKGROUND:** Antibody responses to the inactivated seasonal influenza vaccine in patients with atopic dermatitis (AD) have not been carefully characterized. **OBJECTIVE:** The primary objective of this study was to compare antibody responses to intradermal vaccination in participants with moderate/severe AD with those in nonatopic participants. Secondary objectives were to evaluate the effect of route of administration, Staphylococcus aureus skin colonization, and disease severity on vaccine response. **METHODS:** This was an open-label study conducted in the 2012-2013 influenza season at 5 US clinical sites. A total of 360 participants with moderate/severe AD or nonatopic subjects were assessed for eligibility, 347 of whom received intradermal or intramuscular vaccination per label and were followed for 28 days after vaccination. The primary outcome was the difference in the proportion of participants achieving seroprotection (hemagglutination-inhibition antibody titer >/=1:40 on day 28 after vaccination). **RESULTS:** Seroprotection rates for influenza B, H1N1, and H3N2 were not different (1) between participants with AD and nonatopic participants receiving intradermal vaccination and (2) between AD participants receiving intradermal and intramuscular vaccination. After intradermal, but not intramuscular, vaccination, participants with AD with S aureus colonization experienced (1) lower seroprotection and seroconversion rates and lower hemagglutination-inhibition antibody titer geometric mean fold increase against influenza B and (2) lower seroconversion rates against influenza H1N1 than noncolonized participants with AD. **CONCLUSION:** Participants with AD colonized with S aureus exhibited a reduced immune response to influenza vaccination compared with noncolonized participants after intradermal but not intramuscular vaccination. Because most patients with AD are colonized with S aureus, intramuscular influenza vaccination should be given preference in these patients.

OBJECTIVES/HYPOTHESIS: Patients with chronic rhinosinusitis (CRS) who experience minimal reductions in quality of life (QoL) may present for treatment despite QoL scores comparable to controls without CRS. This study seeks to identify cofactors influencing patients with CRS and low 22-item Sinonasal Outcome Test (SNOT-22) scores to seek care. STUDY DESIGN: Prospective, multicenter, observational cohort. METHODS: Patients with CRS were enrolled between April 2011 and September 2015. Patients with sinonasal mucocele or unilateral sinus opacification were excluded. Control subjects without CRS were enrolled for comparison. Low-SNOT CRS was defined as a SNOT-22 score < 20. RESULTS: A total of 774 subjects (low-SNOT CRS, n = 38; high-SNOT CRS, SNOT-22 >/= 20, n = 641; controls without CRS, n = 95) were enrolled. Low SNOT scores were identified in 6% of subjects with CRS. After adjustment, low-SNOT CRS and control groups without CRS reported similar baseline average SNOT-22 total scores (P = .879). Unexpectedly, compared to controls, low-SNOT CRS patients had significantly better average psychological (2.1 +/- 2.3 vs. 5.8 +/- 6.0; P = .030) and sleep dysfunction (2.7 +/- 3.4 vs. 6.0 +/- 5.2; P = .016) scores. Fourteen of 38 (37%) low-SNOT patients elected to undergo endoscopic sinus surgery (ESS), with a significantly lower likelihood of reporting a minimal clinically important difference (MCID) when compared to high-SNOT patients (43% vs. 82%; P < .001) after a mean follow-up of approximately 15 months. CONCLUSIONS: Low-SNOT CRS patients represent an outlier population for which measures of QoL fail to identify factors influencing the decision to seek treatment. Low-SNOT CRS patients electing ESS have a decreased likelihood of reporting MCIDs following ESS. Further study is required to identify novel factors associated with treatment-seeking behavior in this population. LEVEL OF EVIDENCE: 3B Laryngoscope, 127:22-28, 2017.


Despite widespread use of the Bacillus Calmette-Guerin vaccine, tuberculosis, caused by infection with Mycobacterium tuberculosis, remains a leading cause of morbidity and mortality worldwide. As CD8+ T cells are critical to tuberculosis host defense and a phase 2b vaccine trial of modified vaccinia Ankara expressing Ag85a that failed to demonstrate efficacy, also failed to induce a CD8+ T cell response, an effective tuberculosis vaccine may need to induce CD8+ T cells. However, little is known about CD8, as compared to CD4, antigens in tuberculosis. Herein, we report the results of the first ever HLA allele independent genome-wide CD8 antigen discovery program. Using CD8+ T cells derived from humans with latent tuberculosis infection or tuberculosis and an interferon-gamma ELISPOT assay, we screened a synthetic peptide library representing 10% of the Mycobacterium tuberculosis proteome, selected to be enriched for Mycobacterium tuberculosis antigens. We defined a set of immunodominant CD8 antigens including part or all of 74 Mycobacterium tuberculosis proteins, only 16 of which are previously known CD8 antigens. Immunogenicity was associated with the degree of expression of mRNA and protein. Immunodominant antigens were enriched in cell wall proteins with preferential recognition of Ess protein family members, and within proteins comprising the Mycobacterium tuberculosis secretome. A validation study of immunodominant antigens demonstrated that these antigens were strongly recognized in Mycobacterium tuberculosis-infected individuals from a tuberculosis endemic region in Africa. The tuberculosis vaccine field will likely benefit from this greatly increased known repertoire of CD8 immunodominant antigens and definition of properties of Mycobacterium tuberculosis proteins important for CD8 antigenicity.
INTRODUCTION: Increased plasma homocysteine (HC) is a risk factor for dementia in the general population. Levodopa therapy causes increased plasma HC, but it remains unclear whether elevated plasma HC is associated with cognitive impairment in Parkinson’s disease (PD). METHODS: The study population includes all participants in the Pacific Northwest Udall Center (PANUC) Clinical cohort at the time of the study, consisting of 294 individuals with PD who had a standardized neuropsychological assessment and plasma collection for HC measurement. We tested the hypothesis that elevated plasma HC is inversely related to cognitive function in patients with PD. RESULTS: As expected, plasma HC was positively associated with age, disease duration, disease severity, and levodopa usage, while cognitive function was associated with age, education, gender, and APOE genotype, so subsequent analyses controlled for these covariates. When plasma HC was dichotomized as normal (<14 mumol/L) or elevated (≥14 mumol/L), subjects with hyperhomocysteinemia had lower scores on Digit Symbol (p = 0.031), Hopkins Verbal Learning Task (HVLT) Delayed Recall (p = 0.004), and semantic verbal fluency (p = 0.049). When examined as a continuous variable, plasma HC was inversely associated with HVLT Delayed Recall (p = 0.009) and semantic verbal fluency (p = 0.004), but was not significantly related to Digit symbol, Trail-making test, Judgment of Line Orientation, phonemic verbal fluency, MMSE, or MOCA. When analysis was restricted to non-demented subjects (n = 231), the findings were unchanged. CONCLUSIONS: We conclude that plasma HC is significantly associated with some aspects of cognitive function in PD, and may represent a treatable risk factor for cognitive decline in PD.


The objective of this retrospective study was to evaluate the prevalence of comorbid Posttraumatic stress disorder (PTSD) and the association of PTSD with pain, disease activity, and medication use in ankylosing spondylitis (AS). Veterans with one or more visit to an outpatient rheumatology clinic at a single Veterans Affairs site during a 2-year study period were identified by ICD codes for AS and included if there was documentation of AS diagnosis by a rheumatologist. Data were collected on PTSD diagnosis, demographics, pain scores, disease activity by the Bath AS Disease Activity Index (BASDAI), and medication use. Characteristics were compared by PTSD status using t tests for continuous variables and Chi-square or Fisher’s exact test for categorical variables. Of 113 Veterans with AS, 20 (18%) had a diagnosis of PTSD. Those with PTSD were significantly younger, 52 +/- 17 years, as compared to those without PTSD, 59 +/- 14 years (p = 0.04). BASDAI was recorded for 30% with a mean score of 4.3 +/- 2.0. Those with PTSD had higher mean pain and BASDAI scores as compared to those without PTSD (p = 0.06 for both comparisons). Prescribed medications were similar for both groups in regards to synthetic disease modifying antirheumatic drugs (DMARDs), biologics, and opioids, although those with PTSD were significantly more likely to receive NSAIDs (p = 0.03). Veterans with AS and comorbid PTSD were younger and had higher reported pain and disease activity scores compared to those without PTSD in this single site study. These findings underscore the importance of identifying PTSD in patients with AS.


The human cytomegalovirus (HCMV) terminase complex consists of several components acting together to cleave viral DNA into unit length genomes and translocate them into capsids, a critical process in the production of infectious virions subsequent to DNA replication. Previous studies suggest that the carboxyl-terminal portion of the pUL56 subunit interacts with the pUL89 subunit. However, the specific interacting residues of pUL56...
remain unknown. We identified a conserved sequence in the C-terminal moiety of pUL56 (671WMVVKYMGFF680). Overrepresentation of conserved aromatic amino acids through 20 herpesviruses homologues of pUL56 suggests an involvement of this short peptide into the interaction between the larger pUL56 terminase subunit and the smaller pUL89 subunit. Use of Alpha technology highlighted an interaction between pUL56 and pUL89 driven through the peptide 671WMVVKYMGFF680. A deletion of these residues blocks viral replication. We hypothesize that it is the consequence of the disruption of the pUL56–pUL89 interaction. These results show that this motif is essential for HCMV replication and could be a target for development of new small antiviral drugs or peptidomimetics.


Smooth muscle cells (SMCs) are key regulators of vascular disease and circulating smooth muscle progenitor cells may play important roles in vascular repair or remodelling. We developed enhanced protocols to derive smooth muscle progenitors from murine bone marrow and tested whether factors that are increased in atherosclerotic plaques, namely platelet-derived growth factor-BB (PDGF-BB) and monomeric collagen, can influence the smooth muscle specific differentiation, proliferation, and survival of mouse bone marrow-derived progenitor cells. During a 21 day period of culture, bone marrow cells underwent a marked increase in expression of the SMC markers alpha-SMA (1.93 +/- 0.15 vs. 0.0008 +/- 0.0003 (ng/ng GAPDH) at 0 d), SM22-alpha (1.50 +/- 0.27 vs. 0.005 +/- 0.001 (ng/ng GAPDH) at 0 d) and SM-MHC (0.017 +/- 0.004 vs. 0.001 +/- 0.001 (ng/ng GAPDH) at 0 d). Bromodeoxyuridine (BrdU) incorporation experiments showed that in early culture, the smooth muscle progenitor subpopulation could be identified by high proliferative rates prior to the expression of smooth muscle specific markers. Culture of fresh bone marrow or smooth muscle progenitor cells with PDGF-BB suppressed the expression of alpha-SMA and SM22-alpha, in a rapidly reversible manner requiring PDGF receptor kinase activity. Progenitors cultured on polymerized collagen gels demonstrated expression of SMC markers, rates of proliferation and apoptosis similar to that of cells on tissue culture plastic; in contrast, cells grown on monomeric collagen gels displayed lower SMC marker expression, lower growth rates (319 +/- 36 vs. 635 +/- 97 cells/mm^2), and increased apoptosis (5.3 +/- 1.6% vs. 1.0 +/- 0.5% (Annexin 5 staining)). Our data shows that the differentiation and survival of smooth muscle progenitors are critically affected by PDGF-BB and as well as the substrate collagen structure.


INTRODUCTION: Infectious complications are common after radical cystectomy (RC), and allogeneic blood transfusions may increase infection risk by an immunosuppressive effect. While it has been suggested that perioperative blood transfusion (PBT) may be associated with adverse oncologic outcomes after RC, no large analyses have assessed whether PBT increases the risk of perioperative infection after RC. MATERIALS AND METHODS: We used the Nationwide Inpatient Sample (1998 to 2011) to study the rate of PBT during RC for bladder cancer and identify infectious complications. We compared rates of infectious complications in patients who did and did not receive PBT and developed a multivariable model to assess the independent risk of infectious complication associated with PBT controlling for age, year of surgery, obesity, chronic kidney disease, comorbidity score, and type of urinary diversion. RESULTS: We identified 126,454 RCs performed during the study period. A total of 34,203 (27%) received a PBT. The use of PBT increased over the study period, from 18.4% in 1998 to 31.6% in 2011 (p < 0.0001). Patients who received a PBT had an increased risk of perioperative infectious complications [36.7% versus 27.7%, unadjusted OR (95% CI) = 1.51...
After adjusting for potential confounders, PBT remained an independent predictor of infectious complications [adjusted OR (95% CI) = 1.46 (1.38-1.55), p < 0.0001]. CONCLUSIONS: This analysis provides strong observational evidence that PBT is associated with an increased risk of perioperative infectious complications, which may be secondary to transfusion-related immunomodulation. Urologists should aggressively pursue blood conservation strategies and adhere to evidence-based restrictive transfusion thresholds, particularly given the rising rate of PBT.


Semi-automated software can provide quantitative assessment of atherosclerotic plaques on coronary CT angiography (CTA). The relationship between established qualitative high-risk plaque features and quantitative plaque measurements has not been studied. We analyzed the association between quantitative plaque measurements and qualitative high-risk plaque features on coronary CTA. We included 260 patients with plaque who underwent coronary CTA in the Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography (ROMICAT) II trial. Quantitative plaque assessment and qualitative plaque characterization were performed on a per coronary segment basis. Quantitative coronary plaque measurements included plaque volume, plaque burden, remodeling index, and diameter stenosis. In qualitative analysis, high-risk plaque was present if positive remodeling, low CT attenuation plaque, napkin-ring sign or spotty calcium were detected. Univariable and multivariable logistic regression analyses were performed to assess the association between quantitative and qualitative high-risk plaque assessment. Among 888 segments with coronary plaque, high-risk plaque was present in 391 (44.0%) segments by qualitative analysis. In quantitative analysis, segments with high-risk plaque had higher total plaque volume, low CT attenuation plaque volume, plaque burden and remodeling index. Quantitatively assessed low CT attenuation plaque volume (odds ratio 1.12 per 1 mm³, 95% CI 1.04-1.21), positive remodeling (odds ratio 1.25 per 0.1, 95% CI 1.10-1.41) and plaque burden (odds ratio 1.53 per 0.1, 95% CI 1.08-2.16) were associated with high-risk plaque. Quantitative coronary plaque characteristics (low CT attenuation plaque volume, positive remodeling and plaque burden) measured by semi-automated software correlated with qualitative assessment of high-risk plaque features.


PURPOSE: A prominent symptom of myalgic encephalomyelitis, chronic fatigue syndrome, or systemic exertion intolerance disease (ME/CFS/SEID) is persistent fatigue that is worsened by physical exertion. Here the population effect of a single bout of exercise on fatigue symptoms in people with ME/CFS/SEID was estimated and effect moderators were identified. METHODS: Google Scholar was systematically searched for peer-reviewed articles published between February 1991 and May 2015. Studies were included where people diagnosed with ME/CFS/SEID and matched control participants completed a single bout of exercise and fatigue self-reports were obtained before and after exercise. Fatigue means, standard deviations, and sample sizes were extracted to calculate effect sizes and the 95% confidence interval. Effects were pooled using a random-effects model and corrected for small sample bias to generate mean Delta. Multilevel regression modeling adjusted for nesting of effects within studies. Moderators identified a priori were diagnostic criteria, fibromyalgia comorbidity, exercise factors (intensity, duration, and type), and measurement factors.
RESULTS: Seven studies examining 159 people with ME/CFS/SEID met inclusion criteria, and 47 fatigue effects were derived. The mean fatigue effect was Delta = 0.73 (95% confidence interval = 0.24-1.23). Fatigue increases were larger for people with ME/CFS/SEID when fatigue was measured 4 h or more after exercise ended rather than during or immediately after exercise ceased. CONCLUSIONS: This preliminary evidence indicates that acute exercise increases fatigue in people with ME/CFS/SEID more than that in control groups, but effects were heterogeneous between studies. Future studies with no-exercise control groups of people with ME/CFS/SEID are needed to obtain a more precise estimate of the effect of exercise on fatigue in this population.


Importance: Severe anterior septal deviation and resultant nasal obstruction represent a difficult surgical task to correct. The goal of surgery is to straighten the anterior dorsal and caudal struts, while maintaining nasal tip and midvault support. This study presents a novel extracorporeal septoplasty technique to straighten the crooked anterior septum. Objective: To describe the novel anterior septal transplant technique, which consists of complete resection of the caudal septum and reconstruction with extended spreader grafts and a columellar strut, without a separate caudal septal replacement graft. Design, Setting, and Participants: This study was a retrospective case series at a tertiary academic referral center. Participants were sequential adult patients undergoing anterior septal transplant from January 1, 2008, to December 31, 2015. Main Outcomes and Measures: Patient-reported nasal obstruction using Nasal Obstruction Symptom Evaluation (NOSE) scores and objective photographic analysis. Nasal tip deviation, projection, and rotation were measured. Preoperative and postoperative outcomes were compared. Complications are reported. Results: Seventy-one patients (mean age, 46 years [age range, 16-72 years]; 48 [67.6%] female and 23 [32.4%] male) were included in the case series. Postoperative NOSE scores (mean [SD], 24.00 [24.58]) were significantly better than preoperative NOSE scores (mean [SD], 72.25 [14.55]) (P < .001). A separate cohort of 32 patients (mean age, 42 years [age range, 13-72 years]; 23 [71.9%] female and 9 [28.1%] male) had photographs available for analysis. In the frontal view, nasal deviation improved from a mean (SD) of 2.9 (2.0) degrees before surgery to a mean (SD) of 1.4 (1.7) degrees after surgery (P = .004). In the base view, the deviation was corrected from a mean (SD) of 4.9 (2.8) degrees to a mean (SD) of 1.7 (1.2) degrees (P < .001). Tip rotation and projection were unchanged after surgery. Four patients had mild dorsal irregularities after surgery. Conclusions and Relevance: Anterior septal transplant by the described technique is a safe and effective treatment option for severe anterior septal deviation. Level of Evidence: 4.


OBJECTIVES: To determine if an improvement collaborative of 33 children's hospitals focused on reliable best practice implementation and culture of safety improvements can reduce hospital-acquired conditions (HACs) and serious safety events (SSEs). METHODS: A 3-year prospective cohort study design with a 12-month historical control population was completed by the Children's Hospitals' Solutions for Patient Safety collaborative. Identification and dissemination of best practices related to 9 HACs and SSE reduction focused on key process and culture of safety improvements. Individual hospital improvement teams leveraged the resources of a large, structured children's hospital collaborative using electronic, virtual, and in-person interactions. RESULTS: Thirty-three children's hospitals from across the United States volunteered to be part of the Children's Hospitals' Solutions for Patient Safety collaborative. Thirty-two met all the data submission eligibility requirements for the HAC improvement objective of this study, and 21 participated in the high-reliability culture work aimed at reducing SSEs. Significant harm reduction occurred in 8 of 9 common HACs (range 9%-71%; P < .005 for all). The mean monthly SRE rate decreased 32% (from 0.77 to 0.52; P < .001). The 12-month rolling average SRE rate decreased 50% (from 0.82 to 0.41; P < .001). CONCLUSIONS: Participation in a structured collaborative dedicated to implementing HAC-related best-practice prevention
bundles and culture of safety interventions designed to increase the use of high-reliability organization practices resulted in significant HAC and SSE reductions. Structured collaboration and rapid sharing of evidence-based practices and tools are effective approaches to decreasing hospital-acquired harm.


Genome editing has potential for the targeted correction of germline mutations. Here we describe the correction of the heterozygous MYBPC3 mutation in human preimplantation embryos with precise CRISPR-Cas9-based targeting accuracy and high homology-directed repair efficiency by activating an endogenous, germline-specific DNA repair response. Induced double-strand breaks (DSBs) at the mutant paternal allele were predominantly repaired using the homologous wild-type maternal gene instead of a synthetic DNA template. By modulating the cell cycle stage at which the DSB was induced, we were able to avoid mosaicism in cleaving embryos and achieve a high yield of homozygous embryos carrying the wild-type MYBPC3 gene without evidence of off-target mutations. The efficiency, accuracy and safety of the approach presented suggest that it has potential to be used for the correction of heritable mutations in human embryos by complementing preimplantation genetic diagnosis. However, much remains to be considered before clinical applications, including the reproducibility of the technique with other heterozygous mutations.


Thyroid hormone (TH) signaling regulates cell proliferation, differentiation, and metabolism. Recent studies have implicated TH signaling in cone photoreceptor viability. Using mouse models of retinal degeneration, we demonstrated that antithyroid drug treatment and targeting iodothyronine deiodinases (DIOs) to suppress cellular tri-iodothyronine (T3) production or increase T3 degradation preserves cones. In this work, we investigated the effectiveness of inhibition of the TH receptor (TR). Two genes, THRA and THRB, encode TRs; THRB2 has been associated with cone viability. Using TR antagonists and Thrb2 deletion, we examined the effects of TR inhibition. Systemic and ocular treatment with the TR antagonists NH-3 and 1-850 increased cone density by 30–40% in the Rpe652/2 mouse model of Leber congenital amaurosis and reduced the number of TUNEL+ cells. Cone survival was significantly improved in Rpe652/2 and Cpf1 (a model of achromatopsia with Pde6c defect) mice with Thrb2 deletion. Ventral cone density in Cpf1/Thrb22/2 and Rpe652/2/Thrb22/2 mice was increased by 1- to 4-fold, compared with age-matched controls. Moreover, the expression levels of TR were significantly higher in the cone-degeneration retinas, suggesting locally elevated TR signaling. This work shows that the effects of antithyroid treatment or targeting DIOs were likely mediated by TRs and that suppressing TR protects cones. Our findings support the view that inhibition of TR locally in the retina is a therapeutic strategy for retinal degeneration management.—Ma, H., Yang, F., Butler, M. R., Belcher, J., Redmond, T. M., Placzek, A. T., Scanlan, T. S., Ding, X. Q. Inhibition of thyroid hormone receptor locally in the retina is a therapeutic strategy for retinal degeneration. © FASEB.


Background Although limited, the literature suggests alterations in activation of cognitive control regions in adults and adolescents with a history of childhood abuse. The current study examined whether such alterations are increased in the face of emotionally-distracting as compared to emotionally neutral information, and whether such alterations occur in brain regions that exert cognitive control in a more top-down sustained manner or a more bottom-up transient manner. Methods Participants were young adult women (ages 23–30): one group with a history of childhood physical or sexual abuse (N = 15) and one with no trauma
BACKGROUND: Difficulty turning is a major contributor to mobility disability, falls, and reduced quality of life in older people because it requires dynamic balance control that worsens with age. However, no study has quantified the quality and quantity of turning during normal daily activities in older people. The objective of this pilot study was to monitor turning mobility and its association to falls and cognitive function in a multicenter sample.

METHODS: Three Prognostic Assessment of Life and Limitations After Trauma in the Elderly centers not involved in the newborn GTOS validation study identified subjects aged 65 years to 102 years admitted from 2000 to 2013. The Geriatric Trauma Outcome Score (GTOS) was validated in 2000 and became the sole predictor in a separate logistic regression model to estimate probability of mortality. Model performances were evaluated using misclassification rate, Brier score, and area under the curve.

RESULTS: Demographics (mean ± SD) of subjects with complete data (N = 10,894) were age, 78.3 years ± 8.1 years; ISS, 10.9 ± 8.4; RTS = 7.5 ± 1.1; mortality = 6.9%; blunt mechanism = 98.6%; 3.1% of subjects received PRCs. The penetrating trauma subsample (n = 150) had a higher mortality rate of 20.0%. The misclassification rates for the models were GTOS, 0.065; TRISSB, 0.051; and TRISSP, 0.120. Brier scores were GTOS, 0.052; TRISSB, 0.041; and TRISSP, 0.084. The area under the curves were GTOS, 0.844; TRISSB, 0.889; and TRISSP, 0.897. CONCLUSION: GTOS and TRISS function similarly and accurately in predicting probability of death for injured elders. GTOS has the advantages of a single formula, fewer variables, and no reliance on data collected in the emergency room or by other observers. LEVEL OF EVIDENCE: Prognostic, level II.


BACKGROUND: The nine-center Prognostic Assessment of Life and Limitations After Trauma in the Elderly consortium has validated the Geriatric Trauma Outcome Score (GTOS) as a prognosis calculator for injured elders. We compared GTOS’ performance to that of the Trauma Injury Severity Score (TRISS) in a multicenter sample. METHODS: Three Prognostic Assessment of Life and Limitations After Trauma in the Elderly centers not submitting subjects to the GTOS validation study identified subjects aged 65 years to 102 years admitted from 2000 to 2013. GTOS was specified using the formula [GTOS = age + (Injury Severity Score [ISS] x 2.5) + 22 (if transfused packed red cells (PRC) at 24 hours)]. TRISS uses the Revised Trauma Score (RTS).

dichotomizes age (<55 years = 0 and >/=55 years = 1), and was specified using the updated 1995 beta coefficients. TRISS Penetrating was specified as [TRISSP = -2.5355 + (0.9934 x RTS) + (-0.0651 x ISS) + (-1.1360 x Age)]. TRISS Blunt was specified as [TRISSB = -0.4499 + (0.8085 x RTS Total) + (-0.0835 x ISS) + (-1.7430 x Age)]. Each then became the sole predictor in a separate logistic regression model to estimate probability of mortality. Model performances were evaluated using misclassification rate, Brier score, and area under the curve. RESULTS: Demographics (mean ± SD) of subjects with complete data (N = 10,894) were age, 78.3 years ± 8.1 years; ISS, 10.9 ± 8.4; RTS = 7.5 ± 1.1; mortality = 6.9%; blunt mechanism = 98.6%; 3.1% of subjects received PRCs. The penetrating trauma subsample (n = 150) had a higher mortality rate of 20.0%. The misclassification rates for the models were GTOS, 0.065; TRISSB, 0.051; and TRISSP, 0.120. Brier scores were GTOS, 0.052; TRISSB, 0.041; and TRISSP, 0.084. The area under the curves were GTOS, 0.844; TRISSB, 0.889; and TRISSP, 0.897. CONCLUSION: GTOS and TRISS function similarly and accurately in predicting probability of death for injured elders. GTOS has the advantages of a single formula, fewer variables, and no reliance on data collected in the emergency room or by other observers. LEVEL OF EVIDENCE: Prognostic, level II.


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study was to determine if quality of turning during daily activities is associated with falls and/or cognitive function. METHODS: Thirty-five elderly participants (85 +/- 8 years) wore three Opal inertial sensors. Turning and activity rate were measured. Based on retrospective falls, participants were grouped into nonfallers (N = 16), single fallers (N = 12), and recurrent fallers (N = 7). We also determined which turning characteristic predicted falls in the 6 months following the week of monitoring. RESULTS: Quality of turning was significantly compromised in recurrent fallers compared with nonfallers (p < .05). In contrast, activity rate and mean number of turns per hour were similar across the three groups. Also, quality of turning during a prescribed test was similar across the three groups. Visuospatial and memory functions and the Tinetti Balance Scores were associated with quality of turning. Future falls were related to an increased variability of number of steps to turn. CONCLUSIONS: Continuous monitoring of turning characteristics, while walking during daily activities, is feasible in older people. Turning characteristics during daily life appear to be more sensitive to fall risk than prescribed turning tasks. These findings suggest a slower, less variable, cautious turning strategy in elderly volunteers with a history of falls.


Vitamin D insufficiency is common, correctable, and influenced by genetic factors, and it has been associated with risk of several diseases. We sought to identify low-frequency genetic variants that strongly increase the risk of vitamin D insufficiency and tested their effect on risk of multiple sclerosis, a disease influenced by low vitamin D concentrations. We used whole-genome sequencing data from 2,619 individuals through the UK10K program and deep-imputation data from 39,655 individuals genotyped genome-wide. Meta-analysis of the summary statistics from 19 cohorts identified in CYP2R1 the low-frequency (minor allele frequency = 2.5%) synonymous coding variant g.14900931G>A (p.Asp120Asp) (rs117913124[A]), which conferred a large effect on 25-hydroxyvitamin D (25OHD) levels (-0.43 SD of standardized natural log-transformed 25OHD per A allele; p value = 1.5 x 10^{-88}). The effect on 25OHD was four times larger and independent of the effect of a previously described common variant near CYP2R1. By analyzing 8,711 individuals, we showed that heterozygote carriers of this low-frequency variant have an increased risk of vitamin D insufficiency (odds ratio [OR] = 2.2, 95% confidence interval [CI] = 1.78-2.78, p = 1.26 x 10^{-12}). Individuals carrying one copy of this variant also had increased odds of multiple sclerosis (OR = 1.4, 95% CI = 1.19-1.64, p = 2.63 x 10^{-5}) in a sample of 5,927 case and 5,599 control subjects. In conclusion, we describe a low-frequency CYP2R1 coding variant that exerts the largest effect upon 25OHD levels identified to date in the general European population and implicates vitamin D in the etiology of multiple sclerosis.


BACKGROUND: Community paediatricians’ knowledge of appropriate child safety seat (CSS) use in vehicles may be inadequate. We compared the effectiveness of hands-on and online education in improving and retaining child passenger safety (CPS) knowledge and skills among paediatric trainees. METHODS: Paediatric trainees were randomised to receive hands-on skills training versus a 1-hour online module in CPS. CSS knowledge and installation skills were assessed using a validated 10-item/point questionnaire and an assessment tool respectively at baseline and after 6 months. Preintervention and postintervention knowledge improvement and CSS installation skills between groups were assessed using paired t-tests and effect size (d). RESULTS: Forty-eight students agreed to participate and were randomised. Thirty-nine completed training (hands-on: 23 and online: 15). At entry, no significant differences in learners’ demographics and prior CPS education existed. Baseline CPS knowledge scores did not differ significantly between groups (p=0.26). Postintervention, both groups demonstrated a significant increase in knowledge scores (hands-on=3.1 (95% CI 2.4 to 3.7), p<0.0001; online=2.6 (95% CI 1.9 to 3.3), p<0.0001), though the pre-post gain in knowledge scores were not significantly different between groups (p=0.35). At follow-up, both groups demonstrated a
significant increase in knowledge scores (hands-on=1.8 (95% CI 1.2 to 2.4), p<0.0001; online=1.1 (95% CI 0.7 to 1.6), p<0.0001) with the hands-on group scores significantly better than the online group (p<0.02). The long-term gain in knowledge scores was not significantly different between groups (p=0.12). Baseline CSS installation skill scores did not significantly differ between groups for forward-facing seats (p=0.16) and rear-facing seats (p=0.51). At follow-up, mean CSS installation skill scores significantly increased for the hands-on group (forward-facing seat: 0.8 (95% CI 0.16 to 1.44), p<0.02; rear-facing seat: 1.2 (95% CI 0.6 to 1.7), p<0.001) but not for the online group (forward-facing seat: 0.9 (95% CI -0.08 to 1.9), p=0.07; rear-facing seat: 0.2 (95% CI -1.1 to 0.7), p=0.6). CONCLUSIONS: Among paediatric trainees, hands-on and online CPS education are both effective in improving long-term CPS knowledge. Long-term installation skills for forward-facing and rear-facing CSS persist for hands-on education but are inconclusive for online education.


BACKGROUND: Back pain and falls are common health conditions among older U.S. women. The extent to which back pain is an independent risk factor for falls has not been established. METHODS: We conducted a prospective study among 6,841 community-dwelling U.S. women at least 65 years of age from the Study of Osteoporotic Fractures (SOF). Baseline questionnaires inquired about any back pain, pain severity, and frequency in the past year. During 1 year of follow-up, falls were summed from self-reports obtained every 4 months. Two outcomes were studied: recurrent falls (>/>=2 falls) and any fall (>/>=1 fall). Associations of back pain and each fall outcome were estimated with risk ratios (RRs) and 95% confidence intervals (CIs) from multivariable log-binomial regression. Adjustments were made for age, education, smoking status, fainting history, hip pain, stroke history, vertebral fracture, and Geriatric Depression Scale. RESULTS: Most (61%) women reported any back pain. During follow-up, 10% had recurrent falls and 26% fell at least once. Any back pain relative to no back pain was associated with a 50% increased risk of recurrent falls (multivariable RR = 1.5, 95% CI: 1.3, 1.8). Multivariable RRs for recurrent falls were significantly elevated for all back pain symptoms, ranging from 1.4 (95% CI: 1.1, 1.8) for mild back pain to 1.8 (95% CI: 1.4, 2.3) for activity-limiting back pain. RRs of any fall were also significantly increased albeit smaller than those for recurrent falls. CONCLUSIONS: Older community-dwelling women with a recent history of back pain are at increased risk for falls.


OBJECTIVE: To measure variation among four different Electronic Health Record (EHR) system documentation locations versus ‘gold standard’ manual chart review for risk stratification in patients with multiple chronic illnesses. METHODS: Adults seen in primary care with EHR evidence of at least one of 13 conditions were included. EHRs were manually reviewed to determine presence of active diagnoses, and risk scores were calculated using three different methodologies and five EHR documentation locations. Claims data were used to assess cost and utilization for the following year. Descriptive and diagnostic statistics were calculated for each EHR location. Criterion validity testing compared the gold standard verified diagnoses versus other EHR locations and risk scores in predicting future cost and utilization. RESULTS: Nine hundred patients had 2,179 probable diagnoses. About 70% of the diagnoses from the EHR were verified by gold standard. For a subset of patients having baseline and prediction year data (n=750), modeling showed that the gold standard was the best predictor of outcomes on average for a subset of patients that had these data. However, combining all data sources together had nearly equivalent performance for prediction as the gold standard. CONCLUSIONS: EHR data locations were inaccurate 30% of the time, leading to improvement in overall modeling from a gold standard from chart review for individual diagnoses. However, the impact on identification of the highest risk patients was minor, and combining data from different EHR locations was
equivalent to gold standard performance. The reviewer’s ability to identify a diagnosis as correct was influenced by a variety of factors, including completeness, temporality, and perceived accuracy of chart data.


Evaluating protein kinetics in the critically ill population remains a very difficult task. Heterogeneity in the intensive care unit (ICU) population and wide spectrum of disease processes creates complexity in assessing protein kinetics. Traditionally, protein has been delivered in the context of total energy. Focus on energy delivery has recently come into question, as the importance of supplemental protein in patient outcomes has been shown in several recent trials. The ICU patient is prone to catabolism, immobilization, and impaired immunity, which is a perfect storm for massive loss of lean body tissue with a unidirectional flow of amino acids from muscle to immune tissue for immunoglobulin production, as well as liver for gluconeogenesis and acute phase protein synthesis. The understanding of protein metabolism in the ICU has been recently expanded with the discovery of how the mammalian target of rapamycin complex 1 is regulated. The concept of “anabolic resistance” and identifying the quantity of protein required to overcome this resistance is gaining support among critical care nutrition circles. It appears that a minimum of at least 1.2 g/kg/d with levels up to 2.0 g/kg/d of protein or amino acids appears safe for delivery in the ICU setting and may yield a better clinical outcome.


Objective The purpose of this study was to characterize the mechanisms of Günther Tulip filter (GTF) tilting during transfemoral placement in an experimental model with further validation in a clinical series. Materials and methods In an experimental study, 120 GTF placements in an inferior vena cava (IVC) model were performed using 6 configurations of pre-deployment filter position. The angle between the pre-deployment filter axis and IVC axis, and the proximity of the constrained filter legs to IVC wall prior to deployment were evaluated. The association of those pre-deployment factors with post-deployment filter tilting was analyzed. The association noted in the experimental study was then evaluated in a retrospective clinical series of 21 patients. Results In the experimental study, there was a significant association between the pre-deployment angle and post-deployment filter tilting (P < 0.0001). With a low pre-deployment angle (≤ 5°), a significant association was noted between filter tilting and the proximity of the constrained filter legs to the far IVC wall (P = 0.001). In a retrospective clinical study, a significant association between the pre-deployment angle and post-deployment filter tilting was also noted with a linear regression model (P = 0.026). Conclusion Significant association of the pre-deployment angle with post-deployment GTF tilting was shown in both the experimental and clinical studies. The experimental study also showed that proximity of filter legs is relevant when pre-deployment angle is small. Addressing these factors may result in a lower incidence of filter tilting. © 2017 Editions françaises de radiologie


BACKGROUND AND OBJECTIVES: To examine association of lympho-vascular space invasion (LVI SI) with clinicopathological factors and to evaluate survival of women with low-grade serous ovarian carcinoma containing areas of LVI SI. METHODS: This is a multicenter retrospective study examining consecutive cases of surgically treated stage I-IV low-grade serous ovarian carcinoma (n = 178). Archived histopathology slides for the ovarian tumors were reviewed, and LVI SI was scored as present or absent. LVI SI status was correlated to
clinico-pathological findings and survival outcome. RESULTS: LVSI was seen in 79 cases (44.4%, 95% confidence interval [CI] 37.1-51.7). LVSI was associated with increased risk of omental metastasis (87.0% vs 64.9%, odds ratio [OR] 3.62, P = 0.001), high pelvic lymph node ratio (median 12.9% vs 0%, P = 0.012), and malignant ascites (49.3% vs 32.6%, OR 2.01, P = 0.035). On multivariable analysis, controlling for age, stage, and cytoreductive status, presence of LVSI in the ovarian tumor remained an independent predictor for decreased progression-free survival (5-year rates 21.0% vs 35.7%, adjusted-hazard ratio 1.57, 95%CI 1.06-2.34, P = 0.026). LVSI was significantly associated with increased risk of recurrence in lymph nodes (OR 2.62, 95%CI 1.08-6.35, P = 0.047). CONCLUSION: LVSI in the ovarian tumor is associated with adverse clinico-pathological characteristics and decreased progression-free survival in women with low-grade serous ovarian carcinoma.


Objective: Community-academic relationships characterized by collaboration can contribute to the preparation of public health nursing students, sustainability of partnerships over time, and innovative solutions to pressing health problems. The purpose of this study was to describe and understand relationship characteristics in a community-academic partnership over time and how the relationship could be improved. Design and Sample: A descriptive case study was conducted. Study participants included partnership staff, organizational leaders, community residents, and student nurses involved in the partnership between 2011 and 2015. Measures: Methods included focus groups, documents, interviews, and surveys. Results: Four main themes emerged and include analysis findings that capture the relationship characteristics between partners and how the relationship could be improved: Time, Communication, Goals, and Sharing. Conclusions: Findings on how to improve relationship characteristics offer clear suggestions for academic and community partners on ways to move toward collaborative partnerships that can address health inequities and develop a competent and advanced public health nursing workforce in the 21st century. © 2017 Wiley Periodicals, Inc.


The gut has a major influence on the course of the human stress response in critical illness for several reasons; the quantity of its immune tissue, the extent of interface with the external environment, the expanse of the microbiome, and its access to the systemic circulation. In critical illness, it is not uncommon to lose mucosal barrier function, which exposes the host to the downside effects of luminal contents and epithelial cell regulation. In that setting, the microbiome is converted to a pathobiome, upregulation of metabolic and immune responses occurs, and homeostatic defense systems are compromised. Awareness of this process mandates that greater attention be given to the interplay between the gut and systemic responses, and that modulation of the gastrointestinal tract be considered in every therapeutic intervention in the critical care setting.


INTRODUCTION: Medically refractory tremor treatment has evolved over the past half-century from intraoperative thalamotomy to deep brain stimulation (DBS) of the thalamic ventral intermediate nucleus (VIM). Within the past 15years, unilateral radiosurgical VIM thalamotomy has emerged as a comparably efficacious treatment modality. METHODS: An extensive literature search of VIM DBS series was performed; the total cost of VIM DBS was calculated from hospitals geographically representative of the entire United States using current procedural terminology and work relative value unit (RVU) codes. The 2016 Medicare Ambulatory Payment Classification for stereotactic radiosurgery (SRS) was added to the work RVU to determine the total cost of
VIM SRS for both Gamma Knife and linear accelerator SRS. Cost estimates assumed that VIM DBS was performed without intraoperative microelectrode recording. RESULT: The mean unilateral VIM DBS cost was $17,932.41 per patient. For SRS VIM, the total costs for Gamma Knife ($10,811.77) and linear accelerator ($10,726.40) were 40% less expensive than for unilateral VIM DBS. CONCLUSION: Radiosurgery of the VIM is 40% less expensive than unilateral VIM DBS in treatment of medically refractory tremor, regardless of radiosurgical modality. This finding argues for increased radiation oncology involvement in the management of medically refractory tremor patients.


Context Primary Sjögren syndrome is uncommon in children, and the standard clinical criteria used in diagnosis of adult Sjögren syndrome will miss many children with the disease. Floor of mouth ranulas have not been described in Sjögren syndrome. Objective This study aims to describe a novel presentation of juvenile primary Sjögren syndrome, and to present a comprehensive systematic review of the literature regarding the presentation and diagnosis of Sjögren syndrome in children. Data sources Ovid MEDLINE. Study selection A MEDLINE literature search was performed using the following search terms: primary, Sjögren, disease, and children. Results were limited to human subjects and articles written in English between 1981 and 2014. Applicable articles were reviewed and qualitatively summarized. Data extraction Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRIMA). Results Initial MEDLINE search yielded 146 articles, 80 of which were excluded as not clinically pertaining to Sjögren syndrome. An additional 25 were excluded due to lack of pediatric-specific data. Systematic review of the literature revealed no reports of ranula in association with Sjögren syndrome. 6 papers were manually included from review of reference lists of included articles. Our review indicated that recurrent parotitis is the most commonly reported presenting symptom in children, followed by ocular and oral symptoms, musculoskeletal, and renal symptoms. Compared to adults, children are less likely to present with dry eyes and mouth. Limitations All studies were retrospective chart reviews, case series or case reports. Conclusion This is the first report of a child presenting with floor of mouth ranulas in association with Sjögren syndrome. While recurrent parotitis is the most common presentation in children, other salivary gland and extra-salivary manifestations may be seen, and the clinician must maintain a high index of suspicion for underlying Sjögren syndrome. © 2017 Elsevier B.V.


Stat5a is a transcription factor utilized by several cytokine/hormone receptor signaling pathways that promotes transcription of genes associated with proliferation, differentiation, and survival of cancer cells. However, there are currently no clinically approved therapies that directly target Stat5a, despite ample evidence that it contributes to breast cancer pathogenesis. Here, deacetylation of the Stat5a coactivator and chromatin-remodeling protein HMGN2 on lysine residue K2 by HDAC6 promotes Stat5a-mediated transcription and
breast cancer growth. HDAC6 inhibition both in vitro and in vivo enhances HMGN2 acetylation with a concomitant reduction in Stat5a-mediated signaling, resulting in an inhibition of breast cancer growth. Furthermore, HMGN2 is highly acetylated at K2 in normal human breast tissue, but is deacetylated in primary breast tumors and lymph node metastases, suggesting that targeting HMGN2 deacetylation is a viable treatment for breast cancer. Together, these results reveal a novel mechanism by which HDAC6 activity promotes the transcription of Stat5a target genes and demonstrate utility of HDAC6 inhibition for breast cancer therapy. 

IMPLICATIONS: HMGN2 deacetylation enhances Stat5a transcriptional activity, thereby regulating prolactin-induced gene transcription and breast cancer growth. Mol Cancer Res; 14(10); 994-1008. (c)2016 AACR.


The blood-brain barrier (BBB) can be a substantial impediment to achieving therapeutic levels of drugs in the CNS. Certain chemical functionality such as the carboxylic acid is a general liability for BBB permeability preventing significant CNS distribution of a drug from a systemic dose. Here, we report a strategy for CNS-selective distribution of the carboxylic acid containing thyromimetic sobetirome using prodrugs targeted to fatty-acid amide hydrolase (FAAH), which is expressed in the brain. Two amide prodrugs of sobetirome were shown to be efficient substrates of FAAH with Vmax/KM values comparable to the natural endocannabinoid FAAH substrate anandamide. In mice, a systemic dose of sobetirome prodru leads to a substantial approximately 60-fold increase in brain distribution (Kp) of sobetirome compared to an equimolar systemic dose of the parent drug. The increased delivery of sobetirome to the brain from the prodru was diminished by both pharmacological inhibition and genetic deletion of FAAH in vivo. The increased brain exposure of sobetirome arising from the prodrug corresponds to approximately 30-fold increased potency in brain target engagement compared to the parent drug. These results suggest that FAAH-targeted prodrugs can considerably increase drug exposure to the CNS with a concomitant decrease in systemic drug levels generating a desirable distribution profile for CNS acting drugs.


LINE-Alu-VNTR-Alu-like (LAVA) elements comprise a family of non-autonomous, composite, non-LTR retrotransposons specific to gibbons and may have played a role in the evolution of this lineage. A full-length LAVA element consists of portions of repeats found in most primate genomes: CT-rich, Alu-like, and VNTR regions from the SVA retrotransposon, and portions of the AluSz and L1ME5 elements. To evaluate whether the gibbon genome currently harbors functional LAVA elements capable of mobilization by the endogenous LINE-1 (L1) protein machinery and which LAVA components are important for retrotransposition, we established a trans-mobilization assay in HeLa cells. Specifically, we tested if a full-length member of the older LAVA subfamily C that was isolated from the gibbon genome and named LAVAC, or its components, can be mobilized in the presence of the human L1 protein machinery. We show that L1 proteins mobilize the LAVAC element at frequencies exceeding processed pseudogene formation and human SVAE retrotransposition by > 100-fold and >=/=3-fold, respectively. We find that only the SVA-derived portions confer activity, and truncation of the 3' L1ME5 portion increases retrotransposition rates by at least 100%. Tagged de novo insertions integrated into intronic regions in cell culture, recapitulating findings in the gibbon genome. Finally, we present alternative models for the rise of the LAVA retrotransposon in the gibbon lineage.

**PURPOSE:** To investigate the impact of the Orthopaedic Surgery and Sports Medicine Interest Group (OSSMIG) on medical student interest and confidence in core musculoskeletal (MSK) concepts through supplemental education and experiences at a single tertiary, academic institution. **METHODS:** Medical student OSSMIG members at various levels of training were anonymously surveyed at the beginning and end of the 2014-2015 academic year. **RESULTS:** Eighteen (N=18) medical student interest group members completed the survey. Significant improvement in their level of training was observed with regard to respondents’ self-assessed competence and confidence in MSK medicine (p<0.05). Additionally, respondents’ attitudes toward exposure and support from the interest group were significantly higher than those provided by the institution (p<0.05). Members believed OSSMIG increased interest in MSK medicine, improved confidence in their ability to perform orthopedics-related physical exams, strengthened mentorship with residents and attendings, and developed a connection with the Department of Orthopedic Surgery and its residents (median “Strongly Agree,” interquartile range one and two scale items). **CONCLUSION:** Since its inception 8 years ago, OSSMIG has been well received and has positively impacted University of Washington School of Medicine students through various interventions. Surgical interest groups should target both the students interested in primary care and surgery. Medical schools can provide additional exposure to MSK medicine by leveraging interest groups that provide early clinical experiences and supplementary instruction.


Follicular regulatory T (TFR) cells are a subset of CD4+ T cells in secondary lymphoid follicles. TFR cells were previously included in the follicular helper T (TFH) cell subset, which consists of cells that are highly permissive to HIV-1. The permissivity of TFR cells to HIV-1 is unknown. We find that TFR cells are more permissive than TFH cells to R5-tropic HIV-1 ex vivo. TFR cells expressed more CCR5 and CD4 and supported higher frequencies of viral fusion. Differences in Ki67 expression correlated with HIV-1 replication. Inhibiting cellular proliferation reduced Ki67 expression and HIV-1 replication. Lymph node cells from untreated HIV-infected individuals revealed that TFR cells harbored the highest concentrations of HIV-1 RNA and highest levels of Ki67 expression. These data demonstrate that TFR cells are highly permissive to R5-tropic HIV-1 both ex vivo and in vivo. This is likely related to elevated CCR5 levels combined with a heightened proliferative state and suggests that TFR cells contribute to persistent R5-tropic HIV-1 replication in vivo. © 2017 American Society for Microbiology.


Reduced heart rate recovery (HRR) after exercise is associated with increased mortality in cardiac and pulmonary diseases. We sought to evaluate the association between HRR after the 6-minute walk test (6MWT) and outcomes in patients with connective tissue disease-associated pulmonary hypertension (CTD-PH). Data were obtained by review of the medical records. HRR was defined as the difference in heart rate at the end of the 6MWT and after 1 minute (HRR1), 2 minutes (HRR2), and 3 minutes (HRR3) of rest. All patients with pulmonary hypertension and a diagnosis of systemic sclerosis, systemic lupus erythematosus, or mixed connective tissue disease who underwent the 6MWT between August 1, 2009, and October 30, 2011, were included (n = 66). By Kaplan-Meier analysis, HRR1, HRR2, and HRR3 at different cutoff points were all good predictors, with HRR1 of <16 being the best predictor of time to clinical worsening (log-rank P < 0.0001), hospitalization (log-rank P = 0.0001), and survival (log-rank P < 0.003). By proportional hazards regression, patients with HRR1 of <16 were at increased risk of clinical worsening (hazard ratio [HR]: 6.4 [95% confidence interval (CI): 2.6-19.2]; P < 0.0001), hospitalization (HR: 6.6 [95% CI: 2.4-23]; P < 0.0001), and
death (HR: 4.5 [95% CI: 1.6-15.7]; P = 0.003). Patients in the highest tercile (HRR1 of >19) were unlikely to have a clinical worsening event (HR: 0.1 [95% CI: 0.04-0.5]; P = 0.001), to be hospitalized (HR: 0.1 [95% CI: 0.02-0.5]; P = 0.001), or to die (HR: 0.3 [95% CI: 0.07-0.9]; P = 0.04). In conclusion, in patients with CTD-PH, abnormal HRR1 (defined as HRR1 of <16) after the 6MWT is a strong predictor of clinical worsening, survival, and hospitalization. © 2015 by the Pulmonary Vascular Research Institute. All rights reserved.


The transcription factor CREB (cAMP Response-Element Binding Protein) is overexpressed in the majority of acute myeloid leukemia (AML) patients, and this is associated with a worse prognosis. Previous work revealed that CREB overexpression augmented AML cell growth, while CREB knockdown disrupted key AML cell functions in vitro. In contrast, CREB knockdown had no effect on long-term hematopoietic stem cell activity in mouse transduction/transplantation assays. Together, these studies position CREB as a promising drug target for AML. To test this concept, a small molecule inhibitor of CREB, XX-650-23, was developed. This molecule blocks a critical interaction between CREB and its required co-activator CBP (CREB Binding Protein), leading to disruption of CREB-driven gene expression. Inhibition of CBP-CREB interaction induced apoptosis and cell-cycle arrest in AML cells, and prolonged survival in vivo in mice injected with human AML cells. XX-650-23 had little toxicity on normal human hematopoietic cells and tissues in mice. To understand the mechanism of XX-650-23, we performed RNA-seq, ChIP-seq and Cytometry Time of Flight with human AML cells. Our results demonstrate that small molecule inhibition of CBP-CREB interaction mostly affects apoptotic, cell-cycle and survival pathways, which may represent a novel approach for AML therapy.


Despite tremendous advances in critical care, multiple-organ failure continues to be a significant problem. However, in recent years, far fewer patients with multiple-organ failure die early, but many experience ongoing immune dysregulation and are developing persistent inflammation, immunosuppression, and catabolism syndrome (PICS). Most PICS patients are discharged to nonhome destinations, fail to rehabilitate, and succumb to indolent death. From a nutrition perspective, patients with PICS experience persistent inflammation-induced cachexia despite evidenced-based recommended intensive care unit nutrition support. Recent basic and translational research indicates that prolonged expansion of myeloid-derived suppressor cells plays a central role in the pathogenesis of PICS. Myeloid-derived suppressor cells express arginase 1, which depletes arginine, causing immunosuppression and impaired wound healing. This is the rationale for arginine supplementation in PICS. Other nutrition support recommendations for PICS are based on inferences made from other patient populations who experience similar persistent inflammation-induced cachexia. These include patients with established cancers, major burns, and sarcopenia. These patients experience anabolic resistance, but studies show that this can be overcome by providing higher levels of protein and certain specific amino acids. Nutrition support guidelines recommend provision of >1.5 g/kg/d of protein and indicate that higher levels may be needed. Protein composition is also important. There is good evidence that leucine can promote anabolism in patients with cancer and sarcopenia. Finally, anabolic interventions-including intensive insulin, oxandrolone, propranolol, and resistance exercise-have proven to be effective in patients with major burns and are likely relevant in combating PICS cachexia.

The central nucleus of the inferior colliculus (ICC) of the auditory midbrain integrates the majority of ascending auditory information from lower brainstem regions. It receives prominent long-range inhibitory input from the ventral nucleus of the lateral lemniscus (VNLL), a region thought to be important for temporal pattern discrimination. Histological evidence suggests that neurons in the VNLL release both glycine and GABA in the ICC, but functional evidence for their co-release is lacking. We took advantage of the GlyT2-Cre mouse line (both male and female) to target expression of ChR2 to glycinergic afferents in the ICC and made whole-cell recordings in vitro while exciting glycinergic fibers with light. Using this approach it was clear that a significant fraction of glycinergic boutons co-release GABA in ICC. Viral injections were used to target ChR2 expression specifically to glycinergic fibers ascending from the VNLL, allowing for activation of fibers from a single source of ascending input in a way that has not been previously possible in ICC. We then investigated aspects of the glycinergic versus GABAergic current components to probe functional consequences of co-release. Surprisingly, the time course and short-term plasticity of synaptic signaling were nearly identical for the two transmitters. We therefore conclude that the two neurotransmitters may be functionally interchangeable and that multiple receptor subtypes subserving inhibition may offer diverse mechanisms whereby inhibitory homeostasis is maintained.

**SIGNIFICANCE STATEMENT**

Co-release of neurotransmitters is a common feature of the brain. GABA and glycine co-release is particularly common in the spinal cord and brainstem, but its presence in the midbrain is unknown. We show co-release of GABA and glycine for the first time in the central nucleus of the inferior colliculus of the auditory midbrain. Glycine and GABA are both inhibitory neurotransmitters involved in fast synaptic transmission, so we explored differences between the currents to establish a physiological foundation for functional differences in vivo. In contrast to the auditory brainstem, co-released GABAergic and glycinergic currents in midbrain are strikingly similar. This apparent redundancy may ensure homeostasis if one neurotransmitter system is compromised.


Red patches and plaques of the vulva may be manifestations of neoplasms, infections, or inflammatory skin diseases. These diseases can mimic one another clinically; features that generally allow the diseases to be identified on most cutaneous surfaces can be altered in the moist, occluded vulvar environment, making clinical diagnosis difficult. A detailed history and thorough physical examination can point to the likely diagnosis, but biopsy and culture may be needed for diagnosis especially in refractory disease. It is not uncommon for several of these processes to be present concomitantly or complicating other vulvar diseases.


The treatment of epilepsy in older individuals is an increasingly important topic in neurology and an area that all treating neurologists should have familiarity with. As the population ages, the number of patients over 65 who present with new-onset epilepsy will increase, as will the complexity of their comorbid medical and neurological disorders. In older patients, seizures are often unreported, or present with atypical symptoms, making the diagnosis more challenging. Additionally, there are relatively limited data to guide the use of
anti-epileptic medications and other treatments in this patient population. Elderly patients may experience increased side effects from anti-epileptic drugs compared with younger patients and in general, are likely to have a narrower therapeutic window and greater degree of individual variation with respect to side effects. Familiarity with anti-epileptic medication dosing and titration schedules, possible adverse effects, and potential pharmacokinetic and drug interactions can be helpful when considering treatment options and may increase the likelihood of success.


BACKGROUND AND PURPOSE: Mechanical thrombectomy with stent retrievers has become standard of care for treatment of acute ischemic stroke patients because of large vessel occlusion. The STRATIS registry (Systematic Evaluation of Patients Treated With Neurothrombectomy Devices for Acute Ischemic Stroke) aimed to assess whether similar process timelines, technical, and functional outcomes could be achieved in a large real world cohort as in the randomized trials. METHODS: STRATIS was designed to prospectively enroll patients treated in the United States with a Solitaire Revascularization Device and Mindframe Capture Low Profile Revascularization Device within 8 hours from symptom onset. The STRATIS cohort was compared with the interventional cohort of a previously published SEER patient-level meta-analysis. RESULTS: A total of 984 patients treated at 55 sites were analyzed. The mean National Institutes of Health Stroke Scale score was 17.3. Intravenous tissue-type plasminogen activator was administered in 64.0%. The median time from onset to arrival in the enrolling hospital, door to puncture, and puncture to reperfusion were 138, 72, and 36 minutes, respectively. The Core lab-adjudicated modified Thrombolysis in Cerebral Infarction >/=2b was achieved in 87.9% of patients. At 90 days, 56.5% achieved a modified Rankin Scale score of 0 to 2, all-cause mortality was 14.4%, and 1.4% suffered a symptomatic intracranial hemorrhage. The median time from emergency medical services scene arrival to puncture was 152 minutes, and each hour delay in this interval was associated with a 5.5% absolute decline in the likelihood of achieving modified Rankin Scale score 0 to 2. CONCLUSIONS: This largest-to-date Solitaire registry documents that the results of the randomized trials can be reproduced in the community. The decrease of clinical benefit over time warrants optimization of the system of care. CLINICAL TRIAL REGISTRATION: URL: http://www.clinicaltrials.gov. Unique identifier: NCT02239640.


Cost and availability of a database often impede research while the lack of compatibility inhibits collaboration by making merging of databases difficult or impossible. The Global Pregnancy Collaboration (CoLab) has promoted harmonization of studies and standardized data collection to facilitate pregnancy and placental research. Its online database, COLLECT, allows collection of minimal and optimal clinical datasets to accompany basic and applied science studies and provides a placental sample inventory system. COLLECT is available free of charge in LMIC and for $100 per month in HIC. Data is the property of the investigator but with permission can be combined into larger studies across centers and countries. © 2017 The Authors


PURPOSE: Corneal sensation, cell proliferation, and wound healing all depend on adequate corneal innervation. Disruption of corneal innervation can lead to dry eye and delayed wound healing. Our studies in rats and rabbits show that the substituted fluorobenzamide drug FK962 accelerates the extension of neuronal processes and recovery of corneal sensitivity. The purpose of the present study was 1) to determine whether
FK962 induces sprouting and elongation of neurites in cultured monkey trigeminal ganglion cells, and 2) to investigate the involvement of the neurotrophic peptide GDNF in FK962-induced neurite elongation.

**METHODS:** Dissociated, cultured trigeminal ganglion cells, containing neuronal and Schwann cells were cultured for 48 h with or without FK962. Neuronal elongation was evaluated by immunostaining with a neurofilament-specific antibody. Culture with or without GDNF, or with antibody against GDNF, was used to determine the role of GDNF in FK962-induced neurite elongation. **RESULTS:** FK962 or GDNF were found to significantly induce neurite elongation. The GDNF antibody significantly inhibited elongation induced by FK962. **CONCLUSION:** GDNF was found to be a mediator of FK962-induced neurite elongation in a relevant primate model. FK962 may be a candidate drug for treatment of neurotrophic disorders in the human cornea.


**OBJECTIVES:** Most ultrasound-guided regional procedures use an in-plane approach. Out-of-plane approaches may be desirable in some situations but can be difficult because of an inability to visualize the needle until it intersects the plane of the ultrasonic beam. Here we present a novel out-of-plane needle guide, using a retreating depth stop, and compare its performance with unguided in-plane and out-of-plane techniques. **METHODS:** First- and third-year medical students with no or minimal ultrasound experience were recruited for the study. After a brief training session on in-plane and out-of-plane needling techniques, as well as use of the retreating-stop needle guide, they attempted to place a needle as close as possible to a target embedded in porcine tissue. The total time to complete the procedure was measured. Accuracy was measured by a skilled sonographer, who identified the needle tip and measured the distance to the target. The data were tested for significance using an analysis of variance. **RESULTS:** The mean total time spent differed significantly between groups (novel needle guide, 34 seconds; in-plane, 120 seconds; out-of-plane, 113 seconds; P = .021). Needle proximity was on average more accurate with the needle guide, although this difference was not statistically significant (novel needle guide, 8 mm; in-plane, 15 mm; out-of-plane, 14 mm; P = .289). **CONCLUSIONS:** In relatively inexperienced sonographers, the retreating-stop needle guide reduced the procedure time compared with in-plane and out-of-plane techniques. No significant changes in needling accuracy were observed.


**OBJECTIVE:** An increasing number of studies have been conducted to look at anxiety and depression in IBD; however, there is no clear consensus on the prevalence of anxiety and depression in this population. The objective of this systematic review was to compile the existing data on the prevalence of all mood and anxiety disorders in Inflammatory Bowel Disease patients. **METHODS:** A series of comprehensive literature searches of Medline, Cochrane Library, PsycINFO, CINAHL, Embase, AMED, and ProQuest Dissertations were performed through March 2014. Inclusion criteria included peer-reviewed, published scientific articles that reported a measurement of mood or anxiety among IBD patients. Only studies with adults (> /=18 years old) and with more than 10 patients were included. Methodological quality was assessed for all included studies. **RESULTS:** 171 articles were identified with a total of 158,371 participants. Pooled prevalence estimate for anxiety disorders was 20.5% [4.9%, 36.5%] and 35.1% [30.5, 39.7%] for symptoms of anxiety. IBD patients in active disease had higher prevalence of anxiety of 75.6% [65.5, 85.7%] compared to disease remission. Pooled prevalence of depression disorders was 15.2% [9.9%, 20.5%] and was 21.6% [18.7, 24.3%] for symptoms of depression. The prevalence of depressive symptoms was higher in Crohn's disease (25.3% [20.7%, 30.0%]) compared to UC, and higher with active disease (40.7% [31.1%, 50.3%]) compared to IBD patients in remission. **CONCLUSION:** Results from this systematic review indicate that patients with IBD have about a 20% prevalence rate of anxiety and a 15% prevalence rate of depression.

Objective: The objective was to conduct a pilot randomized controlled trial to assess the feasibility, logistics, and potential effect of monthly provider funnel plot feedback reports from Press Ganey data and semiannual face-to-face coaching sessions to improve patient satisfaction scores. Methods: This was a pilot randomized controlled trial of 25 emergency medicine faculty providers in one urban academic emergency department. We enrolled full-time clinical faculty with at least 12 months of baseline Press Ganey data, who anticipated working in the ED for at least 12 additional months. Providers were randomized into intervention or control groups in a 1:1 ratio. The intervention group had an initial 20-minute meeting to introduce the funnel plot feedback tool and standardized feedback based on their baseline Press Ganey scores and then received a monthly e-mail with their individualized funnel plot depicting cumulative Press Ganey scores (compared to their baseline score and the mean score of all providers) for 12 months. The primary outcome was the difference in Press Ganey “doctor-overall” scores between treatment groups at 12 months. We used a weighted analysis of covariance model to analyze the study groups, accounting for variation in the number of surveys by provider and baseline scores. Results: Of 36 eligible faculty, we enrolled 25 providers, 13 of whom were randomized to the intervention group and 12 to the control group. During the study period, there were 815 Press Ganey surveys returned, ranging from four to 71 surveys per provider. For the standardized overall doctor score over 12 months (primary outcome), there was no difference between the intervention and control groups (difference = 1.3 points, 95% confidence interval = -2.4 to 5.9, p = 0.47). Similarly, there was no difference between groups when evaluating the four categories of doctor-specific patient satisfaction scores from the Press Ganey survey (all p > 0.05). Conclusions: In this pilot trial of monthly provider funnel plot Press Ganey feedback reports, there was no difference in patient satisfaction scores between the intervention and control groups after 12 months. While this study was not powered to detect outcome differences, we demonstrate the feasibility, logistics, and effect sizes that could be used to inform future definitive trials. © 2017 Society for Academic Emergency Medicine.


BACKGROUND: Atrial fibrillation and heart failure are 2 of the most common diseases, yet ready means to identify individuals at risk are lacking. The 12-lead ECG is one of the most accessible tests in medicine. Our objective was to determine whether a premature atrial contraction observed on a standard 12-lead ECG would predict atrial fibrillation and mortality and whether a premature ventricular contraction would predict heart failure and mortality. METHODS AND RESULTS: We utilized the CHS (Cardiovascular Health) Study, which followed 5577 participants for a median of 12 years, as the primary cohort. The ARIC (Atherosclerosis Risk in Communities Study), the replication cohort, captured data from 15 792 participants over a median of 22 years. In the CHS, multivariable analyses revealed that a baseline 12-lead ECG premature atrial contraction predicted a 60% increased risk of atrial fibrillation (hazard ratio, 1.6; 95% CI, 1.3-2.0; P<0.001) and a premature ventricular contraction predicted a 30% increased risk of heart failure (hazard ratio, 1.3; 95% CI, 1.0-1.6; P=0.021). In the negative control analyses, neither predicted incident myocardial infarction. A premature atrial contraction was associated with a 30% increased risk of death (hazard ratio, 1.3; 95% CI, 1.1-1.5; P=0.008) and a premature ventricular contraction was associated with a 20% increased risk of death (hazard ratio, 1.2; 95% CI, 1.0-1.3; P=0.044). Similarly statistically significant results for each analysis were also observed in ARIC. CONCLUSIONS: Based on a single standard ECG, a premature atrial contraction predicted
incident atrial fibrillation and death and a premature ventricular contraction predicted incident heart failure and death, suggesting that this commonly used test may predict future disease.


PURPOSE/OBJECTIVES: To determine the feasibility and acceptability of an intervention with targeted cultural and health belief messages to increase rates of mammography among Vietnamese American (VA) immigrant women. . DESIGN: One-group, pre-/post-test, pilot, quasiexperimental design. . SETTING: Portland, Oregon, metropolitan area. . SAMPLE: 40 VA immigrant women aged 50 years or older. . METHODS: Participants who had not had a mammogram within the past 12 months were recruited. The intervention consisted of one interactive group teaching session, followed by individual counseling delivered about 10 days later to overcome barriers to screening. Participants completed a baseline survey prior to the group teaching and again at 12 weeks after the session. . MAIN RESEARCH VARIABLES: The intervention, guided by the Transtheoretical Model of Change and the Health Belief Model, involved movement in stage of change based on women’s readiness, as well as perceived susceptibility, perceived benefits, perceived common barriers, and perceived cultural barriers. Mammogram completion and knowledge of breast cancer and mammography were examined. . FINDINGS: The recruitment response rate was 58%. Knowledge about breast cancer, breast cancer susceptibility, and the benefits of mammography as related to breast cancer significantly increased following the intervention. . CONCLUSIONS: Acceptability of the targeted program, good feasibility, and very low attrition was achieved. . IMPLICATIONS FOR NURSING: This intervention can be adapted for other populations, including other Asian groups, and other cancer screenings.


Background: Vietnamese women are diagnosed with cervical cancer at twice the rate of non-Hispanic White women and the highest compared to Chinese, Filipino, Korean, and Japanese women. The Vietnamese Women’s Health Project, a community-based participatory research partnership, was developed to address this concern. In earlier studies, community members received research training. Objectives: To describe how we developed an innovative curricular research training framework. Community members developed their own learning goals and activities, taught alongside a nurse scientist, and participated in a community interactive research workshop series. Methods: Popular education principles were used to guide team teaching. Topics, learning goals, lesson plans, and an evaluation were developed together. Three, 4-5.5 hour workshops were hosted. Topics included qualitative research, art of hearing data, reflexivity, analysis, validity, and dissemination. Community members and a nurse scientist co-constructed knowledge through participatory methods. The workshops ran concurrent to the study timeline to inform community members’ research activities and vice versa. A range from 8 to 20 participants attended the workshops, of which six community members were team teachers and three facilitated at each workshop. In an evaluation, team teachers reported workshop strengths: an empathetic and trusting learning environment, a sense of ownership in learning, a greater understanding of roles in research partnerships, and a feeling of safety to conduct research with academic investigators. Conclusions: Academic investigators need to be aware that co-constructing knowledge is foundational to long-term sustainability of community-based participatory research partnership (CBPR) partnerships, but requires building team capacity to conduct research collaboratively. © 2017 Johns Hopkins University Press.

Cognitive impairments, uncontrolled drinking, and neuropathological cortical changes characterize alcohol use disorder. Dysfunction of the orbitofrontal cortex (OFC), a critical cortical subregion that controls learning, decision-making, and prediction of reward outcomes, contributes to executive cognitive function deficits in alcoholic individuals. Electrophysiological and quantitative synaptomics techniques were used to test the hypothesis that heavy drinking produces neuroadaptations in the macaque OFC. Integrative bioinformatics and reverse genetic approaches were used to identify and validate synaptic proteins with novel links to heavy drinking in BXD mice. In drinking monkeys, evoked firing of OFC pyramidal neurons was reduced, whereas the amplitude and frequency of postsynaptic currents were enhanced compared with controls. Bath application of alcohol reduced evoked firing in neurons from control monkeys, but not drinking monkeys. Profiling of the OFC synaptome identified alcohol-sensitive proteins that control glutamate release (e.g., SV2A, synaptogyrin-1) and postsynaptic signaling (e.g., GluA1, PRRT2) with no changes in synaptic GABAergic proteins. Western blot analysis confirmed the increase in GluA1 expression in drinking monkeys. An exploratory analysis of the OFC synaptome found cross-species genetic links to alcohol intake in discrete proteins (e.g., C2CD2L, DIRAS2) that discriminated between low- and heavy-drinking monkeys. Validation studies revealed that BXD mouse strains with the D allele at the C2cd2l interval drank less alcohol than B allele strains. Thus, by profiling of the OFC synaptome, we identified changes in proteins controlling glutamate release and postsynaptic signaling and discovered several proteins related to heavy drinking that have potential as novel targets for treating alcohol use disorder.

SIGNIFICANCE STATEMENT Clinical research identified cognitive deficits in alcoholic individuals as a risk factor for relapse, and alcoholic individuals display deficits on cognitive tasks that are dependent upon the orbitofrontal cortex (OFC). To identify neurobiological mechanisms that underpin OFC dysfunction, this study used electrophysiology and integrative synaptomics in a translational nonhuman primate model of heavy alcohol consumption. We found adaptations in synaptic proteins that control glutamatergic signaling in chronically drinking monkeys. Our functional genomic exploratory analyses identified proteins with genetic links to alcohol and cocaine intake across mice, monkeys, and humans. Future work is necessary to determine whether targeting these novel targets reduces excessive and harmful levels of alcohol drinking.


PURPOSE/OBJECTIVE: The purposes of this article are to describe the scientific literature on assessment, prevention, and management of delirium in critically ill children and to articulate the implications for clinical nurse specialists, in translating the evidence into practice. DESCRIPTION: A literature search was conducted in 4 databases—OvidMEDLINE, Cumulative Index to Nursing and Allied Health Literature, PsychINFO, and Web of Science—using the terms “delirium,” “child,” and “critically ill” for the period of 2006 to 2016. OUTCOME: The scientific literature included articles on diagnosis, prevalence, risk factors, adverse outcomes, screening tools, prevention, and management. The prevalence of delirium in critically ill children is up to 30%. Risk factors include age, developmental delay, severity of illness, and mechanical ventilation. Adverse outcomes include increased mortality, hospital length of stay, and cost for the critically ill child with delirium. Valid and reliable delirium screening tools are available for critically ill children. Prevention and management strategies include interventions to address environmental triggers, sleep disruption, integrated family care, and mobilization. CONCLUSION: Delirium is a common occurrence for the critically ill child. The clinical nurse specialist is accountable for leading the implementation of practice changes that are based on evidence to improve patient outcomes. Screening and early intervention for delirium are key to mitigating adverse outcomes for critically ill children.

Current therapies for medulloblastoma, a highly malignant childhood brain tumour, impose debilitating effects on the developing child, and highlight the need for molecularly targeted treatments with reduced toxicity. Previous studies have been unable to identify the full spectrum of driver genes and molecular processes that operate in medulloblastoma subgroups. Here we analyse the somatic landscape across 491 sequenced medulloblastoma samples and the molecular heterogeneity among 1,256 epigenetically analysed cases, and identify subgroup-specific driver alterations that include previously undiscovered actionable targets. Driver mutations were confidently assigned to most patients belonging to Group 3 and Group 4 medulloblastoma subgroups, greatly enhancing previous knowledge. New molecular subtypes were differentially enriched for specific driver events, including hotspot in-frame insertions that target KBTBD4 and 'enhancer hijacking' events that activate PRDM6. Thus, the application of integrative genomics to an extensive cohort of clinical samples derived from a single childhood cancer entity revealed a series of cancer genes and biologically relevant subtype diversity that represent attractive therapeutic targets for the treatment of patients with medulloblastoma. © 2017 Macmillan Publishers Limited, part of Springer Nature. All rights reserved.


Background: Cannabis is increasingly available for the treatment of chronic pain, yet its efficacy remains uncertain. Purpose: To review the benefits of plant-based cannabis preparations for treating chronic pain in adults and the harms of cannabis use in chronic pain and general adult populations. Data Sources: MEDLINE, Cochrane Database of Systematic Reviews, and several other sources from database inception to March 2017. Study Selection: Intervention trials and observational studies, published in English, involving adults using plant-based cannabis preparations that reported pain, quality of life, or adverse effect outcomes. Data Extraction: Two investigators independently abstracted study characteristics and assessed study quality, and the investigator group graded the overall strength of evidence using standard criteria. Data Synthesis: From 27 chronic pain trials, there is low-strength evidence that cannabis alleviates neuropathic pain but insufficient evidence in other pain populations. According to 11 systematic reviews and 32 primary studies, harms in general population studies include increased risk for motor vehicle accidents, psychotic symptoms, and short-term cognitive impairment. Although adverse pulmonary effects were not seen in younger populations, evidence on most other long-term physical harms, in heavy or long-term cannabis users, or in older populations is insufficient. Limitation: Few methodologically rigorous trials; the cannabis formulations studied may not reflect commercially available products; and limited applicability to older, chronically ill populations and patients who use cannabis heavily. Conclusion: Limited evidence suggests that cannabis may alleviate neuropathic pain in some patients, but insufficient evidence exists for other types of chronic pain. Among general populations, limited evidence suggests that cannabis is associated with an increased risk for adverse mental health effects. Primary Funding Source: U.S. Department of Veterans Affairs. (PROSPERO: CRD42016033623).


BACKGROUND: The mechanistic basis for tortuosity of the coronary arteries (TCA) is unclear. The aim of this study was to test the hypothesis that the relative degree of systolic longitudinal shortening of the left ventricle that deforms coaxially oriented coronary arteries is associated with TCA. METHODS: Adult subjects undergoing coronary angiography and comprehensive echocardiography within 3 months were classified dichotomously as with (n = 32) or without (n = 42) TCA defined on the basis of number and severity of coronary angles. Systolic left ventricular (LV) longitudinal deformation was determined by mitral annular plane systolic excursion (MAPSE) from both B-mode displacement and tissue Doppler time-velocity integral; data were indexed to LV diastolic long-axis length. RESULTS: There were no differences between groups with respect to age, gender, hypertension, or coronary artery disease. Patients with TCA had significantly (P < .01) lower LV
Both bimodal cochlear implant and bilateral hearing aid users can exhibit broad binaural pitch fusion, the fusion of dichotically presented tones over a broad range of pitch differences between ears [Reiss, Ito, Eggleston, and Wozny. (2014). J. Assoc. Res. Otolaryngol. 15(2), 235-248; Reiss, Eggleston, Walker, and Oh. (2016). J. Assoc. Res. Otolaryngol. 17(4), 341-356; Reiss, Shayman, Walker, Bennett, Fowler, Hartling, Glickman, Lasarev, and Oh. (2017). J. Acoust. Soc. Am. 143(3), 1909-1920]. Further, the fused binaural pitch is often a weighted average of the different pitches perceived in the two ears. The current study was designed to systematically measure these pitch averaging phenomena in bilateral hearing aid users with broad fusion. The fused binaural pitch of the reference-pair tone combination was initially measured by pitch-matching to monaural comparison tones presented to the pair tone ear. The averaged results for all subjects showed two distinct trends: (1) The fused binaural pitch was dominated by the lower-pitch component when the pair tone was either 0.14 octaves below or 0.78 octaves above the reference tone; (2) pitch averaging occurred when the pair tone was between the two boundaries above, with the most equal weighting at 0.38 octaves above the reference tone. Findings from two subjects suggest that randomization or alternation of the comparison ear can eliminate this asymmetry in the pitch averaging range. Overall, these pitch averaging phenomena suggest that spectral distortions and thus binaural interference may arise during binaural stimulation in hearing-impaired listeners with broad fusion. © 2017 Acoustical Society of America.


Background Emergency department (ED) patients are among the many groups at risk for prescription drug overdose. There is limited research on how best to communicate with ED patients about options for pain management and the risks of opioids. The aim of this study is to pilot test a web-based, patient-centred educational programme that encourages the patient to have an informed discussion about pain medication options with their ED provider. Methods This multisite, randomised trial will evaluate an m-health programme designed to aid the patient in making an informed decision about their pain treatment. Patients reporting to the ED with an injury-related or pain-related chief complaint who agree to participate are randomised to receive the intervention programme, My Healthy Choices, or an attention-matched control. My Healthy Choices pairs tailored education with a patient decision aid to describe what opioid and nonopioid pain medications are, assess the patient’s risk factors for opioid-related adverse effects, and produce a tailored report that patients are encouraged to share with their doctor. Data are collected through surveys at three time points during the ED encounter (baseline, immediately after the intervention and just before discharge), and at a 6-week follow-up survey. The primary outcomes are whether the patient prefers an opioid pain reliever (OPR) and whether the patient takes an OPR. Discussion We hope this programme will facilitate patient-provider communication, as well as reduce the number of prescriptions written for OPRs and thus the number of patients exposed to prescription opioids and the associated risks of addiction and overdose. © 2017. Produced by BMJ Publishing Group Ltd under licence.

Background: Cannabis is available from medical dispensaries for treating posttraumatic stress disorder (PTSD) in many states of the union, yet its efficacy in treating PTSD symptoms remains uncertain. Purpose: To identify ongoing studies and review existing evidence regarding the benefits and harms of plant-based cannabis preparations in treating PTSD in adults. Data Sources: MEDLINE, the Cochrane Library, and other sources from database inception to March 2017. Study Selection: English-language systematic reviews, trials, and observational studies with a control group that reported PTSD symptoms and adverse effects of plant-based cannabis use in adults with PTSD. Data Extraction: Study data extracted by 1 investigator was checked by a second reviewer; 2 reviewers independently assessed study quality, and the investigator group graded the overall strength of evidence by using standard criteria. Data Synthesis: Two systematic reviews, 3 observational studies, and no randomized trials were found. The systematic reviews reported insufficient evidence to draw conclusions about benefits and harms. The observational studies found that compared with nonuse, cannabis did not reduce PTSD symptoms. Studies had medium and high risk of bias, and overall evidence was judged insufficient. Two randomized trials and 6 other studies examining outcomes of cannabis use in patients with PTSD are ongoing and are expected to be completed within 3 years. Limitation: Very scant evidence with medium to high risk of bias. Conclusion: Evidence is insufficient to draw conclusions about the benefits and harms of plant-based cannabis preparations in patients with PTSD, but several ongoing studies may soon provide important results. Primary Funding Source: U.S. Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Quality Enhancement Research Initiative. (PROSPERO: CRD42016033623).


Immature astrocytes and blood vessels enter the developing mammalian retina at the optic nerve head and migrate peripherally to colonize the entire retinal nerve fiber layer (RNFL). Retinal vascularization is arrested in retinopathy of prematurity (ROP), a major cause of bilateral blindness in children. Despite their importance in normal development and ROP, the factors that control vascularization of the retina remain poorly understood. Because astrocytes form a reticular network that appears to provide a substrate for migrating endothelial cells, they have long been proposed to guide angiogenesis. However, whether astrocytes do in fact impose a spatial pattern on developing vessels remains unclear, and how astrocytes themselves are guided is unknown. Here we explore the cellular mechanisms that ensure complete retinal coverage by astrocytes and blood vessels in mouse. We find that migrating astrocytes associate closely with the axons of retinal ganglion cells (RGCs), their neighbors in the RNFL. Analysis of Robo1; Robo2 mutants, in which RGC axon guidance is disrupted, and Math5 (Atoh7) mutants, which lack RGCs, reveals that RGCs provide directional information to migrating astrocytes that sets them on a centrifugal trajectory. Without this guidance, astrocytes exhibit polarization defects, fail to colonize the peripheral retina, and display abnormal fine-scale spatial patterning. Furthermore, using cell type-specific chemical–genetic tools to selectively ablate astrocytes, we show that the astrocyte template is required for angiogenesis and vessel patterning. Our results are consistent with a model whereby RGC axons guide formation of an astrocytic network that subsequently directs vessel development. © 2017 Wiley Periodicals, Inc.

INTRODUCTION: En bloc resection of high-cervical chordomas is a technically challenging procedure associated with significant morbidity. Two key components of this procedure include the approach and the method of spinal reconstruction. A limited number of reported cases of en bloc resection of high-cervical chordomas have been reported in the literature. CASE PRESENTATION: We report a novel case using an expandable cage to reconstruct the anterior spinal column above C2 with fixation to the clivus. We also report a novel anterior approach to the high-cervical spine via a midline labiomialdibular glossotomy. We detail the management of complications related to 2 instances of wound dehiscence and hardware exposure requiring two additional operations. The final surgical procedure involved explantation of the anterior cervical plate and use of a vascularized radial graft to close the posterior pharyngeal defect and protect the hardware. At 26-month follow-up, the patient remained disease free without any neurologic deficit. DISCUSSION: We report the novel use of the midline labiomialdibular glossotomy for surgical approach and reconstruction of the anterior column to the clivus with an expandable cage. The unique features of this operative strategy allowed the surgical team to tailor the construct intraoperatively, resulting in solid arthrodesis without significant neurologic sequelae. CONCLUSIONS: Labiomialdibular glossotomy for approach to high anterior cervical chordomas followed by craniospinal reconstruction to the clivus with an expandable cage represents a novel technique for managing high cervical chordomas.


In the face of starvation, animals will engage in high-risk behaviors that would normally be considered maladaptive. Starving rodents, for example, will forage in areas that are more susceptible to predators and will also modulate aggressive behavior within a territory of limited or depleted nutrients. The neural basis of these adaptive behaviors likely involves circuits that link innate feeding, aggression and fear. Hypothalamic agouti-related peptide (AgRP)-expressing neurons are critically important for driving feeding and project axons to brain regions implicated in aggression and fear. Using circuit-mapping techniques in mice, we define a disynaptic network originating from a subset of AgRP neurons that project to the medial nucleus of the amygdala and then to the principal bed nucleus of the stria terminals, which suppresses territorial aggression and reduces contextual fear. We propose that AgRP neurons serve as a master switch capable of coordinating behavioral decisions relative to internal state and environmental cues.


Although small molecule inhibitors of B-cell receptor-associated kinases revolutionized therapy in chronic lymphocytic leukemia, they provide for incomplete responses. Pro-survival signaling emanating from the microenvironment may foster therapeutic resistance of the malignant B-cells resident in the protective lymphoid niches. BAFF is critical in survival of both healthy and neoplastic B-cells. However, the pro-survival pathways triggered by BAFF have not been fully characterized. Here we show that BAFF elicited resistance to spontaneous and drug-induced apoptosis in stromal co-cultures, induced activation of both canonical and non-canonical NFkB signaling pathways and triggered B-cell receptor signaling in chronic lymphocytic leukemia cells, independent of IGHV mutational status. SYK, a proximal kinase in the B-cell receptor signaling cascade, acted via STAT3 to bolster transcription of the anti-apoptotic protein Mcl-1, thereby contributing to apoptosis resistance in BAFF-stimulated cells. SYK inhibitor entospletinib downregulated Mcl-1, abrogating BAFF-mediated cell survival. BAFF-B-cell receptor crosstalk in neoplastic B-cells was mediated by SYK interaction with TRAF2/TRAF3 complex. Thus, SYK inhibition is a promising therapeutic strategy uniquely poised to antagonize crosstalk between BAFF and B-cell receptor, thereby disrupting the pro-survival microenvironment signaling in chronic lymphocytic leukemia.

Background and Objective: To determine the diagnostic yield of systemic work-up in white dot syndromes. PATIENTS AND METHODS: A retrospective chart review. RESULTS: Eighty-six consecutive patients with a diagnosis of a white dot syndrome were identified. Forty-three had a diagnosis of birdshot chorioretinopathy. Overall, 395 diagnostic tests were performed with a diagnostic yield of 11.9%. The test with the greatest diagnostic yield was HLAA29 typing (89%). Four patients had abnormal angiotensin converting enzyme levels. No patients had a positive rapid plasma reagin or fluorescent treponemal antibody absorption test. Four patients had positive tuberculosis testing and required treatment. The mean number of tests performed per diagnosis group ranged from 0.3 in multiple evanescent white dot syndrome to 5.6 in multifocal choroiditis and panuveitis. Diagnostic testing was found to be the most expensive in birdshot chorioretinopathy, with a mean cost of $504.82. CONCLUSIONS: Diagnostic yield of systemic workup was low in this patient population. Rather than performing an exhaustive work-up, the authors advocate for a limited work-up tailored to pretest clinical suspicion.


We analyzed chromatin dynamics and transcriptional activity of human embryonic stem cell (hESC)-derived cardiac progenitor cells (CPCs) and KDR+/CD34+ endothelial cells generated from different mesodermal origins. Using an unbiased algorithm to hierarchically rank genes modulated at the level of chromatin and transcription, we identified candidate regulators of mesodermal lineage determination. HOPX, a non-DNA-binding homeodomain protein, was identified as a candidate regulator of blood-forming endothelial cells. Using HOPX reporter and knockout hESCs, we show that HOPX regulates blood formation. Loss of HOPX does not impact endothelial fate specification but markedly reduces primitive hematopoiesis, acting at least in part through failure to suppress Wnt/beta-catenin signaling. Thus, chromatin state analysis permits identification of regulators of mesodermal specification, including a conserved role for HOPX in governing primitive hematopoiesis.


Huntington’s disease (HD) is a fatal genetic disorder characterized by cell death of medium-sized spiny neurons (MSNs) in the striatum, traditionally attributed to excessive glutamate inputs and/or receptor sensitivity. While changes in corticostriatal projections have typically been studied in mouse models of HD, morphological and functional alterations in thalamostriatal projections have received less attention. In this study, an adeno-associated virus expressing channelrhodopsin-2 under the calcium/calmodulin-dependent protein kinase Ilalpha promoter was injected into the sensorimotor cortex or the thalamic centromedian-parafascicular nuclear complex in the R6/2 mouse model of HD, to permit selective activation of corticostriatal or thalamostriatal projections, respectively. In symptomatic R6/2 mice, peak amplitudes and areas of corticostriatal glutamate AMPA and NMDA receptor-mediated responses were reduced. In contrast, although peak amplitudes of AMPA and NMDA receptor-mediated thalamostriatal responses also were reduced, the areas remained unchanged due to an increase in response decay times. Blockade of glutamate reuptake further increased response areas and slowed rise and decay times of NMDA responses. These effects appeared more pronounced at thalamostriatal synapses of R6/2 mice, suggesting increased activation of extrasynaptic NMDA receptors. In addition, the probability of glutamate release was higher at thalamostriatal than corticostriatal synapses, particularly in R6/2 mice. Morphological studies indicated that
the density of all excitatory synaptic contacts onto MSNs was reduced, which matches the basic electrophysiological findings of reduced amplitudes. There was a consistent reduction in the area of spines but little change in presynaptic terminal size, indicating that the postsynaptic spine may be more significantly affected than presynaptic terminals. These results highlight the significant and differential contribution of the thalamostriatal projection to glutamate excitotoxicity in HD.


Background Context: Non-operative management is a common initial treatment for patients with adult spinal deformity (ASD) despite reported superiority of surgery with regard to outcomes. Ineffective medical care is a large source of resource drain on the health system. Characterization of patients with ASD likely to elect for operative treatment from non-operative management may allow for more efficient patient counseling and cost savings. Purpose: This study aimed to identify deformity and disability characteristics of patients with ASD who ultimately convert to operative treatment compared with those who remain non-operative and those who initially choose surgery. Study Design/Setting: A retrospective review was carried out. Patient Sample: A total of 510 patients with ASD (189 non-operative, 321 operative) with minimum 2-year follow-up comprised the patient sample. Outcome Measures: Oswestry Disability Index (ODI), Short-Form 36 Health Assessment (SF-36), Scoliosis Research Society questionnaire (SRS-22r), and spinopelvic radiographic alignment were the outcome measures. Methods: Demographic, radiographic, and patient-reported outcome measures (PROMs) from a cohort of patients with ASD prospectively enrolled into a multicenter database were evaluated. Patients were divided into three treatment cohorts: Non-operative (NON=initial non-operative treatment and remained non-operative), Operative (OP=initial operative treatment), and Crossover (CROSS=initial non-operative treatment with subsequent conversion to operative treatment). NON and OP groups were propensity score-matched (PSM) to CROSS for baseline demographics (age, body mass index, Charlson Comorbidity Index). Time to crossover was divided into early (<1 year) and late (>1 year). Outcome measures were compared across and within treatment groups at four time points (baseline, 6 weeks, 1 year, and 2 years). Results: Following PSM, 118 patients were included (NON=39, OP=38, CROSS=41). Crossover rate was 21.7% (41/189). Mean time to crossover was 394 days. All groups had similar baseline sagittal alignment, but CROSS had larger pelvic incidence and lumbar lordosis (PI-LL) mismatch than NON (11.9° vs. 3.1°, p=.032). CROSS and OP had similar baseline PROM scores; however, CROSS had worse baseline ODI, PCS, SRS-22r (p<.05). At time of crossover, CROSS had worse ODI (35.7 vs. 27.8) and SRS Satisfaction (2.6 vs. 3.3) compared with NON (p<.05). Alignment remained similar for CROSS from baseline to conversion; however, PROMs (ODI, PCS, SRS Activity/Pain/Total) worsened (p<.05). Early and late crossover evaluation demonstrated CROSS-early (n=25) had worsening ODI, SRS Activity/Pain at time of crossover (p<.05). From time of crossover to 2-year follow-up, CROSS-early had less SRS Appearance/Mental improvement compared with OP. Both CROSS-early/late had worse baseline, but greater improvements, in ODI, PCS, SRS Pain/Total compared with NON (p<.05). Baseline alignment and disability parameters increased crossover odds-Non with Schwab T/L/D curves and ODI≥40 (odds ratio [OR]: 3.05, p=.031), and Non with high PI-LL modifier grades ("++/+++”) and ODI≥40 (OR: 5.57, p=.007) were at increased crossover risk. Conclusions: High baseline and increasing disability over time drives conversion from non-operative to operative ASD care. CROSS patients had similar spinal deformity but worse PROMs than NON. CROSS achieved similar 2-year outcome scores as OP. Profiling at first visit for patients at risk of crossover may optimize physician counseling and cost savings. © 2017.

Since 2015, Society of Critical Care Medicine/American Society for Parenteral and Enteral Nutrition and Canadian critical care nutrition support guidelines have both been updated. Despite a similar evidentiary basis, there remain key differences between guideline recommendations. These differences in recommendations may pose confusion for the clinician and may encumber widespread applicability. The aim of this review was to enhance practitioner confidence in applying critical care nutrition support guidelines to patient care in their settings by outlining the similarities and differences between the American and Canadian methods for guideline development and describing the key differences and reasons behind the differences.


Obesity has become a worldwide epidemic with a disproportionate increase in grade III obesity. Bariatric surgery offers an attractive option for sustained weight loss compared with traditional methods such as exercise and diet. Micronutrient deficiencies are common and clinically significant after bariatric surgery. These deficiencies are related to a combination of patient and surgical variables. A thorough understanding of specific micronutrient deficiencies is necessary for early recognition and optimal management. The purpose of this review is to describe indications, outcomes, and types of bariatric procedures, risk factors, and mechanisms for micronutrient deficiencies, as well as outline specific vitamin and trace element deficiencies after bariatric surgery. © 2017 The American Society for Parenteral and Enteral Nutrition.


Intracellular delivery of mRNA holds great potential for vaccine discovery and development. Despite increasing recognition of the utility of lipid-based nanoparticles (LNPs) for intracellular delivery of mRNA, particle engineering is hindered by insufficient understanding of endosomal escape, which is believed to be a main limiter of cytosolic availability and activity of the nucleic acid inside the cell. Using a series of CRISPR-based genetic perturbations of the lysosomal pathway, we have identified that late endosome/lysosome (LE/Ly) formation is essential for functional delivery of exogenously presented mRNA. Lysosomes provide a spatiotemporal hub to orchestrate mTOR signaling and are known to control cell proliferation, nutrient sensing, ribosomal biogenesis, and mRNA translation. Through modulation of the mTOR pathway we were able to enhance or inhibit LNP-mediated mRNA delivery. To further boost intracellular delivery of mRNA, we screened 212 bioactive lipid-like molecules that are either enriched in vesicular compartments or modulate cell signaling. Surprisingly, we have discovered that leukotriene antagonists, clinically approved for treatment of asthma and other lung diseases, enhance intracellular mRNA delivery in vitro (over 3-fold, p < 0.005) and in vivo (over 2-fold, p < 0.005). Understanding LNP-mediated intracellular delivery will inspire the next generation of RNA therapeutics that have high potency and limited toxicity.


BACKGROUND: In the phase 3 RADIANT-4 trial, everolimus increased progression-free survival compared with placebo in patients with advanced, progressive, non-functional, well-differentiated gastrointestinal or lung neuroendocrine tumours (NETs). We now report the health-related quality of life (HRQOL) secondary endpoint. METHODS: RADIANT-4 is a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial.
trial done in 97 centres in 25 countries worldwide. Adults (aged ≥18 years) were eligible for the study if they had pathologically confirmed, advanced (unresectable or metastatic), non-functional, well-differentiated (grade 1 or 2) NETs of lung or gastrointestinal origin. Patients were randomly allocated (2:1) using block randomisation (block size of three) by an interactive voice response system to receive oral everolimus (10 mg per day) or placebo, both with best supportive care, with stratification by tumour origin, WHO performance status, and previous somatostatin analogue treatment. HRQOL was assessed with the Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire at baseline (visit 2, day 1), every 8 weeks (+/- 1 week) during the study for the first 12 months after randomisation, and every 12 weeks thereafter until study drug discontinuation. The primary endpoint, reported previously, was progression-free survival assessed by central review; HRQOL was a prespecified secondary endpoint. The prespecified secondary outcome measure was time to definitive deterioration (>7 points) in FACT-G total score. Analyses were done on the full analysis set, consisting of all randomised patients, by intention to treat. Only data obtained while receiving the randomly allocated treatment were included in this analysis. Enrolment for RADIANT-4 was completed on Aug 23, 2013, but the trial is ongoing pending final analysis of the key secondary endpoint of overall survival. This trial is registered with ClinicalTrials.gov, number NCT01524783. FINDINGS: Between April 3, 2012, and Aug 23, 2013, 302 patients were enrolled; 205 were randomly allocated everolimus and 97 were assigned placebo. At baseline, 193 (94%) of 205 patients assigned everolimus and 95 (98%) of 97 allocated placebo had completed either fully or partly the FACT-G questionnaire; at week 48, 70 (83%) of 84 patients assigned everolimus and 22 (85%) of 26 allocated placebo completed FACT-G. Median time to definitive deterioration in FACT-G total score was 11.27 months (95% CI 9.27-19.35) with everolimus and 9.23 months (5.52-not estimable) with placebo (adjusted hazard ratio 0.81, 95% CI 0.55-1.21; log-rank p=0.31). INTERPRETATION: HRQOL was maintained for patients with advanced, non-functional, gastrointestinal or lung NETs, with no relevant differences noted between the everolimus and placebo groups. In view of the previous RADIANT-4 findings of longer progression-free survival with everolimus, our findings suggest that everolimus delays disease progression while preserving overall HRQOL, even with the usual toxic effects related to active targeted drug treatment for cancer. FUNDING: Novartis Pharmaceuticals.


The physiological state of a cell is governed by a multitude of processes and can be described by a combination of mechanical, spatial and temporal properties. Quantifying cell dynamics at multiple scales is essential for comprehensive studies of cellular function, and remains a challenge for traditional end-point assays. We introduce an efficient, non-invasive computational tool that takes time-lapse images as input to automatically detect, segment and analyze unlabeled live cells; the program then outputs kinematic cellular shape and migration parameters, while simultaneously measuring cellular stiffness and viscosity. We demonstrate the capabilities of the program by testing it on human mesenchymal stem cells (huMSCs) induced to differentiate towards the osteoblastic (huOB) lineage, and T-lymphocyte cells (T cells) of naive and stimulated phenotypes. The program detected relative cellular stiffness differences in huMSCs and huOBs that were comparable to those obtained with studies that utilize atomic force microscopy; it further distinguished naive from stimulated T cells, based on characteristics necessary to invoke an immune response. In summary, we introduce an integrated tool to decipher spatiotemporal and intracellular dynamics of cells, providing a new and alternative approach for cell characterization.


BACKGROUND: Accurate determination of recipient cytomegalovirus (CMV) serostatus before allogeneic hematopoietic stem cell transplantation (HSCT) is critical, as it is the most important predictor of post-transplant CMV infection and remains associated with non-relapse mortality. The purpose of this study was
to assess a recipient dual-testing strategy before HSCT. METHODS: CMV serologic testing was performed before allogeneic HSCT using 2 different assays: reference laboratory (RL) and American Red Cross (ARC). In all cases, blood samples were obtained for RL testing either before ARC testing (median 130 days before HSCT [range 12-2594]) or at the same time (median 25 days before HSCT [range 8-129]). The results of serologic testing were correlated with CMV viremia post HSCT. RESULTS: Of 287 recipients evaluated, 76 (26.5%) had discordant results, of which 74 (97.4%) tested RL-/ARC+. Ten had RL and ARC testing performed on simultaneously obtained samples, 3 of which (30%) were discordant (3 [100%] RL-/ARC+). Acute myeloid leukemia and receipt of blood product transfusion in the interval between testing were associated with RL-/ARC+ discordance. Correlation with viremia after HSCT suggested that RL-/ARC+ discordance was caused by detection of anti-CMV immunoglobulin transferred in transfused blood products and reduced specificity of the ARC assay. CONCLUSION: CMV-seronegative hematopoietic stem cell transplant recipients may be misclassified as seropositive if testing is performed after receipt of blood products or when using assays optimized for sensitivity at the expense of specificity. This misclassification may negatively affect post-HSCT outcomes for individual patients and studies that rely on accurate CMV serology reporting.


Obesity is a worldwide epidemic, and those suffering from obesity have increased morbidity and mortality rates. There are various causes of obesity and many treatment options for patients suffering from obesity, including nonsurgical treatments. However, bariatric surgery is often the best choice for optimal weight loss and the attenuation of comorbidities. Currently, laparoscopic sleeve gastrectomy is the most common type of bariatric surgery in the United States due to its technical simplicity, feasibility, and overall positive outcomes. This article discusses bariatric surgical criteria and selection, expected perioperative course, potential complications after surgery, and nursing implications for the care of bariatric patients. A case report is used to exemplify stages of surgical care and follow-up treatment for patients who undergo laparoscopic sleeve gastrectomy.


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 early and established RA were analysed. X-rays were scored using van der Heijde-modified or Genant-modified Sharp methods. MRIs were scored using Outcome Measures in Rheumatology (OMERACT) RA MRI Score (RAMRIS). Data were analysed at the patient level using multivariable logistic regression and receiver operating characteristic curve analyses. RESULTS: Progression of MRI erosion scores at Weeks 12 and 24 predicted progression of X-ray erosions at Weeks 24 and 52, with areas under the curve (AUCs) of 0.64 and 0.74, respectively. 12-week and 24-week changes in MRI osteitis scores were similarly predictive of 24-week and 52-week X-ray erosion progressions; pooled AUCs were 0.78 and 0.77, respectively. MRI changes in synovitis at Weeks 12 and 24 also predicted progression of X-ray joint damage (erosion and joint-space narrowing) at Weeks 24 and 52 (AUCs=0.72 and 0.65, respectively). CONCLUSIONS: Early changes in joint damage and inflammation detected with MRI predict changes in joint damage evident on subsequent X-rays. These findings support the use of MRI as a valid method for monitoring structural damage in short-duration RCTs.


Even following long periods of abstinence, individuals with anxiety disorders have high rates of relapse to drugs of abuse. Although many current models of relapse demonstrate effects of acute stress on drug-seeking, most of these studies examine stressful experiences that occur in close temporal and physical proximity to the reinstatement test. Here, we assess the effects of a stressful experience in one context on fear and drug-seeking in a different context. We adapt the stress-enhanced fear learning procedure to examine impacts on drug-seeking long after the stressful experience occurred. We find massive footshock in a distinct environment produced an acute increase in corticosterone, long-term hyper-responsivity to a single shock in different contexts with extensive histories of drug-seeking behaviors, enhancements in cocaine-induced conditioned place preference in mice, and persistent enhancements in cue-induced reinstatement of methamphetamine-seeking behavior in rats. Together, these experiments demonstrate that an acute trauma causes persistent changes in responsivity to mild stressors and drug-seeking behavior in other contexts, which mirrors aspects of the comorbidity between post-traumatic stress disorder and substance use disorders. These behavioral approaches provide novel procedures for investigating basic mechanisms underlying this comorbidity and they provide powerful tools for testing preclinical pharmacological and behavioral interventions.


There is currently great interest in developing drugs that stimulate myelin repair for use in demyelinating diseases such as multiple sclerosis. Thyroid hormone plays a key role in stimulating myelination during development and also controls the expression of important genes involved in myelin repair in adults. Because endogenous thyroid hormone in excess lacks a generally useful therapeutic index, it is not used clinically for indications other than hormone replacement; however, selective thyromimetics such as sobetirome offer a therapeutic alternative. Sobetirome is the only clinical-stage thyromimetic that is known to cross the blood-brain-barrier (BBB) and we endeavored to increase the BBB permeability of sobetirome using a prodrug strategy. Ester prodrugs of sobetirome were prepared based on literature reports of improved BBB permeability with other carboxylic acid containing drugs and BBB permeability was assessed in vivo. One sobetirome prodrug, ethanolamine ester 11, was found to distribute more sobetirome to the brain compared to an equimolar peripheral dose of unmodified sobetirome. In addition to enhanced brain levels, prodrug 11 displayed lower sobetirome blood levels and a brain/serum ratio that was larger than that of unmodified sobetirome. Thus, these data indicate that an ester prodrug strategy applied to sobetirome can deliver increased concentrations of the active drug to the central nervous system (CNS), which may prove useful in the treatment of CNS disorders.


OBJECTIVE: In 2006, 13 sites were provided with one-time pilot funding to provide supported employment (SE) to Veterans with traumatic brain injury (TBI) history. In 2014, we surveyed SE providers at pilot and non-pilot sites that did not receive this funding. Our objectives were to identify any pilot and non-pilot site differences
regarding current: (1) provision of SE to Veterans with TBI; (2) staffing and communication between the SE and polytrauma/TBI teams; and (3) provider perceptions on facilitators and barriers to providing, and suggestions for improving. SE. SETTING: Veterans Health Administration (VHA) SE programs. DESIGN: Mixed methods cross-sectional survey study. PARTICIPANTS: Providers included a total of 54 SE supervisors and 90 vocational rehabilitation specialists (VRSs). INTERVENTIONS: Not applicable. MAIN OUTCOME MEASURES: Web-based surveys of forced-choice and open-ended items included questions on SE team characteristics, communication with polytrauma/TBI teams, and experiences with providing SE to Veterans with TBI history. RESULTS: SE was provided to Veterans with TBI at 100% of pilot and 59.2% of non-pilot sites (p = .09). However, VRSs at pilot sites reported that communication with the polytrauma/TBI team about SE referrals was more frequent than at non-pilot sites (p = .003). In open-ended items, suggestions for improving SE were similar across pilot and non-pilot sites, and included increasing staffing for VRSs and case management, enhancing communication and education between SE and polytrauma/TBI teams, and expanding the scope of the SE program so that eligibility is based on employment support need, rather than diagnosis. CONCLUSIONS: These findings may contribute to an evidence base that informs SE research and clinical directions on service provision, resource allocation, team integration efforts, and outreach to Veterans with TBI who have employment support needs.


Normal-appearing white matter (NAWM) surrounding WMHs is associated with decreased structural integrity and perfusion, increased risk of WMH growth, and is referred to as the WMH penumbra. Studies comparing structural and cerebral blood flow (CBF) penumbras within the same individuals are lacking, however, and would facilitate our understanding of mechanisms resulting in WM damage. This study aimed to compare both CBF and structural WMH penumbras in non-demented aging. Eighty-two elderly volunteers underwent 3T-MRI including fluid attenuated inversion recovery (FLAIR), pulsed arterial spin labeling and diffusion tensor imaging (DTI). A NAWM layer mask was generated for periventricular and deep WMHs. Mean CBF, DTI-fractional anisotropy (DTI-FA), DTI-mean diffusivity (DTI-MD) and FLAIR intensity for WMHs and its corresponding NAWM layer masks were computed and compared against its mean within total brain NAWM using mixed effects models. For both periventricular and deep WMHs, DTI-FA, DTI-MD and FLAIR intensity changes extended 2-9 mm surrounding WMHs (p </.05), while CBF changes extended 13-14 mm (p </.05). The CBF penumbra is more extensive than structural penumbras in relation to WMHs and includes WM tissue both with and without microstructural changes. Findings implicate CBF as a potential target for the prevention of both micro and macro structural WM damage.


STUDY DESIGN.: Prospective multicenter analysis of Adult Spinal Deformity (ASD) patients. OBJECTIVE.: To introduce the lumbar pelvic angle (LPA), a novel parameter of spinopelvic alignment. SUMMARY OF BACKGROUND DATA.: The T1 Pelvic angle (TPA), a measure of global spinopelvic alignment, correlates with HRQOL, but it may not be measurable on all intraoperative x-rays. In patients with prior interbody fusion at L5-S1, the plane of the S1 endplate can be blurred, creating error in PI-LL measure. The Lumbar Pelvic Angle (LPA) is more readily measured on intraoperative imaging than the TPA. METHODS.: ASD patients were included with
either coronal Cobb angle >20°, SVA>5?cm, thoracic kyphosis>60°, or PT >25°. Measures of disability included ODI, SRS and SF36. Baseline and 2-yr follow-up radiographic and HRQOL outcomes were evaluated. Linear regressions compared LPA with radiographic parameters and HRQOL.

RESULTS.: 852 ASD patients (407 operative) were enrolled (mean age 53.7). Baseline LPA correlated with PI-LL (r?=?0.79), PT (r?=?0.78), TPA (r?=?0.82) and SVA (r?=?0.61) (all p?<?0.001). PI-LL, LPA and TPA correlated with ODI (r?=?0.42/0.29/0.45), SF36 PCS (-0.43/-0.28/-0.45) SRS (-0.354/-0.23/-0.37) with all p?<?0.001. At 2-years follow-up, LPA correlated with PI-LL (r?=?0.77), PT (r?=?0.78), TPA (r?=?0.83) and SVA (r?=?0.57) (all p?<?0.001). Categorizing patients by increasing LPA (<7°; 7–15°; >15°) revealed progressive increases in all HRQOL, PI-LL (3.2°/12.7°/32.4°) and TPA (9.7°/20.1°/34.6°) with all p?<?0.001. Moderate disability (ODI?=?40) corresponded to LPA 10.1°, PI-LL 12.6° and TPA 20.6°. Mild disability (ODI?=?20) corresponded to LPA 7.2°, PI-LL 4.2° and TPA 14.7°. CONCLUSIONS.: LPA correlates with TPA, PI-LL and HRQOL in ASD patients. LPA can be used as an intraoperative tool to gauge correction with a target LPA of less than 7.2°. LPA predicts global alignment as it correlates with baseline and 2 year TPA and SVA. Along with the CTPA and TPA, LPA completes the fan of spinopelvic alignment.

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Neural injury triggers swift responses from glia, including glial migration and phagocytic clearance of damaged neurons. The transcriptional programs governing these complex innate glial immune responses are still unclear. Here, we describe a novel injury assay in adult Drosophila that elicits widespread glial responses in the ventral nerve cord (VNC). We profiled injury-induced changes in VNC gene expression by RNA sequencing (RNA-seq) and found that responsive genes fall into diverse signaling classes. One factor, matrix metalloproteinase-1 (MMP-1), is induced in Drosophila ensheathing glia responding to severed axons. Interestingly, glial induction of MMP-1 requires the highly conserved engulfment receptor Draper, as well as AP-1 and STAT92E. In MMP-1 depleted flies, glia do not properly infiltrate neuropil regions after axotomy and, as a consequence, fail to clear degenerating axonal debris. This work identifies Draper-dependent activation of MMP-1 as a novel cascade required for proper glial clearance of severed axons.


Tissue repair is an integral component of cancer treatment (e.g., due to surgery, chemotherapy, radiation). Previous work has emphasized the immunosuppressive effects of tumors on adaptive immunity and has shown that surgery incites cancer metastases. However, the extent to which and how tumors may alter the clinically-relevant innate immune process of wound healing remains an untapped potential area of improvement for treatment, quality of life, and ultimately, mortality of cancer patients. In this study, 3.5 mm full-thickness dermal excisional wounds were placed on the dorsum of immunocompetent female mice with and without non-malignant flank AT-84 murine oral squamous cell carcinomas. Wound closure rate, inflammatory cell number and inflammatory signaling in wounds, and circulating myeloid cell concentrations were compared between tumor-bearing and tumor-free mice. Tumors delayed wound closure, suppressed inflammatory signaling, and altered myeloid cell trafficking in wounds. An in vitro scratch "wounding" assay of adult dermal fibroblasts treated with tumor cell-conditioned media supported the in vivo findings. This study demonstrates that tumors are sufficient to disrupt fundamental and clinically-relevant innate immune functions. The understanding of these underlying mechanisms provides potential for therapeutic interventions capable of improving the treatment of cancer while reducing morbidities and mortality.

**OBJECTIVES/HYPOTHESIS:** Superior pediatric orbital subperiosteal abscesses (SPAs) are less common than medial ones, and clinical features specific to patients with superior SPAs have not been well defined. Clinical characteristics between patients with superior and medial SPAs are compared to determine whether superior location is a risk factor for surgical intervention.

**STUDY DESIGN:** Retrospective cohort study.

**METHODS:** The target population consisted of patients diagnosed with an SPA and seen by the pediatric otolaryngology service at a tertiary children's hospital between January 2010 and October 2014. Imaging characteristics including proptosis, hypoglobus, intraorbital air, and abscess volume as well as treatment interventions were reviewed.

**RESULTS:** Forty patients between 5 and 17 years of age treated for an orbital SPA were identified. Thirteen patients were identified as having superior SPAs; 27 had medial SPAs. The average ages in the two groups were 10.92 and 9.26 years, respectively. The odds ratio for surgical treatment per each increasing year of age was 1.5 (P = .004). The proportion of patients requiring surgery was significantly different between the groups (12/13 superior vs. 13/27 medial, P = .01). The predominant organism group cultured in surgical patients was Streptococcus anginosus (8/24, 29.17%). Superior SPA patients had significantly more proptosis, hypoglobus, and abscess volume on computed tomography scan.

**CONCLUSIONS:** Patients with superior SPAs may present with more advanced disease, leading to a higher rate of characteristics such as proptosis, hypoglobus, and intraorbital air, factors that would predispose to surgical drainage. We found that abscess volume was the most predictive of surgery. LEVEL OF EVIDENCE: 4 *Laryngoscope, 127*:735-740, 2017.


**BACKGROUND:** Targeting CD30 with monoclonal antibodies in Hodgkin lymphoma (HL) and anaplastic large cell lymphoma (ALCL) has had profound clinical success. However, adverse events, mainly mediated by the toxin component of the conjugated antibodies, cause treatment discontinuation in many patients. Targeting CD30 with T cells expressing a CD30-specific chimeric antigen receptor (CAR) may reduce the side effects and augment antitumor activity.

**METHODS:** We conducted a phase I dose escalation study in which 9 patients with relapsed/refractory HL or ALCL were infused with autologous T cells that were gene-modified with a retroviral vector to express the CD30-specific CAR (CD30.CAR-Ts) encoding the CD28 costimulatory endodomain. Three dose levels, from 0.2 x 10^8 to 2 x 10^8 CD30.CAR-Ts/m^2, were infused without a conditioning regimen. All other therapy for malignancy was discontinued at least 4 weeks before CD30.CAR-T infusion. Seven patients had previously experienced disease progression while being treated with brentuximab.

**RESULTS:** No toxicities attributable to CD30.CAR-Ts were observed. Of 7 patients with relapsed HL, 1 entered complete response (CR) lasting more than 2.5 years after the second infusion of CD30.CAR-Ts, 1 remained in continued CR for almost 2 years, and 3 had transient stable disease. Of 2 patients with ALCL, 1 had a CR that persisted 9 months after the fourth infusion of CD30.CAR-Ts. CD30.CAR-T expansion in peripheral blood peaked 1 week after infusion, and CD30.CAR-Ts remained detectable for over 6 weeks. Although CD30 may also be expressed by normal activated T cells, no patients developed impaired virus-specific immunity.

**CONCLUSION:** CD30.CAR-Ts are safe and can lead to clinical responses in patients with HL and ALCL, indicating that further assessment of this therapy is warranted. TRIAL REGISTRATION: ClinicalTrials.gov NCT01316146. FUNDING: National Cancer Institute (3P50CA126752, R01CA131027 and P30CA125123), National Heart, Lung, and Blood Institute (R01HL114564), and Leukemia and Lymphoma Society (LLSTR 6227-08).


Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma affecting children and is often diagnosed with concurrent metastases. Unfortunately, few effective therapies have been discovered that improve the long-term survival rate for children with metastatic disease. Here we determined effectiveness of targeting the receptor tyrosine kinase, EphB4, in both alveolar and embryonal RMS either directly through the inhibitory antibody, VasG3, or indirectly by blocking both forward and reverse signaling of EphB4 binding to EphrinB2, cognate ligand of EphB4. Clinically, EphB4 expression in eRMS was correlated with longer survival. Experimentally, inhibition of EphB4 with VasG3 in both aRMS and eRMS orthotopic xenograft and allograft models failed to alter tumor progression. Inhibition of EphB4 forward signaling using soluble EphB4 protein fused with murine serum albumin failed to affect eRMS model tumor progression, but did moderately slow progression in murine aRMS. We conclude that inhibition of EphB4 signaling with these agents is not a viable monotherapy for rhabdomyosarcoma.


Objective: To study the effects of alemtuzumab on HIV persistence in an HIV-infected individual on antiretroviral therapy (ART) with Sezary syndrome, a rare malignancy of CD4+ T cells. Design: Case report. Methods: Blood was collected 30 and 18 months prior to presentation with Sezary syndrome, at the time of presentation and during alemtuzumab. T-cell subsets in malignant (CD7-CD26-TCR- VBeta2+) and nonmalignant cells were quantified by flow cytometry. HIV-DNA in total CD4+ T cells, in sorted malignant and nonmalignant CD4+ T cells, was quantified by PCR and clonal expansion of HIV-DNA assessed by full-length next-generation sequencing. Results: HIV-hepatitis B virus coinfection was diagnosed and antiretroviral therapy initiated 4 years prior to presentation with Sezary syndrome and primary cutaneous anaplastic large cell lymphoma. The patient received alemtuzumab 10 mg three times per week for 4 weeks but died 6 weeks post alemtuzumab. HIV-DNA was detected in nonmalignant but not in malignant CD4+ T cells, consistent with expansion of a noninfected CD4+ T-cell clone. Full-length HIV-DNA sequencing demonstrated multiple defective viruses but no identical or expanded sequences. Alemtuzumab extensively depleted T cells, including more than 1 log reduction in total T cells and more than 3 log reduction in CD4+ T cells. Finally, alemtuzumab decreased HIV-DNA in CD4+ T cells by 57% but HIV-DNA remained detectable at low levels even after depletion of nearly all CD4+ T cells. Conclusion: Alemtuzumab extensively depleted multiple T-cell subsets and decreased the frequency of but did not eliminate HIV-infected CD4+ T cells. Studying the effects on HIV persistence following immune recovery in HIV-infected individuals who require alemtuzumab for malignancy or in animal studies may provide further insights into novel cure strategies. Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.


The presence of a nonheme metal, such as copper and iron, in the heme-copper oxidase (HCO) superfamily is critical to the enzymatic activity of reducing O2 to H2O, but the exact mechanism the nonheme metal ion uses to confer and fine-tune the activity remains to be understood. We herein report that manganese and cobalt can bind to the same nonheme site and confer HCO activity in a heme-nonheme biosynthetic model in myoglobin. While the initial rates of O2 reduction by the Mn, Fe, and Co derivatives are similar, the percentages of reactive oxygen species (ROS) formation are 7%, 4%, and 1% and the total turnovers are 5.1 +/- 1.1, 13.4 +/- 0.7, and 82.5 +/- 2.5, respectively. These results correlate with the trends of nonheme-
metal-binding dissociation constants (35, 22, and 9 µM) closely, suggesting that tighter metal binding can prevent ROS release from the active site, lessen damage to the protein, and produce higher total turnover numbers. Detailed spectroscopic, electrochemical, and computational studies found no evidence of redox cycling of manganese or cobalt in the enzymatic reactions and suggest that structural and electronic effects related to the presence of different nonheme metals lead to the observed differences in reactivity. This study of the roles of nonheme metal ions beyond the Cu and Fe found in native enzymes has provided deeper insights into nature’s choice of metal ion and reaction mechanism and allows for finer control of the enzymatic activity, which is a basis for the design of efficient catalysts for the oxygen reduction reaction in fuel cells.


This document updates the colorectal cancer (CRC) screening recommendations of the U.S. Multi-Society Task Force of Colorectal Cancer (MSTF), which represents the American College of Gastroenterology, the American Gastroenterological Association, and The American Society for Gastrointestinal Endoscopy. CRC screening tests are ranked in 3 tiers based on performance features, costs, and practical considerations. The first-tier tests are colonoscopy every 10 years and annual fecal immunochemical test (FIT). Colonoscopy and FIT are recommended as the cornerstones of screening regardless of how screening is offered. Thus, in a sequential approach based on colonoscopy offered first, FIT should be offered to patients who decline colonoscopy. Colonoscopy and FIT are recommended as tests of choice when multiple options are presented as alternatives. A risk-stratified approach is also appropriate, with FIT screening in populations with an estimated low prevalence of advanced neoplasia and colonoscopy screening in high prevalence populations. The second-tier tests include CT colonography every 5 years, the FIT-fecal DNA test every 3 years, and flexible sigmoidoscopy every 5 to 10 years. These tests are appropriate screening tests, but each has disadvantages relative to the tier 1 tests. Because of limited evidence and current obstacles to use, capsule colonoscopy every 5 years is a third-tier test. We suggest that the Septin9 serum assay (Epigenomics, Seattle, Wash) not be used for screening. Screening should begin at age 50 years in average-risk persons, except in African Americans in whom limited evidence supports screening at 45 years. CRC incidence is rising in persons under age 50, and thorough diagnostic evaluation of young persons with suspected colorectal bleeding is recommended. Discontinuation of screening should be considered when persons up to date with screening, who have prior negative screening (particularly colonoscopy), reach age 75 or have <10 years of life expectancy. Persons without prior screening should be considered for screening up to age 85, depending on age and comorbidities. Persons with a family history of CRC or a documented advanced adenoma in a first-degree relative age <60 years or 2 first-degree relatives with these findings at any age are recommended to undergo screening by colonoscopy every 5 years, beginning 10 years before the age at diagnosis of the youngest affected relative or age 40, whichever is earlier. Persons with a single first-degree relative diagnosed at ≥60 years with CRC or an advanced adenoma can be offered average-risk screening options beginning at age 40 years. © 2017 by the American College of Gastroenterology.


Erratum to: Chapter 5 in: D. Alberts et al. (eds.), Supportive Cancer Care, DOI 10.1007/978-3-319-24814-1_5. Suzanne M. Rhodes, Jennifer Gabbard, Ateefa Chaudhury, Briana Ketterer were not listed among the authors. © Springer International Publishing Switzerland 2016. All rights reserved.
Researchers have noted the potential of very brief technology-based multimedia interventions to disseminate positive parenting practices in pediatric primary care. Such interventions are well-accepted and reported as useful, but no study has objectively assessed their effects on target parenting behaviors. To determine the effects of a 4-min video intervention on effective instruction delivery, a multiphase multiple-baseline across participants design was used to sequentially expose parent-child dyads (N = 3) to the following conditions: Baseline, Video Intervention, Video Intervention + Self-Feedback, Video Intervention + Self-Feedback + Researcher-Feedback. Parent-child dyads were directly observed and parent behavior was coded for effective instruction delivery. Each dyad showed improvement in effective instruction delivery in response to the intervention. For 2/3 dyads, feedback phases resulted in additive gains. The results demonstrate that in addition to being well-accepted and perceived as useful, ultra-brief multimedia interventions hold potential to alter specific parenting behaviors. © 2016 American Psychological Association.

BACKGROUND: The National Academies of Sciences, Engineering, and Medicine (formerly the Institute of Medicine) recently recommended inclusion of postdischarge health-related quality of life (HRQoL) and patient-reported outcomes (PROs) metrics to benchmark the quality of trauma care. Currently, these measures are not routinely collected at most trauma centers. We sought to determine the feasibility and value of adding such long-term outcome measures to trauma registries. METHODS: As part of the FORTE (Functional Outcomes and Recovery after Trauma Emergencies) project, we included patients with an Injury Severity Score of 9 or greater, admitted to the Brigham and Women’s Hospital in Boston, MA, who were identified retrospectively using the institutional trauma registry and contacted 6 or 12 months after injury to participate in a telephone survey evaluating HRQoL (Short Form 12 [SF-12]), PROs (Trauma Quality of Life), posttraumatic stress disorder, return to work, residential status, and health care utilization. RESULTS: Data were collected for 171 of 394 eligible patients: 85/189 (45%) at 6 months and 86/205 (42%) at 12 months; 25%/29% (6/12 months) patients could not be contacted, 15%/16% (6/12 months) declined to participate, and 15%/13% (6/12 months) were interested in participating at another time but were not reached again. Approximately 20% patients screened positive for posttraumatic stress disorder, and half had not yet returned to work. There were significant reductions in SF-12 physical composite scores relative to population norms (mean, 50 [SD, 10]) at 6 months (mean, 44; 95% confidence interval [CI], 41-47) and 12 months (45; 95% CI, 42-47); no difference was noted in the SF-12 mental composite scores (6 months: 51 [95% CI, 48-54]; 12 months: 50 [95% CI, 46-53]). CONCLUSIONS: Trauma patients reported considerable impairment 6 and 12 months after injury. Routine collection of PROs and HRQoL provides important data regarding trauma outcomes beyond mortality and will enable the development of quality improvement metrics that better reflect patients’ postinjury experiences. Improved and alternate methods for collection of these data need to be developed to enhance response rates before widespread adoption across trauma centers in the United States. LEVEL OF EVIDENCE: Prognostic/epidemiologic, level II; Therapeutic, level III.
aberrations, transcriptional features, and clinical outcomes. We report change-of-function SRSF2 mutations. Within D3-UM, EIF1AX- and SRSF2/UF3B1-mutant tumors have distinct somatic copy number alterations and DNA methylation profiles, providing insight into the biology of these low- versus intermediate-risk clinical mutation subtypes.


BACKGROUND AND AIMS: EUS-guided FNA (EUS-FNA) is the primary method used to obtain pancreatic tissue for preoperative diagnosis. Accumulating evidence suggests diagnostic and prognostic information may be obtained by gene-expression profiling of these biopsy specimens. RNA sequencing (RNAseq) is a newer method of gene-expression profiling, but published data are scant on the use of this method on pancreas tissue obtained via EUS-FNA. The aim of this study was to determine whether RNAseq of EUS-FNA biopsy samples of undiagnosed pancreatic masses can reliably discriminate between benign and malignant tissue.

METHODS: In this prospective study, consenting adults presented to 2 tertiary care hospitals for EUS of suspected pancreatic mass. Tissue was submitted for RNAseq. The results were compared with cytopathologic diagnosis, surgical pathology diagnosis, or benign clinical follow-up of at least 1 year. RESULTS: Forty-eight patients with solid pancreatic mass lesions were enrolled. Nine samples were excluded because of inadequate RNA and 3 because of final pathologic diagnosis of neuroendocrine tumor. Data from the first 13 patients were used to construct a linear classifier, and this was tested on the final 23 patients (15 malignant and 8 benign lesions). RNAseq of EUS-FNA biopsy samples distinguishes ductal adenocarcinoma from benign pancreatic solid masses with a sensitivity of .87 (range, .58-.98) and specificity of .75 (range, .35-.96). CONCLUSIONS: This proof-of-principle study suggests RNAseq of EUS-FNA samples can reliably detect adenocarcinoma and may provide a new method to evaluate more diagnostically challenging pancreatic lesions.


This study analyzed the impact of sex, hemodynamic profile, and valve fusion pattern on aortopathy associated with bicuspid aortic valve (BAV). The National Heart Lung and Blood Institute-sponsored National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) provided comprehensive information on a large population of well-characterized patients with BAV. Of 969 enrolled patients with BAV, 551 (57%, 77% male) had already undergone valvular and/or aortic surgery. Echocardiographic imaging data were available on 339 unoperated or preoperative participants who formed the basis of this study. BAV function was normal in 45 (14%), with a predominant aortic regurgitation (AR) in 127 (41%) and a predominant aortic stenosis (AS) in 76 (22%). Moderate-severe AR was associated with larger sinus of Valsalva (SOV) diameters compared with normal function and AS (all p <0.01). Moderate-severe AS was associated with a larger ascending aortic (AscAo) diameter compared with normal function (p = 0.003) but not with AR. The SOV diameter was larger in men than in women (3.7 +/- 0.7 vs 3.3 +/- 0.6 cm, p <0.0001), whereas AscAo diameters were comparable (3.9 +/- 0.9 vs 3.7 +/- 0.9 cm, p = 0.08). Right-left commissural fusion was associated with a larger SOV diameter (3.7 +/- 0.7 vs 3.3 +/- 0.6 cm, p <0.0001) compared with a right-noncoronary fusion pattern. Predominant AR was more common in men (45% vs 27%, p = 0.004), whereas AS was more common in women (29% vs 18%, p = 0.04). In conclusion, in the GenTAC Registry, AR was associated with diffuse (annular, SOV, and AscAo) enlargement, whereas moderate-severe AS was only associated with AscAo enlargement. Male sex and right-left cusp pattern of cusp fusion were associated with larger SOV diameters and a greater likelihood of AR, whereas women had a higher prevalence of AS.

BACKGROUND: Allograft healing (ligamentization) after reconstruction of the anterior cruciate ligament (ACL) is dependent on multiple factors, including tissue processing, host biologic environment, and biomechanical stressors. Magnetic resonance imaging (MRI) can be used to assess graft maturation after ACL reconstruction. HYPOTHESIS: A significant difference will exist in the MRI analysis between 2 distinct allograft constructs. Specifically, the MRI signal-to-noise quotient (SNQ) value will be smaller in quadrupled hamstring tendon (HT) allografts compared with doubled tibialis anterior (TA) allografts due to the difference in graft geometry (surface area-to-volume ratio). STUDY DESIGN: Cohort study; Level of evidence, 2. METHODS: Prospectively collected data from a subset of patients who participated in a randomized controlled trial at a single center from July 2010 to April 2012 were reviewed. Patients underwent ACL reconstruction using either HT or TA allografts. Six months postoperatively, 32 patients underwent noncontrast MRI to assess ligamentization. The SNQ was calculated for the allograft using sagittal noncontrast T2-weighted MRI as follows: SNQ = (Sgraft - Squadriceps)/Sbackground. Graft properties including sagittal and coronal angle as well as tibial and femoral tunnel location were measured. All participants completed validated patient-reported outcome measures preoperatively and at 2 years postoperatively. RESULTS: The mean MRI SNQ for the HT and TA allografts was 2.56 +/- 2.41 and 3.15 +/- 3.38, respectively (P = .57). For the entire group, there was a significant correlation between MRI SNQ and both sagittal graft angle (P = .02) and sagittal tibial tunnel position (P < .001). We did not find a significant correlation between the tibial tunnel location in the coronal plane, coronal graft angle, or location of the femoral tunnel and the MRI SNQ. CONCLUSION: Allograft ligamentization 6 months postoperatively, as assessed by MRI, is dependent on position of the tibial tunnel in the sagittal plane as well as sagittal graft orientation. We did not detect a difference in graft maturation at 6 months between the tibialis anterior and hamstring tendon allografts. This is the only study to our knowledge that directly compares quadrupled HT allografts and doubled TA allografts using postoperative MRI.


BACKGROUND: Conduct a prospective randomized study to compare clinical outcomes of anterior cruciate ligament (ACL) reconstruction using quadrupled hamstring tendon (HT) allograft or doubled tibialis anterior (TA) allograft. Limited level 1 data exist comparing outcomes of different soft tissue allograft constructs for ACL reconstruction. We hypothesized no difference would exist in the patient reported outcomes (PRO), arthrometric testing, or rate of re-rupture between the two constructs. METHODS: Ninety eight subjects undergoing primary ACL reconstruction were randomized to HT (n=47) or TA (n=51) allograft. Subjects completed validated (PRO) measures pre-operatively, and six months and two years post-operatively. Arthrometric testing was performed at six months to assess integrity of the reconstruction. RESULTS: Fifty-eight percent of subjects (57/98) completed a two-year follow up. Allograft re-tear rates were similar between groups (6.2% HT vs. 4.0% TA, respectively, p=1.0). The relative risk of re-tear in the HT group was 1.5 compared to the TA group (p=0.7). The TA group improved significantly more on the physical portion of the VR-12 (p=0.046) and Lysholm score (p=0.014) compared to the HT group. There was no difference in the change from baseline for the other PRO scores at two years. CONCLUSIONS: Our data indicate no difference in graft failure rate and similar improvement from baseline in most PRO scores between treatment groups after two years. Based on these findings, TA allograft appears to provide a reliable and satisfactory option for patients who elect to undergo allograft ACL reconstruction.

The recent emergence of alternative polyadenylation (APA) as an engine driving transcriptomic diversity has stimulated the development of sequencing methodologies designed to assess genomewide polyadenylation events. The goal of these approaches is to enrich, partition, capture and ultimately sequence poly(A) site junctions. However, these methods often require poly(A) enrichment, 3’ linker ligation steps, and RNA fragmentation, which can necessitate higher levels of starting RNA, increase experimental error and potentially introduce bias. We recently reported a click-chemistry based method for generating RNAseq libraries called ‘Click-Seq’. Here, we adapt this method to direct the cDNA synthesis specifically toward the 3’UTR/poly(A) tail junction of cellular RNA. With this novel approach, we demonstrate sensitive and specific enrichment for poly(A) site junctions without the need for complex sample preparation, fragmentation or purification. Poly(A)-ClickSeq (PAC-seq) is therefore a simple procedure that generates high-quality RNA-seq poly(A) libraries. As a proof-of-principle, we utilized PAC-seq to explore the poly(A) landscape of both human and Drosophila cells in culture and observed outstanding overlap with existing poly(A) databases and also identified previously unannotated poly(A) sites. Moreover, we utilize PAC-seq to quantify and analyze APA events regulated by CFIm25 illustrating how this technology can be harnessed to identify alternatively polyadenylated RNA. © The Author(s) 2017.


The corticotropin-releasing factor (CRF) system plays a role in alcohol consumption, and its dysregulation can contribute to alcohol use disorder. This system includes four peptide ligands: CRF, urocortin (Ucn)1, Ucn2, and Ucn3. Historically, attention focused on CRF, however, Ucn1 also plays a critical role in excessive alcohol use. This review covers evidence for this contribution and contrasts the role of Ucn1 with CRF. While CRF can promote binge consumption, this regulation occurs through generalized mechanisms that are not specific for alcohol. In contrast, inhibition of Ucn1 action specifically blunts escalation of alcohol drinking. Lesions, genetic knockout, and RNA interference experiments indicate that the centrally projecting Edinger-Westphal nucleus is the neuroanatomical source of Ucn1 critical for alcohol drinking. We propose that the contributions of Ucn1 to excessive drinking likely occur through enhancing rewarding properties of alcohol and symptoms of alcohol withdrawal, whereas CRF drives dependence-induced drinking at later stages of alcohol use. The transition from occasional binge drinking to dependence intricately depends on CRF system plasticity and coordination of CRF and Ucn1. © 2017 Elsevier Inc.


PURPOSE OF REVIEW: A central question for the HIV cure field is to determine new ways to target clinically relevant, latently and actively replicating HIV-infected cells beyond resting memory CD4 T cells, particularly in anatomical areas of low drug penetrability. RECENT FINDINGS: HIV eradication strategies being positioned for targeting HIV for extinction in the CD4 T-cell compartment may also show promise in non-CD4 T-cells reservoirs. Furthermore, several exciting novel therapeutic approaches specifically focused on HIV clearance from non-CD4 T-cell populations are being developed. SUMMARY: Although reservoir validity in these non-CD4 T cells continues to remain debated, this review will highlight recent advances and make an argument as to their clinical relevancy as we progress towards an HIV cure.

This systematic review was designed to compare the complications of acoustic neuroma surgery via the suboccipital retrosigmoid approach in the sitting versus lateral positions. Searches for randomized trials and observational studies about the complications of acoustic neuroma surgery were performed in five medical databases (through October 2015) including PubMed, MEDLINE (In-Process and Other Non-Indexed Citations), EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and PsycINFO. Primary outcomes in this study were venous air emboli, neuropsychological defects, CSF leak, facial and abducens nerves palsy, postoperative deafness, hydrocephalus and mortality. Secondary outcomes were total tumor removal, facial and cochlear nerves preservation and ataxia. 843 abstracts and titles were reviewed and 10 studies (two non-randomized comparative studies and 8 non-comparative case series) were included for data extraction. Because of the heterogeneity of the studies, small number of participants and methodological shortcomings, findings were evaluated qualitatively. No impressive advantage was found in surgical or neurological outcomes for use of the sitting or lateral positions in patients with acoustic neuroma surgery. According to the available evidence, it seems that both sitting and lateral positions can be used with an equivalent safety for acoustic neura surgery via the retrosigmoid suboccipital approach. There seems a clear need for comparative studies to compare harms and other outcomes for these two positions.


**BACKGROUND & AIMS:** There is an unclear role for colonoscopy in the evaluation of symptomatic individuals younger than 50 years old. We aimed to determine the prevalence of large polyps (>9 mm) or tumors in individuals 40 to 49 years old who underwent colonoscopy for various signs and symptoms, and compare the results with those from average-risk individuals ages 50 to 54 years who underwent screening colonoscopy. **METHODS:** We collected data from a national endoscopy database, from 2000 through 2012, and identified patients 40 to 49 years old who underwent colonoscopy for bleeding and nonbleeding indications. The prevalence of large polyps (>9 mm) or tumors was compared with the prevalence in a reference group (n = 99,713 average-risk individuals ages 50-54 undergoing screening colonoscopy). **RESULTS:** A total of 65,892 patients ages 40 to 49 years underwent colonoscopy for a variety of indications. Significantly larger proportions of male and female patients with hematochezia without anemia or iron-deficiency anemia (IDA) had large polyps or tumors (7.2%) compared with the reference group (men, 7.2% vs 6.2%; P = .0001; and women, 5.5% vs 4.1%; P < .0001). Patients with weight loss, anemia or IDA, or hematochezia with anemia or IDA did not have a significantly higher prevalence of large polyps or tumors than the reference group. Significantly lower proportions of patients with general gastrointestinal symptoms (pain, bloating, or change in bowel habits) had advanced neoplasia compared with the reference group (men, 3.9% vs 6.2%; P < .0001; and women, 2.7% vs 4.1%; P < .0001). **CONCLUSIONS:** An analysis of a national endoscopy database supports the role of colonoscopy to evaluate hematochezia in patients 40 to 49 years old. A lower proportion of patients with anemia, weight loss, and general abdominal symptoms had large polyps or tumors compared with average-risk patients 50 to 54 years old. A significantly lower proportion of patients younger than 50 years with general gastrointestinal symptoms had large polyps; these patients are therefore less likely to benefit from colonoscopy.


By virtue of their religious principles, Jehovah’s Witnesses (JWs) generally object to receiving blood products, raising numerous ethical, legal, and medical challenges for providers who care for these patients, especially in the emergent setting. In this review, we discuss several areas relevant to the care of JWs, including the current literature on "bloodless" medical care in the setting of peri- and intra-operative management, acute blood
loss, trauma, pregnancy, and malignancy. We have found that medical and administrative efforts in the form of bloodless medicine and surgery programs can be instrumental in helping to reduce risks of morbidity and mortality in these patients. Planning prior to an anticipated event associated with blood loss or anemia (such as elective surgery, pregnancy, and chemotherapy) is critical. Specifically, bloodless medicine programs should prioritize vigilant early screening and management of anemias, early establishment of patient wishes regarding transfusion, and the incorporation of those wishes into multidisciplinary medical and surgical care. Although there are now a variety of human- and non-human-based products available as transfusion alternatives, the degree and quality of evidence to support their use varies significantly between products and is also largely dependent on the clinical setting. This article is protected by copyright. All rights reserved.


OBJECTIVE: To characterize anticipatory postural adjustments (APAs) across a variety of step initiation tasks in people with Parkinson disease (PD) and healthy subjects. DESIGN: Cross-sectional study. Step initiation was analyzed during self-initiated gait, perceptual cued gait, and compensatory forward stepping after platform perturbation. People with PD were assessed on and off levodopa. SETTING: University research laboratory. PARTICIPANTS: People (N=31) with PD (n=19) and healthy aged-matched subjects (n=12). INTERVENTIONS: Not applicable. MAIN OUTCOME MEASURES: Mediolateral (ML) size of APAs (calculated from center of pressure recordings), step kinematics, and body alignment. RESULTS: With respect to self-initiated gait, the ML size of APAs was significantly larger during the cued condition and significantly smaller during the compensatory condition (P<.001). Healthy subjects and patients with PD did not differ in body alignment during the stance phase prior to stepping. No significant group effect was found for ML size of APAs between healthy subjects and patients with PD. However, the reduction in APA size from cued to compensatory stepping was significantly less pronounced in PD off medication compared with healthy subjects, as indicated by a significant group by condition interaction effect (P<.01). No significant differences were found comparing patients with PD on and off medications. CONCLUSIONS: Specific stepping conditions had a significant effect on the preparation and execution of step initiation. Therefore, APA size should be interpreted with respect to the specific stepping condition. Across-task changes in people with PD were less pronounced compared with healthy subjects. Antiparkinsonian medication did not significantly improve step initiation in this mildly affected PD cohort.


Quality improvement efforts are an increasingly expanding focus for perinatal care providers across the United States. From successful hospital-level initiatives, there has been a growing effort to use and implement quality improvement work in substantive and meaningful ways. This article summarizes the foundations of maternal-focused, birth-focused, and neonatal-focused quality improvement initiatives to highlight the underpinnings and potential future directions of current state-level perinatal quality care collaboratives.


INTRODUCTION: The relationship between the Los Angeles (LA) grade of esophagitis and acid exposure by pH monitoring is unclear. The aim of this study was to correlate the results of pH testing in patients with esophagitis to determine at what LA grade of esophagitis a pH test is not necessary. METHODS: A
A retrospective review was performed of the records of all patients who underwent upper endoscopy and were found to have esophagitis graded using the LA system and who had pH monitoring from 2014 to 2016. An abnormal pH test was determined based on the DeMeester score. RESULTS: There were 56 patients with a median age of 57 years. Esophagitis was LA grade A in 19, B in 20, C in 15 and D in 2 patients. An abnormal pH score was present in 47 patients (84%). All patients with C or D esophagitis had an abnormal pH score compared to 79% and 75% of patients with A and B esophagitis, respectively. CONCLUSIONS: The presence of LA C or D esophagitis was always associated with increased esophageal acid exposure on pH testing and is proof of reflux disease. However, pH testing is recommended prior to antireflux surgery in patients with LA A or B esophagitis.


BACKGROUND: The objective of this study was to evaluate the mechanical and histological properties of a fully absorbable poly-4-hydroxybutyrate/absorbable barrier composite mesh (Phasix ST) compared to partially absorbable (Ventralight ST), fully absorbable (Phasix), and biologically derived (Strattice) meshes in a porcine model of ventral hernia repair. METHODS: Bilateral abdominal surgical defects were created in twenty-four Yucatan pigs, repaired with intraperitoneal (Phasix ST, Ventralight ST) or retromuscular (Phasix, Strattice) mesh, and evaluated at 12 and 24 weeks (n = 6 mesh/group/time point). RESULTS: Prior to implantation, Strattice demonstrated significantly higher (p < 0.001) strength (636.6 +/- 192.1 N) compared to Ventralight ST (206.9 +/- 11.3 N), and Phasix (200.6 +/- 25.2 N). At 12 and 24 weeks, mesh/repair strength was significantly greater than NAW (p < 0.01 in all cases), and no significant changes in strength were observed for any meshes between 12 and 24 weeks (p > 0.05). Phasix mesh/repair strength was significantly greater than Strattice (p < 0.001) at 12 and 24 weeks, and Ventralight ST mesh/repair strength was significantly greater than Phasix ST mesh (p < 0.05) at 24 weeks. At 12 and 24 weeks, Phasix ST and Ventralight ST were associated with mild inflammation and minimal-mild fibrosis/neovascularization, with no significant differences between groups. At both time points, Phasix was associated with minimal-mild inflammation/fibrosis and mild neovascularization. Strattice was associated with minimal inflammation/fibrosis, with minimal neovascularization at 12 weeks, which increased to mild by 24 weeks. Strattice exhibited significantly less neovascularization than Phasix at 12 weeks and significantly greater inflammation at 24 weeks due to remodeling. CONCLUSIONS: Phasix ST demonstrated mechanical and histological properties comparable to partially absorbable (Ventralight ST) and fully resorbable (Phasix) meshes at 12 and 24 weeks in this model. Data also suggest that fully absorbable meshes with longer-term resorption profiles may provide improved mechanical and histological properties compared to biologically derived scaffolds.


Prenatal androgens are largely responsible for growth and differentiation of the genital tract and testis and for organization of the control mechanisms regulating male reproductive physiology and behavior. The aim of the present study was to evaluate the impact of inappropriate exposure to excess testosterone (T) during the first trimester of fetal development on the reproductive function, sexual behavior, and fertility potential of rams. We found that biweekly maternal T propionate (100 mg) treatment administered from Day 30-58 of gestation significantly decreased (P < 0.05) postpubertal scrotal circumference and sperm concentration. Prenatal T exposure did not alter ejaculate volume, sperm motility and morphology or testis morphology. There was, however, a trend for more T-exposed rams than controls to be classified as unsatisfactory potential breeders during breeding soundness examinations. Postnatal serum T concentrations were not affected by prenatal T exposure, nor was the expression of key testicular genes essential for spermatogenesis.
and steroidogenesis. Basal serum LH did not differ between treatment groups, nor did pituitary responsiveness to GnRH. T-exposed rams, like control males, exhibited vigorous libido and were sexually attracted to estrous females. In summary, these results suggest that exposure to exogenous T during the first trimester of gestation can negatively impact spermatogenesis and compromise the reproductive fitness of rams.


We report functional and structural evidence for GluA2-lacking Ca2+-permeable AMPARs (CP-AMPARs) at the mature hair cell ribbon synapse. By using the methodological advantages of three species (of either sex), we demonstrate that CP-AMPARs are present at the hair cell synapse in an evolutionarily conserved manner. Via a combination of in vivo electrophysiological and Ca2+ imaging approaches in the larval zebrafish, we show that hair cell stimulation leads to robust Ca2+ influx into afferent terminals. Prolonged application of AMPA caused loss of afferent terminal responsiveness, whereas blocking CP-AMPARs protects terminals from excitotoxic swelling. Immunohistochemical analysis of AMPAR subunits in mature rat cochlea show regions within synapses lacking the GluA2 subunit. Paired recordings from adult bullfrog auditory synapses demonstrate that CP-AMPARs mediate a major component of glutamatergic transmission. Together, our results support the importance of CP-AMPARs in mediating transmission at the hair cell ribbon synapse. Further, excess Ca2+ entry via CP-AMPARs may underlie afferent terminal damage following excitotoxic challenge, suggesting that limiting Ca2+ levels in the afferent terminal may protect against cochlear synaptopathy associated with hearing loss. **SIGNIFICANCE STATEMENT** A single incidence of noise overexposure causes damage at the hair cell synapse that later leads to neurodegeneration and exacerbates age-related hearing loss. A first step toward understanding cochlear neurodegeneration is to identify the cause of initial excitotoxic damage to the postsynaptic neuron. Using a combination of immunohistochemical, electrophysiological, and Ca2+ imaging approaches in evolutionarily divergent species, we demonstrate that Ca2+-permeable AMPARs (CP-AMPARs) mediate glutamatergic transmission at the adult auditory hair cell synapse. Overexcitation of the terminal causes Ca2+ accumulation and swelling that can be prevented by blocking CP-AMPARs. We demonstrate that CP-AMPARs mediate transmission at this first-order sensory synapse and that limiting Ca2+ accumulation in the terminal may protect against hearing loss.


**BACKGROUND:** Despite the well-known fact that antibiotics (AB) are not effective against viruses, many patients ask for - and all too often doctors provide - AB for treating URTIs. Over-prescribing of AB is one of the key causes for the development of bacterial resistance, which the U.S. Centers for Disease Control and Prevention (CDC) calls “one of the world’s most pressing public health problems”. In addition to the CDC initiated “Get Smart About Antibiotics” campaign, focused on educating doctors the public about the importance of appropriate AB use, other programs tackling this problem include the development of new treatment paradigms. Data published at the Oregon Health & Science University demonstrated that a ‘wait-and-see’ approach, without an AB prescription for the treatment of acute childhood ear infections, was as quick, safe, and effective in resolving the infections as an AB prescription (Spiro DM, Tay KY, Arnold DH, Dziura JD, Baker MD, Shapiro ED. Wait-and-See Prescription for the Treatment of Acute Otitis Media. *JAMA* 2006; 296:1235-1241). **OBJECTIVE:** To try and reduce inappropriate prescribing practices, a wait and see or delayed approach requires patients to return for a prescription if their symptoms persist or worsen. The aim of this study was to determine whether treatment with Mucinex D (Reckitt Benckiser LLC, Parsippany, New
Jersey) lowers the use of antibiotics in the treatment of URTIs when compared with placebo. METHODS: Patients aged 18 to 75 years with symptoms of acute URTIs were randomized to 1200 mg guaifenesin/120 mg pseudoephedrine hydrochloride extended-release, bilayer tablets or matching placebo for 7 consecutive days. Eligible patients met physician’s criteria for antibiotic therapy but were considered suitable for a wait and see approach (withholding antibiotics for >/=48 hours). Patients recorded symptom ratings via an interactive voice response system. RESULTS: One thousand one hundred eighty-nine patients enrolled; data are presented for the modified intent-to-treat population (n = 1179). At Day 8, significantly fewer patients receiving guaifenesin/pseudoephedrine versus placebo desired antibiotics (4.2% vs 8.0%). No adverse effects were reported due to patients not taking antibiotics. Significant reductions in URTI symptoms were observed for extended-release guaifenesin/pseudoephedrine versus placebo, from Day 1 throughout the study; however, the proportion of patients experiencing overall relief at the Day 4 evening assessment (primary end point) did not reach statistical significance. Treatment-related adverse events were reported in 9.8% and 4.7% of patients receiving guaifenesin/pseudoephedrine and placebo, respectively. CONCLUSIONS: The study found that a wait and see approach was associated with decreased antibiotic use. In addition, the use of a guaifenesin pseudoephedrine combination product provided an effective symptom control compared to a placebo and a well-tolerated first-line strategy for the management of URTIs. This study was not designed to assess the effects of guaifenesin or pseudoephedrine individually. Other limitations include the need for better clinical methods to assess the effectiveness of treatments for acute symptoms of patients with URTIs. ClinicalTrials.gov identifier: NCT01202279.


As one of the most commonly read online sources of medical information, Wikipedia is an influential public health platform. Its medical content, community, collaborations and challenges have been evolving since its creation in 2001, and engagement by the medical community is vital for ensuring its accuracy and completeness. Both the encyclopaedia’s internal metrics as well as external assessments of its quality indicate that its articles are highly variable, but improving. Although content can be edited by anyone, medical articles are primarily written by a core group of medical professionals. Diverse collaborative ventures have enhanced medical article quality and reach, and opportunities for partnerships are more available than ever. Nevertheless, Wikipedia’s medical content and community still face significant challenges, and a socioecological model is used to structure specific recommendations. We propose that the medical community should prioritise the accuracy of biomedical information in the world’s most consulted encyclopaedia.


Objective: To determine the proportion of women presenting for an induced abortion in Ghana who could use a gestational wheel to determine if they had reached at least 13 weeks or fewer than 13 weeks of pregnancy accurately. Methods: The present cross-sectional study was conducted at four facilities in Ghana between February 1, and July 31, 2014. Women aged at least 18 years seeking induced abortions who had not previously been informed of the length of their pregnancy by a clinician were enrolled. Women self-assessed pregnancy duration using a gestational wheel before a clinician assessed the length via clinical assessment and bimanual exam for use as a respective reference point. The proportion of participants who used the wheel successfully was calculated. Results: The study enrolled 780 participants, 770 of whom used the gestational wheel. Of these, 221 (28.7%) could use the wheel without verbal instructions, and 465 (60.4%) described it as easy to use. Agreement in pregnancy-length assessments was recorded for 728 (94.5%) patients. There were 10 (1.3%) and 28 (3.6%) participants who made evaluations with "low-risk disagreement" and "high-risk disagreement" with the clinician assessment, respectively. Conclusion: Almost
all participants could use the gestational wheel to date their pregnancies correctly. This tool could help women perform medical abortions safely in the community, reducing morbidity and mortality from unsafe abortions. © 2017 International Federation of Gynecology and Obstetrics.


OBJECTIVE: There are no evidence-based guidelines on the preferred approach to treating early-life epilepsy. We examined initial therapy selection in a contemporary US cohort of children with newly diagnosed, nonsyndromic, early-life epilepsy (onset before age three years). METHODS: Seventeen pediatric epilepsy centers participated in a prospective cohort study of children with newly diagnosed epilepsy with onset under 36 months of age. Details regarding demographics, seizure types, and initial medication selections were obtained from medical records. RESULTS: About half of the 495 enrolled children with new-onset, nonsyndromic epilepsy were less than 12 months old at the time of diagnosis (n = 263, 53%) and about half (n = 260, 52%) had epilepsy with focal features. Of 464 who were treated with monotherapy, 95% received one of five drugs: levetiracetam (n = 291, 63%), oxcarbazepine (n = 67, 14%), phenobarbital (n = 57, 12%), topiramate (n = 16, 3.4%), and zonisamide (n = 13, 2.8%). Phenobarbital was prescribed first for 50 of 163 (31%) infants <6 months old versus seven of 300 (2.3%) of children six months or older (P < 0.0001). Although the first treatment varied across study centers (P < 0.0001), levetiracetam was the most commonly prescribed medication regardless of epilepsy presentation (focal, generalized, mixed/uncertain). Between the first and second treatment choices, 367 (74%) of children received levetiracetam within the first year after diagnosis. CONCLUSIONS: Without any specific effort, the pediatric epilepsy community has developed an unexpectedly consistent approach to initial treatment selection for early-life epilepsy. This suggests that a standard practice is emerging and could be utilized as a widely acceptable basis of comparison in future drug studies.


Adolescent ingestions are common reasons for calls to poison centers in United States. As opposed to younger children who mostly have unintentional exposures, adolescent ingestions often result from intentional use. This manuscript reviews recent reports on adolescent ingestions related to intentional abuse, self-harm, and use of opioid medications. © 2017 Elsevier Inc.


The thalamus connects the cortex with other brain regions and supports sensory perception, movement, and cognitive function via numerous distinct nuclei. However, the mechanisms underlying the development and organization of diverse thalamic nuclei remain largely unknown. Here we report an intricate ontogenetic logic of mouse thalamic structures. Individual radial glial progenitors in the developing thalamus actively divide and produce a cohort of neuronal progeny that shows striking spatial configuration and nuclear occupation related to functionality. Whereas the anterior clonal cluster displays relatively more tangential dispersion and contributes predominantly to nuclei with cognitive functions, the medial ventral posterior
clonal cluster forms prominent radial arrays and contributes mostly to nuclei with sensory- or motor-related activities. Moreover, the first-order and higher-order sensory and motor nuclei across different modalities are largely segregated clonally. Notably, sonic hedgehog signaling activity influences clonal spatial distribution. Our study reveals lineage relationship to be a critical regulator of nonlaminated thalamus development and organization.


BACKGROUND AND PURPOSE: MR imaging can be used to measure structural changes in the brains of individuals with multiple sclerosis and is essential for diagnosis, longitudinal monitoring, and therapy evaluation. The North American Imaging in Multiple Sclerosis Cooperative steering committee developed a uniform high-resolution 3T MR imaging protocol relevant to the quantification of cerebral lesions and atrophy and implemented it at 7 sites across the United States. To assess intersite variability in scan data, we imaged a volunteer with relapsing-remitting MS with a scan-rescan at each site.

MATERIALS AND METHODS: All imaging was acquired on Siemens scanners (4 Skyra, 2 Tim Trio, and 1 Verio). Expert segmentations were manually obtained for T1-hypointense and T2 (FLAIR) hyperintense lesions. Several automated lesion-detection and whole-brain, cortical, and deep gray matter volumetric pipelines were applied. Statistical analyses were conducted to assess variability across sites, as well as systematic biases in the volumetric measurements that were site-related.

RESULTS: Systematic biases due to site differences in expert-traced lesion measurements were significant (P < .01 for both T1 and T2 lesion volumes), with site explaining >90% of the variation (range, 13.0 - 16.4 mL in T1 and 15.9 - 20.1 mL in T2) in lesion volumes. Site also explained >80% of the variation in most automated volumetric measurements. Output measures clustered according to scanner models, with similar results from the Skyra versus the other 2 units.

CONCLUSIONS: Even in multicenter studies with consistent scanner field strength and manufacturer after protocol harmonization, systematic differences can lead to severe biases in volumetric analyses.


OBJECTIVES: Preterm premature rupture of membranes (PPROM) is a major contributor to overall preterm birth (PTB) rates. A short interpregnancy interval (IPI) is a well-known risk factor for PTB. It is unknown if a short IPI specifically affects the risk of developing PPROM in a subsequent pregnancy. We sought to determine the association between IPI and the risk of PPROM in a subsequent pregnancy.

METHODS: A retrospective cohort study using the Missouri birth certificate database of singleton births from 2003 to 2013 was conducted. A short IPI (delivery of the prior pregnancy to conception of the index pregnancy) was defined as <=6 months. IPI >6 months was categorized into two groups: IPI 7-23 months and IPI >/=24 months. PPROM was defined as premature rupture of membranes between 160 and 366 weeks. Multivariable logistic regression was conducted to determine the association between IPI and PPROM while controlling for maternal age, race, body mass index (BMI), education level, use of social services (Medicaid insurance, food stamps, or participation in the WIC [Women, Infants, and Children] program), tobacco use, and history of PTB. Secondary outcome included the gestational age at delivery, categorized into five subgroups (</=240, 241-280, 281-320, 321-340, and 341-366 weeks).

RESULTS: 474,957 subjects with singleton gestations had data available to calculate the IPI. Of these, 1.4% (n = 6797) experienced PPROM. IPI </=6 months was significantly associated with an increased risk of developing PPROM compared with patients with IPI >/=24 months (odds ratio [OR] 1.80, 95% CI 1.70-1.90, p < .001). A higher proportion of women with IPI </=6 months delivered between 281 and 320 weeks compared to the other two IPI groups (27.0 versus 15.0 and 16.4%, p < .001). Individual maternal factors associated with an increased risk of PPROM included advanced maternal age, African American race, BMI <18.5 kg/m2, BMI >/=30 kg/m2, use of social services, tobacco use, and a prior PTB.

CONCLUSION: Our data demonstrate that an IPI of </=6 months is significantly
associated with an increased risk of developing PPROM in the subsequent pregnancy. Of greater clinical relevance is that these women were more likely to deliver between 281 and 320 weeks as compared with women with a longer IPI. Novel to this study is the establishment of a specific link between a short IPI and PPROM with subsequent early delivery. Several maternal demographic factors known to be associated with PTB risk were also found to be associated with an increased risk of PPROM. Further studies are necessary to elucidate plausible biologic mechanisms ultimately leading to the development and implementation of preventive and therapeutic strategies for this high-risk cohort.


PURPOSE: Hiatal hernias are a common finding on radiographic or endoscopic studies. Hiatal hernias may become symptomatic or, less frequently, can incarcerate or become a volvulus leading to organ ischemia. This review examines latest evidence on the diagnostic workup and management of hiatal hernias. METHODS: A literature review of contemporary and latest studies with highest quality of evidence was completed. This information was examined and compiled in review format. RESULTS: Asymptomatic hiatal and paraesophageal hernias become symptomatic and necessitate repair at a rate of 1% per year. Watchful waiting is appropriate for asymptomatic hernias. Symptomatic hiatal hernias and those with confirmed reflux disease require operative repair with an anti-reflux procedure. Key operative steps include the following: reduction and excision of hernia sac, 3 cm of intraabdominal esophageal length, crural closure with mesh reinforcement, and an anti-reflux procedure. Repairs not amenable to key steps may undergo gastropexy and gastrostomy placement as an alternative procedure. CONCLUSIONS: Hiatal hernias are commonly incidental findings. When hernias become symptomatic or have reflux disease, an operative repair is required. A minimally invasive approach is safe and has improved outcomes.


BACKGROUND: Although most patients with atopic dermatitis (AD) are effectively managed with topical medication, a significant minority require systemic therapy. Guidelines for decision making about advancement to systemic therapy are lacking. OBJECTIVE: To guide those considering use of systemic therapy in AD and provide a framework for evaluation before making this therapeutic decision with the patient. METHODS: A subgroup of the International Eczema Council determined aspects to consider before prescribing systemic therapy. Topics were assigned to expert reviewers who performed a topic-specific literature review, referred to guidelines when available, and provided interpretation and expert opinion. RESULTS: We recommend a systematic and holistic approach to assess patients with severe signs and symptoms of AD and impact on quality of life before systemic therapy. Steps taken before commencing systemic therapy include considering alternate or concomitant diagnoses, avoiding trigger factors, optimizing topical therapy, ensuring adequate patient/caregiver education, treating coexistent infection, assessing the impact on quality of life, and considering phototherapy. LIMITATIONS: Our work is a consensus statement, not a systematic review. CONCLUSION: The decision to start systemic medication should include assessment of severity and quality of life while considering the individual’s general health status, psychologic needs, and personal attitudes toward systemic therapies.


The introduction of mild cognitive impairment (MCI) as a diagnostic category adds to the challenges of diagnosing Alzheimer’s Disease (AD). No single marker has been proven to accurately categorize patients into their
respective diagnostic groups. Thus, previous studies have attempted to develop fused predictors of AD and MCI. These studies have two main limitations. Most do not simultaneously consider all diagnostic categories and provide suboptimal fused representations using the same set of modalities for prediction of all classes.

In this work, we present a combined framework, cascaded multiview canonical correlation (CaMCCo), for fusion and cascaded classification that incorporates all diagnostic categories and optimizes classification by selectively combining a subset of modalities at each level of the cascade. CaMCCo is evaluated on a data cohort comprising 149 patients for whom neurophysiological, neuroimaging, proteomic and genomic data were available. Results suggest that fusion of select modalities for each classification task outperforms (mean AUC = 0.92) fusion of all modalities (mean AUC = 0.54) and individual modalities (mean AUC = 0.90, 0.53, 0.71, 0.73, 0.62, 0.68). In addition, CaMCCo outperforms all other multi-class classification methods for MCI prediction (PPV: 0.80 vs. 0.67, 0.63). © 2017 The Author(s).


Neonatal CD4(+) T cells have traditionally been viewed as deficient in their capacity to produce Th1 cytokines in response to polyclonal or Ag-specific stimuli. Thus, defining unique aspects of CD4(+) T cell activation and development into Th1 effector cells in neonates is essential to the successful development of novel vaccines and immunotherapies to protect infants from intracelluar pathogens. Using highly purified naive CD4(+) T cells derived from cord and adult peripheral blood, we compared the impact of anti-CD3 stimulation plus costimulation through TLR-2 performed in the absence of APC on CD4(+) T cell cytokine production, proliferation, and expression of activation markers. In both age groups, TLR-2 costimulation elicited activation of naive CD4(+) T cells, characterized by robust production of IL-2 as well as key Th1-type cytokines IFN-gamma and TNF-alpha. TLR-2 costimulation also dramatically reduced naive T cell production of the immunosuppressive cytokine IL-10. We observed that neonatal naive CD4(+) T cells are uniquely sensitive to TLR-2-mediated costimulation, which enabled them to produce equivalent amounts of IFN-gamma and more IL-2 when compared with adult responses. Thus, neonatal CD4(+) T cells have a distinctive propensity to use TLR-2-mediated costimulation for development into proinflammatory Th1 effectors, and interventions that target CD4(+) T cell TLR-2-mediated responses may be exploited to enhance neonatal adaptive immunity.


Purpose: To describe histopathologic features of an eye with retinal angiomatous proliferation (RAP) secondary to age-related macular degeneration treated with serial ranibizumab injections and to correlate these findings with spectral domain optical coherence tomography. Methods: Histopathologic features from serial sections through the globe of a 93-year-old man with age-related macular degeneration were studied and compared with spectral domain optical coherence tomography images obtained 7 weeks before his death. Results: The pathologic correlate of ranibizumab-treated RAP was a circumscribed, branching paucicellular vascular complex extending from the inner plexiform layer to Bruch membrane. The histopathologic findings corresponded to an area of hyperreflectivity on spectral domain optical coherence tomography imaging, substantiating the reported tomographic appearance of RAP lesions. A frank anastomosis with choroidal or retinal vasculature was not seen in this treated RAP lesion. There was a lack of retinal pigment epithelium underlying the lesion in an area of retinal pigment epithelium detachment. The elastic portion of Bruch membrane appeared intact. Treatment with ranibizumab over an extended period of time may have been associated with a loss of cellularity of the RAP lesion. Conclusion: In a patient with ARMD extensively treated with ranibizumab, color fundus photography, fluorescein angiography and SD-OCT images of RAP correlated histopathologically with a paucicellular intraretinal vascular complex.
Epstein-Barr virus (EBV) encodes >44 viral microRNAs (miRNAs) that are differentially expressed throughout infection, can be detected in EBV-positive tumors, and manipulate several biological processes including cell proliferation, apoptosis, and immune responses. Here, we show that EBV BHRF1-2 miRNAs block NF-kB activation following treatment with pro-inflammatory cytokines, specifically interleukin-1 beta. Analysis of EBV PAR-CLIP miRNA targetome datasets combined with pathway analysis revealed multiple BHRF1-2 miRNA targets involved in interleukin signaling pathways. By further analyzing changes in cellular gene expression patterns, we identified the interleukin-1 receptor 1 (IL1R1) as a direct target of miR-BHRF1-2-5p. Targeting of the IL1R1 3’ UTR by EBV miR-BHRF1-2-5p was confirmed using 3’ UTR luciferase reporter assays and western blot assays. Manipulation of EBV BHRF1-2 miRNA activity in latently-infected B cells altered steady-state cytokine levels and disrupted IL-1beta responsiveness. These studies demonstrate functionally relevant BHRF1-2 miRNA interactions during EBV infection, which is an important step in understanding their roles in pathogenesis. Importance IL-1 signaling plays an important role in inflammation and early activation of host innate immune responses following virus infection. Here, we demonstrate that a viral miRNA downregulates the IL-1 receptor 1 during EBV infection, which consequently alters the responsiveness of cells to IL-1 stimuli and changes the cytokine expression levels within infected cell populations. We postulate that this viral miRNA activity not only disrupts IL-1 autocrine and paracrine signaling loops that can alert effector cells to sites of infection, but also provides a survival advantage by dampening excessive inflammation that may be detrimental to the infected cell.


OBJECTIVES: To evaluate whether objectively measured sleep characteristics are associated with mortality risk independent of inflammatory burden and comorbidity. METHODS: The Osteoporotic Fractures in Men Sleep Study (conducted in 2003-2005) included community-dwelling older men (n = 2531; average [standard deviation (SD)] age = 76.3 (5.5) years). Sleep measures from in-home polysomnography and wrist actigraphy and assessments of serum inflammatory markers levels (C-reactive protein, interleukin-6, tumor necrosis factor alpha, tumor necrosis factor alpha soluble receptor II, and interferon-gamma) were obtained. Vital status was ascertained over an average (SD) follow-up of 7.4 (1.9 SD) years. RESULTS: Three of the seven main sleep measures examined were independently associated with greater inflammatory burden. Mortality risk associated with prolonged (>10% total sleep time) blood oxygen desaturation and short (<5 hours) sleep duration was attenuated to nonsignificance after adjusting for inflammatory burden or medical burden/lifestyle factors. Severe blood oxygen desaturation (adjusted hazard ratio [aHR] = 1.57, 95% confidence interval [CI] = 1.11-2.22), sleep fragmentation (aHR = 1.32, 95% CI = 1.12-1.57), and a lower percentage of sleep in rapid eye movement (aHR per SD = 0.90, 95% CI = 0.93-0.97) were independently associated with mortality. CONCLUSIONS: Short sleep duration and prolonged blood oxygen desaturation were independently associated with inflammatory burden, which attenuated associations between these sleep characteristics and mortality. Medical and life-style factors also substantially attenuated most sleep-mortality associations, suggesting complex relations between sleep, inflammation, and disease. Sleep fragmentation, severe blood oxygen desaturation, and the percentage of sleep time in rapid eye movement were independently related to mortality risk. Future studies with repeated measures of mediators/confounds will be necessary to achieve a mechanistic understanding of sleep-related mortality risk.

Pain is often described as a "biopsychosocial" process, yet social influences on pain and underlying neural mechanisms are only now receiving significant experimental attention. Expression of pain by one individual can be communicated to nearby individuals by auditory, visual, and olfactory cues. Conversely, the perception of another's pain can lead to physiological and behavioral changes in the observer, which can include induction of hyperalgesia in "bystanders" exposed to "primary" conspecifics in which hyperalgesia has been induced directly. The current studies were designed to investigate the neural mechanisms responsible for the social transfer of hyperalgesia in bystander mice housed and tested with primary mice in which hyperalgesia was induced using withdrawal (WD) from voluntary alcohol consumption. Male C57BL/6J mice undergoing WD from a two-bottle choice voluntary alcohol-drinking procedure served as the primary mice. Mice housed in the same room served as bystanders. Naive, water-drinking controls were housed in a separate room. Immunohistochemical mapping identified significantly enhanced Fos immunoreactivity (Fos-ir) in the anterior cingulate cortex (ACC) and insula (INS) of bystander mice compared to naive controls, and in the dorsal medial hypothalamus (DMH) of primary mice. Chemogenetic inactivation of the ACC but not primary somatosensory cortex reversed the expression of hyperalgesia in both primary and bystander mice. These studies point to an overlapping neural substrate for expression of socially transferred hyperalgesia and that expressed during alcohol WD.


The past decade has appreciated rapid advance in identifying the once elusive intestinal stem cell (ISC) populations that fuel the continual renewal of the epithelial layer. This advance was largely driven by identification of novel stem cell marker genes, revealing the existence of quiescent, slowly- and active-cycling ISC populations. However, a critical barrier for translating this knowledge to human health and disease remains elucidating the functional interplay between diverse stem cell populations. Currently, the precise hierarchical and regulatory relationships between these ISC populations are under intense scrutiny. The classical theory of a linear hierarchy, where quiescent and slowly-cycling stem cells self-renew but replenish an active-cycling population, is well established in other rapidly renewing tissues such as the haematopoietic system. Efforts to definitively establish a similar stem cell hierarchy within the intestinal epithelium have yielded conflicting results, been difficult to interpret, and suggest non-conventional alternatives to a linear hierarchy. While these new and potentially paradigm-shifting discoveries are intriguing, the field will require development of a number of critical tools, including highly specific stem cell marker genes along with more rigorous experimental methodologies, to delineate the complex cellular relationships within this dynamic organ system.


OBJECTIVES/HYPOTHESIS: The objective of this investigation was to evaluate endoscopic sinus surgery (ESS) outcomes for chronic rhinosinusitis (CRS) between medical centers to determine if differences in quality-of-life outcomes were detectable. In addition, we sought to identify significant, independent cofactors toward the development of an ESS-specific risk-adjustment model so that ESS outcomes may be appropriately compared between institutions and healthcare providers. STUDY DESIGN: Prospective, multicenter, observational cohort. METHODS: Study participants elective ESS for CRS were enrolled and randomly selected in equal numbers from three academic clinical practices in North America between April 2011 and May 2015. The magnitude of average 6-month postoperative improvement in patient-related outcome measures (PROMs) was compared between enrollment sites using multivariate linear regression modeling. RESULTS: A total of 228 participants met inclusion criteria and were included for final analyses (n = 76 per site). The prevalence of septal deviation/septoplasty and oral corticosteroid-dependent conditions was significantly different between enrollment sites (P ≤ 0.004). Each enrollment site generated significant within-subject improvement across all PROMs after ESS (P < 0.001); however, average unadjusted
magnitudes of improvement were significantly different between sites for the primary outcome measure. After controlling for baseline PROMs, septal deviation, steroid-dependent conditions, and medication use variables, enrollment site was no longer associated with significant outcome differences (P = 0.535).

CONCLUSION: Comparison of surgeon outcomes of ESS is feasible and must take into account a number of baseline patient characteristics. Further studies will be critical toward developing an ESS-specific risk-adjustment model and enabling a robust comparison of surgeon outcomes. LEVEL OF EVIDENCE: 2c.


OBJECTIVES/HYPOTHESIS: To assess safety and efficacy of a steroid-releasing implant in improving surgical outcomes when placed in the frontal sinus opening (FSO) following endoscopic sinus surgery (ESS) in patients with chronic rhinosinusitis (CRS). STUDY DESIGN: Prospective, multicenter, randomized, blinded trial using an intrapatient control design. METHODS: Eighty adult (≥18 years) CRS patients who underwent successful bilateral frontal sinusotomy were randomized to receive a steroid-releasing implant in one FSO, whereas the contralateral control side received no implant. All patients received standard postoperative care. Endoscopic evaluations recorded at 30-days postendoscopic sinus surgery (ESS) were graded real time by clinical investigators and by an independent, blinded sinus surgeon to assess the need for postoperative interventions in the FSO. RESULTS: Implants were successfully placed in all 80 frontal sinuses, resulting in 100% implant delivery success. At 30-days post-ESS, steroid-releasing implants provided a statistically significant (P = 0.0070) reduction in the need for postoperative interventions compared to surgery alone by an independent reviewer, representing 38% relative reduction. Clinical investigators reported statistically significant reduction in this measure at 30 days (P < 0.0001) and 90 days (P = 0.0129). Clinical investigators also reported a 55.6% reduction in the need for oral steroid interventions (P = 0.0015), 75% reduction in the need for surgical interventions (P = 0.0225), 16.7% reduction in inflammation score, 54.3% reduction in restenosis rate (P = 0.0002), and 32.2% greater diameter of FSO (P < 0.0001) on treated sides compared to control at 30 days. No implant-related adverse events were reported. CONCLUSION: This study demonstrates the efficacy of steroid-releasing implants in improving outcomes of frontal sinus surgery. LEVEL OF EVIDENCE: 1b. Laryngoscope, 126:2659-2664, 2016.


International implementation of the patient-centered medical home (PCMH) model for delivering primary care has dramatically increased in the last decade. A majority of research on PCMH’s impact has emphasized the care provided by clinically trained staff. In this article, we report our ethnographic analysis of data collected from Department of Veterans Affairs staff implementing PACT, the VA version of PCMH. Teams were trained to use within-team delegation, largely accomplished through attention to clinical licensure, to differentiate staff in providing efficient, patient-centered care. In doing so, PACT may reinforce a clinically defined culture of care that countermands PCMH ideals. Such competing rubrics for care are brought into relief through a focus on the care work performed by clerks. Ethnographic analysis identifies clerks’ care as a kind of emotional dirty work, signaling important areas for future anthropological study of the relationships among patient-centered care, stigma, and clinical authority.


**BACKGROUND AND AIMS:** To expedite a consult resolution, referring physicians sometimes inflate the urgency and need for endoscopic workup. The aim of the present decision analysis was to study the impact of inflationary indication on the expected benefits to gastroenterologists and referring physicians. **METHODS:** The study aims were pursued in terms of game theory and medical decision analysis using decision trees. Different outcomes associated with true versus false urgent indication in immediate versus delayed endoscopy were ranked according to different preference schemes of gastroenterologists versus referring physicians. **RESULTS:** The decision analysis shows that inflating the urgency of indication for endoscopy reduces the benefit from the perspective of gastroenterologists and referring physicians alike. Raising the level of false urgent indications results in a lost opportunity for immediate endoscopy among patients with true urgent indications and, thus, diminishes the overall benefit of endoscopy. By comparison, all other influences play only a marginal role. For referring physicians, the small benefit of expediting nonurgent endoscopies by exaggerated claims does not compensate for the concomitant loss of truly needed endoscopy slots. For gastroenterologists, a small benefit derived from delaying endoscopies in patients with false urgent endoscopies rapidly wears off as inflationary indications become common practice. **CONCLUSION:** An underlying communication problem between referring physicians and gastroenterologists needs to be resolved by educating referring physicians about the operative exigencies of endoscopy units and about the true appearance of alarm symptoms in common digestive diseases.


**BACKGROUND:** Environmental risk factors associated with ethnicity may contribute to the occurrence of Barrett’s metaplasia. **AIM:** To investigate the interaction between ethnicity and Helicobacter pylori infection in the occurrence of Barrett’s metaplasia among patients undergoing oesophago-gastro-duodenoscopy. **METHODS:** The Miraca Life Sciences Database is an electronic repository of histopathological patient records. A case-control study evaluated the influence of age, gender, ethnicity and histological diagnosis of H. pylori on the occurrence of Barrett’s metaplasia. **RESULTS:** The total study population comprised 596,479 subjects, of whom 76,475 harboured a diagnosis of Barrett’s metaplasia. Male sex, age and H. pylori infection in declining order exerted the strongest influence on the occurrence of BM. In comparison with the population comprising Caucasians and African Americans, Barrett’s metaplasia was less common among subjects of African (OR = 0.09, 95% CI = 0.01-0.43), Middle Eastern (0.26, 0.20-0.34), East Asian (0.35, 0.31-0.40), Indian (0.39, 0.32-0.47), Hispanic (0.62, 0.59-0.64) or Jewish descent (0.50, 0.45-0.54), but more common among subjects of Northern European descent (1.14, 1.03-1.26). With the exception of Jews and Northern Europeans, all other ethnic subgroups were characterised 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 Barrett’s metaplasia (R² = 0.82, P < 0.001), as well as dysplasia or oesophageal adenocarcinoma (R² = 0.81, P < 0.001). **CONCLUSION:** Our analysis reveals an inverse relationship between the prevalence of Barrett’s metaplasia and H. pylori gastritis among different ethnic groups within the United States.


**BACKGROUND:** The rarity of mutations in PALB2, CHEK2 and ATM make it difficult to estimate precisely associated cancer risks. Population-based family studies have provided evidence that at least some of these mutations are associated with breast cancer risk as high as those associated with rare BRCA2 mutations. We aimed to estimate the relative risks associated with specific rare variants in PALB2, CHEK2 and ATM via a multicentre
case-control study. METHODS: We genotyped 10 rare mutations using the custom iCOGS array: PALB2 c.1592delT, c.2816T>G and c.3113G>A, CHEK2 c.349A>G, c.538C>T, c.715G>A, c.1036C>T, c.1312G>T, and c.1343T>G and ATM c.7271T>G. We assessed associations with breast cancer risk (42 671 cases and 42 164 controls), as well as prostate (22 301 cases and 22 320 controls) and ovarian (14 542 cases and 23 491 controls) cancer risk, for each variant. RESULTS: For European women, strong evidence of association with breast cancer risk was observed for PALB2 c.1592delT OR 3.44 (95% CI 1.39 to 8.52, p=7.1x10^{-5}), PALB2 c.3113G>A OR 4.21 (95% CI 1.84 to 9.60, p=6.9x10^{-8}) and ATM c.7271T>G OR 11.0 (95% CI 1.42 to 85.7, p=0.0012). We also found evidence of association with breast cancer risk for three variants in CHEK2, c.349A>G OR 2.26 (95% CI 1.29 to 3.95), c.1036C>T OR 5.06 (95% CI 1.09 to 23.5) and c.538C>T OR 1.33 (95% CI 1.05 to 1.67) (p</=0.017). Evidence for prostate cancer risk was observed for CHEK2 c.1343T>G OR 3.03 (95% CI 1.53 to 6.03, p=0.0006) for African men and CHEK2 c.1312G>T OR 2.21 (95% CI 1.06 to 4.63, p=0.030) for European men. No evidence of association with ovarian cancer was found for any of these variants. CONCLUSIONS: This report adds to accumulating evidence that at least some variants in these genes are associated with an increased risk of breast cancer that is clinically important.


BACKGROUND: Quantitative assessment of optic nerve damage is important in the evaluation of optic neuritis (ON) and multiple sclerosis (MS). OBJECTIVE: To detect optic nerve damage using optical coherence tomography (OCT) and OCT angiography in MS. METHODS: Peripapillary retinal nerve fibre layer (NFL) thickness, macular ganglion cell complex (GCC) thickness and Optic Nerve Head Flow Index (ONH-FI) were measured. The ONH-FI was defined as flow signal averaged over the optic disc. Diagnostic accuracy was evaluated by the area under the receiver-operating characteristics curve (AROC). RESULTS: Sixty-eight eyes of 45 MS participants and 55 eyes of 32 healthy controls (HCs) were analysed. Of MS eyes, 25 had a history of ON (MS+ON) and 43 didn't (MS-ON). MS-ON and MS+ON eyes had reductions in ONH-FI (p=0.031 and p=0.001, respectively), GCC thickness (p=0.245 and p<0.001, respectively), and NFL thickness (p=0.003 and p=0.024, respectively), compared with HCs. The highest AROC (0.940) was achieved by the logistic regression combination of all three variables, which was significantly higher than other variables (p=0.018). CONCLUSION: MS produces both retinal structural loss and decreased ONH perfusion in MS eyes with and without history of ON. The combination of perfusion and structural measurements enhances detection of optic nerve damage in MS. OCT angiography may be a useful additional retinal marker in evaluation of ON in MS.


BACKGROUND: Decision aids are interventions that support patients by making their decisions explicit, providing information about options and associated benefits/harms, and helping clarify congruence between decisions and personal values. OBJECTIVES: To assess the effects of decision aids in people facing treatment or screening decisions. SEARCH METHODS: Updated search (2012 to April 2015) in CENTRAL; MEDLINE; Embase; PsycINFO; and grey literature; includes CINAHL to September 2008. SELECTION CRITERIA: We included published randomized controlled trials comparing decision aids to usual care and/or alternative interventions. For this update, we excluded studies comparing detailed versus simple decision aids. DATA COLLECTION AND ANALYSIS: Two reviewers independently screened citations for inclusion, extracted data, and assessed risk of bias. Primary outcomes, based on the International Patient Decision Aid Standards (IPDAS), were attributes related to the choice made and the decision-making process. Secondary outcomes were behavioural, health, and health system effects. We pooled results using mean differences (MDs) and risk ratios (RRs), applying a random-effects model. We conducted a subgroup analysis of studies that used the patient decision aid to prepare for the consultation and of those that used it in the consultation. We used
Importance: We examined whether resuscitation care and outcomes vary by the racial composition of the neighborhood where out-of-hospital cardiac arrests (OHCA)s occur. Objective: To evaluate the association between bystander treatments (cardiopulmonary resuscitation and automatic external defibrillation) and timing of emergency medical services personnel on OHCA outcomes according to the racial composition of the neighborhood where the OHCA event occurred. Design, Setting, and Participants: This retrospective observational cohort study examined patients with OHCA from January 1, 2008, to December 31, 2011, using data from the Resuscitation Outcomes Consortium. Neighbors where OHCA occurred were classified by census tract, based on percentage of black residents: less than 25%, 25% to 50%, 51% to 75%, or more than 75%. Multilevel mixed-effects logistic regression modeling examined the association between racial
composition of neighborhoods and OHCA survival, adjusting for patient, neighborhood, and treatment characteristics. Main Outcomes and Measures: Survival to discharge, return of spontaneous circulation on emergency department arrival, and favorable neurologic status at discharge. Results: We examined 22,816 adult patients with nontraumatic OHCA at Resuscitation Outcomes Consortium sites in the United States. The median age of patients with OHCA was 64 years (IQR, 51-78). Compared with patients who experienced OHCA in neighborhoods with a lower proportion of black residents, those in neighborhoods with more than 75% black residents were slightly younger, were more frequently women, had lower rates of initial shockable rhythm, and less frequently experienced OHCA in a public location. The percentage of patients with OHCA receiving bystander cardiopulmonary resuscitation or a lay automatic external defibrillation was inversely associated with the percentage of black residents in neighborhoods. Compared with OHCA in predominantly white neighborhoods (<25% black), those with OHCA in mixed to majority black neighborhoods had lower adjusted survival rates to hospital discharge (25%-50% black: odds ratio, 0.76; 95% CI, 0.61-0.93; 51%-75% black: odds ratio, 0.67; 95% CI, 0.49-0.90; >75% black: odds ratio, 0.63; 95% CI, 0.50-0.79; P < .001). There was similar mortality risk for black and white patients with OHCA in each neighborhood racial quantile. When the primary model included geographic site, there was an attenuated nonsignificant association between racial composition in a neighborhood and survival. Conclusions and Relevance: Those with OHCA in predominantly black neighborhoods had the lowest rates of bystander cardiopulmonary resuscitation and automatic external defibrillation use and significantly lower likelihood for survival compared with predominantly white neighborhoods. Improving bystander treatments in these neighborhoods may improve cardiac arrest survival.


Auditory augmented reality (AR) requires accurate estimation of spatial information conveyed in the natural scene, coupled with accurate spatial synthesis of virtual sounds to be integrated within it. Solutions to both problems should consider the capabilities and limitations of the human binaural system, in order to maximize relevant over distracting acoustic information and enhance perceptual integration across AR layers. Recent studies have measured how human listeners integrate spatial information across multiple conflicting cues, revealing patterns of "perceptual weighting" that sample the auditory scene in a robust but spectrotemporally sparse manner. Such patterns can be exploited for binaural analysis and synthesis, much as time-frequency masking patterns are exploited by perceptual audio codecs, to improve efficiency and enhance perceptual integration.


Vulvodynia is a common condition that negatively affects sexual health and quality of life for many women. A new classification system has been adopted that divides vulvodynia into subtypes based on pain characteristics. Diagnosis relies on ruling out possible contributing pathologic conditions. A multidisciplinary approach to treatment is likely to achieve the best outcome for all types. Medical therapy with systemic neuromodulators is suggested for generalized vulvodynia. For patients with vestibulodynia, topical therapy may be beneficial. Vestibulectomy has a high success rate and may be a good option if the patient is not responding to treatment.


Purpose Depression symptoms are common among patients with lung cancer; however, longitudinal changes and their impact on survival are understudied. Methods This was a prospective, observational study from the
Cancer Care Outcomes Research and Surveillance Consortium from five US geographically defined regions from September 2003 through December 2005. Patients enrolled within 3 months of their lung cancer diagnosis were eligible. The eight-item Center for Epidemiologic Studies Depression scale was administered at diagnosis and 12 months' follow-up. The main outcome was survival, which was evaluated using Kaplan-Meier curves and adjusted Cox proportional hazards modeling. Results Among 1,790 participants, 681 (38%) had depression symptoms at baseline and an additional 105 (14%) developed new-onset depression symptoms during treatment. At baseline, depression symptoms were associated with increased mortality (hazard ratio [HR], 1.17; 95% CI, 1.03 to 1.32; P = .01). Participants were classified into the following four groups based on longitudinal changes in depression symptoms from baseline to follow-up: never depression symptoms (n = 640), new-onset depression symptoms (n = 105), depression symptom remission (n = 156), and persistent depression symptoms (n = 254) and HRs were calculated. Using the never-depression symptoms group as a reference group, HRs were as follows: new-onset depression symptoms, 1.50 (95% CI, 1.12 to 2.01; P = .006); depression symptom remission, 1.02 (95% CI, 0.79 to 1.31; P = .89), and persistent depression symptoms, 1.42 (95% CI, 1.15 to 1.75; P = .001). At baseline, depression symptoms were associated with increased mortality among participants with early-stage disease (stages I and II; HR, 1.61; 95% CI, 1.26 to 2.04), but not late-stage disease (stages III and IV; HR, 1.05; 95% CI, 0.91 to 1.22). At follow-up, depression symptoms were associated with increased mortality among participants with early-stage disease (HR, 1.71; 95% CI, 1.27 to 2.31) and those with late-stage disease (HR, 1.32; 95% CI, 1.04 to 1.69).

Conclusion Among patients with lung cancer, longitudinal changes in depression symptoms are associated with differences in mortality, particularly among patients with early-stage disease. Symptom remission is associated with a similar mortality rate as never having had depression.


Maternal high-fat-diet (HFD) consumption during pregnancy decreased fetal body weight and impacted development of hypothalamic melanocortin neural circuitry in nonhuman primate offspring. We investigated whether these impairments during gestation persisted in juvenile offspring and examined the interaction between maternal and early postnatal HFD consumption. Adult dams consumed either a control diet (CTR; 15% calories from fat) or a high-saturated-fat diet (HFD; 37% calories from fat) during pregnancy. Offspring were weaned onto a CTR or HFD at ~8 mo of age. Offspring from HFD-fed dams displayed early catch-up growth and elevated body weight at 6 and 13 mo of age. Maternal and postnatal HFD exposure reduced the amount of agouti-related peptide fibers in the paraventricular nucleus of the hypothalamus. Postnatal HFD consumption also decreased the amount of agouti-related peptide fibers in the arcuate nucleus of the hypothalamus. Postnatal HFD was associated with decreased food intake and increased activity. These results support and extend our previous findings of maternal diet effects on fetal development and reveal, for the first time in a nonhuman primate model, that maternal HFD-induced disturbances in offspring body weight regulation extended past gestation into the juvenile period. Maternal HFD consumption increases the risk for offspring developing obesity, with the developmental timing of HFD exposure differentially impacting the melanocortin system and energy balance regulation. The present findings provide translational insight into human clinical populations, suggesting that profound health consequences may await individuals later in life following intrauterine and postnatal HFD exposure.


OBJECTIVE: To investigate development of cognitive and motor functions in healthy adolescents and to explore whether hazardous drinking affects the normal developmental course of those functions. METHOD:
Purpose: Ewing sarcoma (EWS) is a devastating soft tissue sarcoma affecting predominantly young individuals. Tyrosine kinases (TK) and associated pathways are continuously activated in many malignancies, including EWS; these enzymes provide candidate therapeutic targets. Experimental Design: Two high-throughput screens (a siRNA library and a small-molecule inhibitor library) were performed in EWS cells to establish candidate targets. Spleen tyrosine kinase (SYK) phosphorylation was assessed in EWS patients and cell lines. SYK was inhibited by a variety of genetic and pharmacological approaches, and SYK-regulated pathways were investigated by cDNA microarrays. The transcriptional regulation of MALAT1 was examined by ChIP-

Many studies have explored how neuromodulators affect synaptic function, yet little is known about how they modify computations at the microcircuit level. In the dorsal cochlear nucleus (DCN), a region that integrates auditory and multisensory inputs from two distinct pathways, serotonin (5-HT) enhances excitability of principal cells, predicting a generalized reduction in sensory thresholds. Surprisingly, we found that when looked at from the circuit level, 5-HT enhances signaling only from the multisensory input, while decreasing input from auditory fibers. This effect is only partially explained by an action on auditory nerve terminals. Rather, 5-HT biases processing for one input pathway by simultaneously enhancing excitability in the principal cell and in a pathway-specific feed-forward inhibitory interneuron. Thus, by acting on multiple targets, 5-HT orchestrates a fundamental shift in representation of convergent auditory and multisensory pathways, enhancing the potency of non-auditory signals in a classical auditory pathway.


BACKGROUND CONTEXT: Minimally invasive lumbar spinal stenosis procedures have uncertain long-term value.

PURPOSE: This study sought to characterize factors affecting the long-term cost-effectiveness of such procedures using interspinous spacer devices (“spacers”) relative to decompression surgery as a case study.

STUDY DESIGN: Model-based cost-effectiveness analysis. PATIENT SAMPLE: The Medicare Provider Analysis and Review database for the years 2005-2009 was used to model a group of 65-year-old patients with spinal stenosis who had no previous spine surgery and no contraindications to decompression surgery. OUTCOME MEASURES: Costs, quality-adjusted life years, and cost per quality-adjusted life year gained. METHODS: A Markov model tracked health utility and costs over 10 years for a 65-year-old cohort under three care strategies: conservative care, spacer surgery, and decompression surgery. Incremental cost-effectiveness ratios (ICER) reported as cost per quality-adjusted life year (QALY) gained included direct medical costs for surgery. Medicare claims data were used to estimate complication rates, reoperation and related costs within 3 years. Utilities and long-term reoperation rates for decompression were derived from published studies. Spacer failure requiring reoperation beyond 3 years and post-spacer health utilities are uncertain and were evaluated through sensitivity analyses. In the base-case, the spacer failure rate was held constant for years 4-10 (cumulative failure: 47%). In a “worst-case” analysis, the 10-year cumulative reoperation rate was increased steeply (to 90%). Threshold analyses were performed to determine the impact of failure and post-spacer health utility on the cost-effectiveness of spacer surgery. RESULTS: The spacer strategy had an ICER of $89,500/QALY gained under base-case assumptions, and remained under $100,000 as long as the 10-yr cumulative probability of reoperation did not exceed 54%. Under worst-case assumptions, the spacer ICER was $482,000/QALY and fell below $100,000 only if post-spacer utility was 0.01 greater than post-decompression utility or the cost of spacer surgery was $1,600 less than the cost of decompression surgery. CONCLUSIONS: Spacers may provide a reasonably cost-effective initial treatment option for patients with lumbar spinal stenosis. Their value is expected to improve if procedure costs are lower in outpatient settings where these procedures are increasingly being done. Decision analysis is useful for characterizing the long-
term cost-effectiveness potential for minimally invasive spinal stenosis treatments and highlights the importance of complication rates and prospective health utility assessment.


Glucomatous axon injury occurs at the level of the optic nerve head (ONH) in response to uncontrolled intraocular pressure (IOP). The temporal response of ONH astrocytes (glial cells responsible for axonal support) to elevated IOP remains unknown. Here, we evaluate the response of actin-based astrocyte extensions and integrin-based signaling within the ONH to 8 hours of IOP elevation in a rat model. IOP elevation of 60 mm Hg was achieved under isoflurane anesthesia using anterior chamber cannulation connected to a saline reservoir. ONH astrocytic extension orientation was significantly and regionally rearranged immediately after IOP elevation (inferior ONH, 43.2 degrees +/- 13.3 degrees with respect to the anterior-posterior axis versus 84.1 degrees +/- 1.3 degrees in controls, p<0.05), and re-orientated back to baseline orientation 1 day post IOP normalization. ONH axonal microtubule filament label intensity was significantly reduced 1 and 3 days post IOP normalization, and returned to control levels on day 5. Phosphorylated focal adhesion kinase (FAK) levels steadily decreased after IOP normalization, while levels of phosphorylated paxillin (a downstream target of FAK involved in focal adhesion dynamics) were significantly elevated 5 days post IOP normalization. The levels of phosphorylated cortactin (a downstream target of Src kinase involved in actin polymerization) were significantly elevated 1 and 3 days post IOP normalization and returned to control levels by day 5. No significant axon degeneration was noted by morphologic assessment up to 5 days post IOP normalization. Actin-based astrocyte structure and signaling within the ONH are significantly altered within hours after IOP elevation and prior to axonal cytoskeletal rearrangement, producing some responses that recover rapidly and others that persist for days despite IOP normalization.


BACKGROUND: Suicide is a critical public health problem around the globe. Asian populations are characterized by elevated suicide rates and a tendency to seek social support from family and friends over mental health professionals. Gatekeeper training programs have been developed to train frontline individuals in behaviors that assist at-risk individuals in obtaining mental health treatment. The purpose of this study is to assess the efficacy of a brief, multi-component gatekeeper intervention in promoting suicide prevention in a high-risk Asian community in the United States. METHODS: We adapted an evidence-based gatekeeper training into a two-hour, multi-modal and interactive event for Japanese-Americans and related stakeholders. Then we evaluated the intervention compared to an attention control using mixed methods. RESULTS: A sample of 106 community members participated in the study. Intervention participants (n = 85) showed significant increases in all three types of intended gatekeeper behavior, all four measures of self-efficacy, and both measures of social norms relevant to suicide prevention, while the control group (n = 48) showed no significant improvements. Additional results showed significantly higher satisfaction and no adverse experiences associated with the gatekeeper training. The separate collection of qualitative data, and integration with the quantitative survey constructs confirmed and expanded understanding about the benefits of the intervention. CONCLUSIONS: A brief, multi-modal gatekeeper training is efficacious in promoting positive gatekeeper behaviors and self-efficacy for suicide prevention in an at-risk ethnic minority population of Japanese Americans.
OBJECTIVES/HYPOTHESIS: Nasal obstruction is a cardinal symptom in diagnosing chronic rhinosinusitis (CRS), and decreased sleep quality (SQ) and quality of life (QOL) are commonly reported in CRS. It is, however, unclear what role nasal obstruction severity plays in this decreased SQ and QOL. Using validated instruments, we evaluated the relationship between nasal obstruction severity, SQ, and QOL. STUDY DESIGN: Prospective case series. METHODS: Patients with CRS refractory to standard medical therapy (n = 28) were prospectively enrolled and completed the Nasal Obstruction Symptom Evaluation (NOSE), Pittsburg Sleep Quality Index (PSQI), Rhinosinusitis Disability Index, and the 22-item Sinonasal Outcome Test. CRS disease severity was evaluated with computed tomography and endoscopy. NOSE scores were compared to SQ, QOL, and disease severity measures. Spearman correlations were used to identify significant associations between measures. RESULTS: All patients reported symptomatic nasal obstruction (NOSE score >/= 30), whereas poor sleep (PSQI >/= 5) was reported by 82%. The NOSE sleeping subdomain correlated strongly with the PSQI total score, whereas other elements of the NOSE instrument correlated weakly or not at all with this measurement of SQ. Nasal obstruction correlated weakly with disease-specific QOL and had no correlation with the PSQI total. CONCLUSIONS: Nasal obstruction appears to have a limited association with CRS-specific QOL and CRS-associated decrease in SQ. Further, the NOSE instrument, because it contains a question about sleep, may have overlap with the PSQI as a measure of SQ. The total NOSE score in CRS patients does not appear to be purely a measure of nasal obstruction. LEVEL OF EVIDENCE: 4 Laryngoscope, 126:1971-1976, 2016.
OBJECTIVE: We determined in patients with pulmonary arterial (PA) hypertension (PAH) whether in addition to increased production of elastase by PA smooth muscle cells previously reported, PA elastic fibers are susceptible to degradation because of their abnormal assembly. APPROACH AND RESULTS: Fibrillin-1 and elastin are the major components of elastic fibers, and fibrillin-1 binds bone morphogenetic proteins (BMPs) and the large latent complex of transforming growth factor-beta1 (TGFbeta1). Thus, we considered whether BMPs like TGFbeta1 contribute to elastic fiber assembly and whether this process is perturbed in PAH particularly when the BMP receptor, BMPR2, is mutant. We also assessed whether in mice with Bmpr2/1a compound heterozygosity, elastic fibers are susceptible to degradation. In PA smooth muscle cells and adventitial fibroblasts, TGFbeta1 increased elastin mRNA, but the elevation in elastin protein was dependent on BMPR2; TGFbeta1 and BMP4, via BMPR2, increased extracellular accumulation of fibrillin-1. Both BMP4- and TGFbeta1-stimulated elastic fiber assembly was impaired in idiopathic (I) PAH-PAH adventitial fibroblasts versus control cells, particularly those with hereditary (H) PAH and a BMPR2 mutation. This was related to profound reductions in elastin and fibrillin-1 mRNA. Elastin protein was increased in IPAH PA adventitial fibroblast by TGFbeta1 but only minimally so in BMPR2 mutant cells. Fibrillin-1 protein increased only modestly in IPAH or HPAH PAH adventitial fibroblasts stimulated with BMP4 or TGFbeta1. In Bmpr2/1a heterozygote mice, reduced PA fibrillin-1 was associated with elastic fiber susceptibility to degradation and more severe pulmonary hypertension. CONCLUSIONS: Disrupting BMPR2 impairs TGFbeta1- and BMP4-mediated elastic fiber assembly and is of pathophysiologic significance in PAH.


OBJECTIVE: The aim of this Outcome Measures in Rheumatology (OMERACT) Working Group was to determine the core set of outcome domains and subdomains for measuring the effectiveness of shared decision-making (SDM) interventions in rheumatology clinical trials. METHODS: Following the OMERACT Filter 2.0, and based on a previous literature review of SDM outcome domains and a nominal group process at OMERACT 2014, (1) an online Delphi survey was conducted to gather feedback on the draft core set and refine its domains and subdomains, and (2) a workshop was held at the OMERACT 2016 meeting to gain consensus on the draft core set. RESULTS: A total of 170 participants completed Round 1 of the Delphi survey, and 116 completed Round 2. Respondents came from 29 countries, with 49% being patients/caregivers. Results showed that 14 out of the 17 subdomains within the 7 domains exceeded the 70% criterion (endorsement ranged from 83% to 100% of respondents). At OMERACT 2016, only 8% of the 96 attendees were patients/caregivers. Despite initial votes of support in breakout groups, there was insufficient comfort about the conceptualization of these 7 domains and 17 subdomains for these to be endorsed at OMERACT 2016 (endorsement ranged from 17% to 68% of participants). CONCLUSION: Differences between the Delphi survey and consensus meeting may be explained by the manner in which the outcomes were presented, variations in participant characteristics, and the context of voting. Further efforts are needed to address the limited understanding of SDM and its outcomes among OMERACT participants.


PURPOSE: The impact of a quality-assessment dashboard and individualized pharmacist performance feedback on the adherence of order verification was evaluated. METHODS: A before-and-after study was conducted at a 1,440-bed academic medical center. Adherence of order verification was defined as orders verified according to institution-derived, medication-related guidelines and policies. Formulas were developed to assess the adherence of verified orders to dosing guidelines using patient-specific height, weight, and serum creatinine clearance values from the electronic medical record at the time of pharmacist verification. A total of 5
medications were assessed by the formulas for adherence and displayed on the dashboard: ampicillin-sulbactam, ciprofloxacin, piperacillin-tazobactam, acyclovir, and enoxaparin. Adherence of order verification was assessed before (May 1–July 31, 2015) and after (November 1, 2015–January 31, 2016) individualized performance feedback was given based on trends identified by the quality-assessment dashboard. RESULTS: There was a significant increase in the overall adherence rate postintervention (90.1% versus 91.9%, \( p = 0.040 \)). Among the 34 pharmacists who participated, the percentage of pharmacists with at least 90% overall adherence increased postintervention (52.9% versus 70.6%, \( p = 0.103 \)). Time to verification was similar before and after the study intervention (median, 6.0 minutes; interquartile range, 3–13 minutes). The rate of documentation for nonadherent orders increased significantly postintervention (57.1% versus 68.5%, \( p = 0.019 \)). CONCLUSION: The implementation of the quality-assessment dashboard, educational sessions, and individualized performance feedback significantly improved pharmacist order-verification adherence to institution-derived, medication-related guidelines and policies and the documentation rate of nonadherent orders.


BACKGROUND: Assessment of the retropharyngeal lymph nodes is essential in the treatment for oropharyngeal squamous cell carcinoma (SCC). Transoral robotic retropharyngeal lymph node dissection (RPLND) may provide valuable staging information and guide selection of adjuvant therapy in a transoral robotic surgery (TORS) treatment paradigm. METHODS: Outcomes were compared between 30 patients with oropharyngeal SCC with tonsillar primaries undergoing RPLND and 37 stage-matched cases without RPLND. RESULTS: Retropharyngeal metastasis was confirmed in 6 patients undergoing RPLND. Compared with 37 stage-matched controls, there were no differences in length of stay, length of feeding tube dependence, net change in perioperative weight, or rates of hemorrhage and postoperative complications. RPLND altered adjuvant treatment recommendations in 1 of 30 patients. CONCLUSION: RPLND is technically feasible by a purely transoral robotic approach. Its performance is not associated with worse swallowing outcomes or rates of complication. In select patients, RPLND may provide valuable staging information and guide the selection of adjuvant therapy.


Microscopic pale-staining acinar nodules were characterized in native pancreas in the 1980s under a variety of names but have been infrequently reported since. We retrospectively studied the frequency and characteristics of pale acinar nodules in allograft pancreas biopsies, as compared to a sampling of native pancreas specimens at our center. Pale acinar nodules were present in 13% (9/69) of allograft biopsies from 22% (7/32) of transplant patients, and 23% (5/22) of native pancreas surgical specimens, although more nodules per pancreas area were present in allograft needle biopsies. Acinar nodules had size of 100 to 700 mum, were periodic acid-Schiff pale, were synaptophysin negative, stained more weakly with keratin CAM 5.2 compared to surrounding parenchyma, and had a low proliferative rate. Ultrastructural evaluation revealed paucity of zymogen granules with dilated cistern-like structures. In our experience, pale acinar nodules have similar features in allograft and native pancreas specimens, yet remain of uncertain etiology and significance.


Kidney transplant recipients are at increased risk for malignancy, with about 5% incidence of cancer in native end-stage kidneys. Carcinoma in the renal allograft is far less common. Prior studies have demonstrated a propensity for renal cell carcinomas (RCCs) of papillary subtypes in end-stage kidneys, and perhaps in
allograft kidneys, but most allograft studies lack detailed pathologic review and predate the current classification system. We reviewed our experience with renal carcinoma in kidney allografts at 2 academic centers applying the International Society of Urological Pathology classification, informed by immunohistochemistry. The incidence of renal allograft carcinoma was about 0.26% in our population. Of 12 allograft carcinomas, 6 were papillary (50%), 4 were clear cell (33%), 1 was clear cell (tubulo)papillary, and 1 chromophobe. Two of the papillary carcinomas had distinctive biphasic glomeruloid architecture matching the newly named “biphasic squamoid alveolar” pattern and were difficult to classify on core biopsies. The 2 cell types had different immunophenotypes in our hands (eosinophilic cells: RCC-/CK34betaE12+ weight keratin +/cyclin D1+; clear cells: RCC+/cytokeratin high molecular weight negative to weak/cyclin D1-). None of the patients experienced cancer recurrences or metastasis. Our study confirms the predilection for papillary RCCs in kidney allografts and highlights the occurrence of rare morphologic variants. Larger studies are needed with careful pathologic review, which has been lacking in the literature.


To maintain core body temperature in mammals, the normal central nervous system (CNS) thermoregulatory reflex networks produce an increase in brown adipose tissue (BAT) thermogenesis in response to skin cooling and an inhibition of the sympathetic outflow to BAT during skin rewarming. In contrast, these normal thermoregulatory reflexes appear to be inverted in hibernation/torpor; thermogenesis is inhibited during exposure to a cold environment, allowing dramatic reductions in core temperature and metabolism, and thermogenesis is activated during skin rewarming, contributing to a return of normal body temperature. Here, we describe two unrelated experimental paradigms in which rats, a nonhibernating/torpid species, exhibit a “thermoregulatory inversion,” which is characterized by an inhibition of BAT thermogenesis in response to skin cooling, and a switch in the gain of the skin cooling reflex transfer function from negative to positive values. Either transection of the neuraxis immediately rostral to the dorsomedial hypothalamus in anesthetized rats or activation of A1 adenosine receptors within the CNS of free-behaving rats produces a state of thermoregulatory inversion in which skin cooling inhibits BAT thermogenesis, leading to hypothermia, and skin warming activates BAT, supporting an increase in core temperature. These results reflect the existence of a novel neural circuit that mediates inverted thermoregulatory reflexes and suggests a pharmacological mechanism through which a deeply hypothermic state can be achieved in nonhibernating/torpid mammals, possibly including humans.


Few studies have evaluated the clinical impact of polymerase chain reaction (PCR) for Staphylococcus aureus bloodstream infections in resource-limited settings that lack direct antimicrobial stewardship intervention. This retrospective cohort study compared patients with standard microbiological identification (n = 343) to those with additional identification by (PCR) (n = 130). Time to initiation of optimal therapy was similar between groups but substantially shorter in the PCR group for those infected with methicillin susceptible S. aureus (median 40.0. h vs. 28.3. h, P = 0.001). After controlling for confounding factors including infectious diseases consultation, the PCR group had a shorter time to initiation of optimal therapy by 9.7. h (95% CI 4.3-15.0. h). Clinical outcomes were similar in the non-PCR and PCR groups. While time to initiation of optimal therapy was shorter in the PCR group, greater reductions may be realized through additional
INTRODUCTION: Prophylaxis is considered the optimal treatment for persons with moderate to severe haemophilia (factor activity between 1-5% of normal and <1% of normal respectively) in countries where safe factor concentrates are available and economically feasible. Historically, prophylactic treatment has not been well studied in the haemophilia B (HB) population due to difficulties in obtaining a sufficiently large sample. AIM: This study examines the prevalence of prophylaxis use among a robust sample of persons with HB in the United States and its association with specific demographic and clinical characteristics. METHODS: Using data collected between 1998 and 2011 for the Centers for Disease Control and Prevention’s Universal Data Collection project, we analysed data on 2428 males with moderate to severe HB aged 2–79 years who were seen at 135 federally funded haemophilia treatment centres. RESULTS: Prevalence of prophylactic treatment in our sample was 35% among children and youth (ages 2–19) and 14% among adults (age 20 and older). Increased HB prophylaxis use was significantly associated with younger age (<40 years), Hispanic ethnicity, severe disease and self-infusion, while decreased use was associated with above-normal body mass index (BMI) in adults. Health care coverage was vital, although type of coverage did not appear to influence access. CONCLUSIONS: Our analysis confirms previous reports of lower prevalence of prophylaxis use among individuals with HB compared to those with haemophilia A and adds to the body of knowledge regarding treatment patterns among a historically understudied population.

Like women, old female rhesus macaques undergo menopause and show many of the same age-associated changes, including perturbed activity/rest cycles and altered circulating levels of many hormones. Previous studies showed that administration of an estrogen agonist increased activity in female monkeys, that hormone therapy (HT) increased activity in postmenopausal women and that obesity decreased activity in women. The present study sought to determine if postmenopausal activity and circulating hormone levels also respond to HT when monkeys are fed a high-fat, high-sugar Western style diet (WSD). Old female rhesus macaques were ovo-hysterectomized (OvH) to induce surgical menopause and fed a WSD for 2 years. Half of the animals received estradiol-17β (E), beginning immediately after OvH, while the other half received placebo. Animals in both groups showed an increase in body weight and a decrease in overall activity levels. These changes were associated with a rise in both daytime and nocturnal serum leptin concentrations, but there was no change in serum concentrations of either cortisol or dehydroepiandrosterone sulfate (DHEAS). These data suggest that 2 years of HT has little or no effect on locomotor activity or circadian hormone patterns in menopausal macaques fed an obesogenic diet. © 2017 The authors Published by Bioscientifica Ltd.

KEY POINTS: The functional synaptic connectivity between olfactory receptor neurons and principal cells within the olfactory bulb is not well understood. One view suggests that mitral cells, the primary output neuron of the olfactory bulb, are solely activated by feedforward excitation. Using focal, single glomerular stimulation, we demonstrate that mitral cells receive direct, monosynaptic input from olfactory receptor neurons. Compared to external tufted cells, mitral cells have a prolonged afferent-evoked EPSC, which serves to amplify the synaptic input. The properties of presynaptic glutamate release from olfactory receptor neurons are similar between mitral and external tufted cells. Our data suggest that afferent input enters the olfactory bulb in a parallel fashion. ABSTRACT: Primary olfactory receptor neurons terminate in anatomically and functionally
discrete cortical modules known as olfactory bulb glomeruli. The synaptic connectivity and postsynaptic responses of mitral and external tufted cells within the glomerulus may involve both direct and indirect components. For example, it has been suggested that sensory input to mitral cells is indirect through feedforward excitation from external tufted cells. We also observed feedforward excitation of mitral cells with weak stimulation of the olfactory nerve layer; however, focal stimulation of an axon bundle entering an individual glomerulus revealed that mitral cells receive monosynaptic afferent inputs. Although external tufted cells had a 4.1-fold larger peak EPSC amplitude, integration of the evoked currents showed that the synaptic charge was 5-fold larger in mitral cells, reflecting the prolonged response in mitral cells. Presynaptic afferents onto mitral and external tufted cells had similar quantal amplitude and release probability, suggesting that the larger peak EPSC in external tufted cells was the result of more synaptic contacts. The results of the present study indicate that the monosynaptic afferent input to mitral cells depends on the strength of odorant stimulation. The enhanced spiking that we observed in response to brief afferent input provides a mechanism for amplifying sensory information and contrasts with the transient response in external tufted cells. These parallel input paths may have discrete functions in processing olfactory sensory input.


Short-term synaptic plasticity is a critical regulator of neural circuits, and largely determines how information is temporally processed. In the olfactory bulb, afferent olfactory receptor neurons respond to increasing concentrations of odorants with barrages of action potentials, and their terminals have an extraordinarily high release probability (Sicard, 1986; Murphy et al. 2004). These features suggest that during naturalistic stimuli, afferent input to the olfactory bulb is subject to strong synaptic depression, presumably truncating the postsynaptic response to afferent stimuli. To examine this issue, we used single glomerular stimulation in mouse olfactory bulb slices to measure the synaptic dynamics of afferent-evoked input at physiological stimulus frequencies. In cell-attached recordings, mitral cells responded to high frequency stimulation with sustained responses, whereas external tufted cells responded transiently. Consistent with previous reports (Murphy et al. 2004), olfactory nerve terminals onto both cell types had a high release probability (0.7), from a single pool of slowly recycling vesicles, indicating that the distinct responses of mitral and external tufted cells to high frequency stimulation did not originate presynaptically. Rather, distinct temporal response profiles in mitral cells and external tufted cells could be attributed to slow dendrodendritic responses in mitral cells, as blocking this slow current in mitral cells converted mitral cell responses to a transient response profile, typical of external tufted cells. Our results suggest that despite strong axodendritic synaptic depression, the balance of axodendritic and dendrodendritic circuitry in external tufted cells and mitral cells, respectively, tunes the postsynaptic responses to high frequency, naturalistic stimulation. This article is protected by copyright. All rights reserved.


**IMPORTANCE:** In locally advanced pancreatic cancer, the role of chemoradiotherapy is controversial and the efficacy of erlotinib is unknown. **OBJECTIVES:** To assess whether chemoradiotherapy improves overall survival of patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine-based induction chemotherapy and to assess the effect of erlotinib on survival. **DESIGN, SETTING, AND PARTICIPANTS:** In LAP07, an international, open-label, phase 3 randomized trial, 449 patients were enrolled between 2008 and 2011. Follow-up ended in February 2013. **INTERVENTIONS:** In the first randomization, 223 patients received 1000 mg/m2 weekly of gemcitabine alone and 219 patients received 1000mg/m2 of gemcitabine plus 100 mg/d of erlotinib. In the second randomization involving patients with progression-free disease after 4 months, 136 patients received 2 months of the same chemotherapy and 133 underwent chemoradiotherapy (54 Gy plus capecitabine). **MAIN OUTCOMES AND MEASURES:** The primary outcome was overall survival from the date of the first randomization. Secondary outcomes were the effect of erlotinib and quality
assurance of radiotherapy on overall survival, progression-free survival of gemcitabine-erlotinib and erlotinib maintenance with gemcitabine alone at the second randomization, and toxic effects. RESULTS: A total of 442 of the 449 patients (232 men; median age, 63.3 years) enrolled underwent the first randomization. Of these, 269 underwent the second randomization. Interim analysis was performed when 221 patients died (109 in the chemoradiotherapy group and 112 in the chemotherapy group), reaching the early stopping boundaries for futility. With a median follow-up of 36.7 months, the median overall survival from the date of the first randomization was not significantly different between chemotherapy at 16.5 months (95% CI, 14.5-18.5 months) and chemoradiotherapy at 15.2 months (95% CI, 13.9-17.3 months; hazard ratio [HR], 1.03; 95% CI, 0.79-1.34; P =.83). Median overall survival from the date of the first randomization for the 223 patients receiving gemcitabine was 13.6 months (95% CI, 12.3-15.3 months) and was 11.9 months (95% CI, 10.4-13.5 months) for the 219 patients receiving gemcitabine plus erlotinib (HR, 1.19; 95% CI, 0.97-1.45; P =.09; 188 deaths vs 191 deaths). Chemoradiotherapy was associated with decreased local progression (32% vs 46%, P =.03) and no increase in grade 3 to 4 toxicity, except for nausea. CONCLUSIONS AND RELEVANCE: In this open-label, randomized trial involving patients with locally advanced pancreatic cancer with disease controlled after 4 months of induction chemotherapy, there was no significant difference in overall survival with chemoradiotherapy compared with chemotherapy alone and there was no significant difference in overall survival with gemcitabine compared with gemcitabine plus erlotinib used as maintenance therapy. © 2016 American Medical Association. All rights reserved.


Myocardial infarction causes sympathetic activation and parasympathetic dysfunction, which increase risk of sudden death due to ventricular arrhythmias. Mechanisms underlying parasympathetic dysfunction are unclear. The aim of this study was to delineate consequences of myocardial infarction on parasympathetic myocardial neurotransmitter levels and the function of parasympathetic cardiac ganglia neurons, and to assess electrophysiological effects of vagal nerve stimulation on ventricular arrhythmias in a chronic porcine infarct model. While norepinephrine levels decreased, cardiac acetylcholine levels remained preserved in border zones and viable myocardium of infarcted hearts. In vivo neuronal recordings demonstrated abnormalities in firing frequency of parasympathetic neurons of infarcted animals. Neurons that were activated by parasympathetic stimulation had low basal firing frequency, while neurons that were suppressed by left vagal nerve stimulation had abnormally high basal activity. Myocardial infarction increased sympathetic inputs to parasympathetic convergent neurons. However, the underlying parasympathetic cardiac neuronal network remained intact. Augmenting parasympathetic drive with vagal nerve stimulation reduced ventricular arrhythmia inducibility by decreasing ventricular excitability and heterogeneity of repolarization of infarct border zones, an area with known proarrhythmic potential. Preserved acetylcholine levels and intact parasympathetic neuronal pathways can explain the electrical stabilization of infarct border zones with vagal nerve stimulation, providing insight into its antiarrhythmic benefit.


Background: Whole-genome sequencing (WGS) in asymptomatic adults might prevent disease but increase health care use without clinical value. Objective: To describe the effect on clinical care and outcomes of adding WGS to standardized family history assessment in primary care. Design: Pilot randomized trial. (ClinicalTrials.gov: NCT 01736566) Setting: Academic primary care practices. Participants: 9 primary care physicians (PCPs) and 100 generally healthy patients recruited at ages 40 to 65 years. Intervention: Patients were randomly assigned to receive a family history report alone (FH group) or in combination with an interpreted WGS report (FH + WGS group), which included monogenic disease risk (MDR) results (associated with Mendelian disorders), carrier variants, pharmacogenomic associations, and polygenic risk estimates for
cardiometabolic traits. Each patient met with his or her PCP to discuss the report. Measurements: Clinical outcomes and health care use through 6 months were obtained from medical records and audiorecorded discussions between PCPs and patients. Patients’ health behavior changes were surveyed 6 months after receiving results. A panel of clinician-geneticists rated the appropriateness of how PCPs managed MDR results. Results: Mean age was 55 years; 58% of patients were female. Eleven FH + WGS patients (22% [95% CI, 12% to 36%]) had new MDR results. Only 2 (4% [CI, 0.01% to 15%]) had evidence of the phenotypes predicted by an MDR result (fundus albipunctatus due to RDH5 and variegate porphyria due to PPOX). Primary care physicians recommended new clinical actions for 16% (CI, 8% to 30%) of FH patients and 34% (CI, 22% to 49%) of FH + WGS patients. Thirty percent (CI, 17% to 45%) and 41% (CI, 27% to 56%) of FH and FH + WGS patients, respectively, reported making a health behavior change after 6 months. Geneticists rated PCP management of 8 MDR results (73% [CI, 39% to 99%]) as appropriate and 2 results (18% [CI, 3% to 52%]) as inappropriate. Limitation: Limited sample size and ancestral and socioeconomic diversity.

Conclusion: Adding WGS to primary care reveals new molecular findings of uncertain clinical utility. Nongeneticist providers may be able to manage WGS results appropriately, but WGS may prompt additional clinical actions of unclear value. © 2017 American College of Physicians.


OBJECTIVES: Glutaric acidemia type I (GA-I) is an inherited neurometabolic disorder caused by deficiency of glutaryl-CoA dehydrogenase (GCDH) and characterized by increased levels of glutaric, 3-OH-glutaric, and glutaconic acids in the brain parenchyma. The increment of these organic acids inhibits glutamate decarboxylase (GAD) and consequently lowers the gamma-aminobutyric acid (GABA) synthesis. Untreated patients exhibit severe neurologic deficits during development, including epilepsy, especially following an acute encephalopathy outbreak. In this work, we evaluated the role of the GABAergic system on epileptogenesis in GA-I using the Gcdh-/- mice exposed to a high lysine diet (Gcdh-/- -Lys). METHODS: Spontaneous recurrent seizures (SRS), seizure susceptibility, and changes in brain oscillations were evaluated by video-electroencephalography (EEG). Cortical GABAergic synaptic transmission was evaluated using electrophysiologic and neurochemical approaches. RESULTS: SRS were observed in 72% of Gcdh-/- -Lys mice, whereas no seizures were detected in age-matched controls (Gcdh+/+ or Gcdh-/- receiving normal diet). The severity and number of PTZ-induced seizures were higher in Gcdh-/- -Lys mice. EEG spectral analysis showed a significant decrease in theta and gamma oscillations and predominant delta waves in Gcdh-/- -Lys mice, associated with increased EEG left index. Analysis of cortical synaptosomes revealed a significantly increased percentage of glutamate release and decreased GABA release in Gcdh-/- -Lys mice that were associated with a decrease in cortical GAD immunoccontent and activity and confirmed by reduced frequency of inhibitory events in cortical pyramidal cells. SIGNIFICANCE: Using an experimental model with a phenotype similar to that of GA-I in humans-the Gcdh-/- mice under high lysine diet (Gcdh-/- -Lys)-we provide evidence that a reduction in cortical inhibition of Gcdh-/- -Lys mice, probably induced by GAD dysfunction, leads to hyperexcitability and increased slow oscillations associated with neurologic abnormalities in GA-I. Our findings offer a new perspective on the pathophysiology of brain damage in GA-I.


Hymenolepis nana, the dwarf tapeworm, is a common intestinal infection of children worldwide. We evaluated infection and risk factor data that were previously collected from 14,761 children aged 2-15 years during a large-scale program in northern Peru. We found that 1,124 of 14,761 children (7.61%) had H. nana infection, a likely underestimate given that only a single stool sample was examined by microscopy for diagnosis. The strongest association with infection was lack of adequate water (adjusted prevalence ratio [aPR] 2.22, 95%
One quarter of those tested did not have a bathroom or latrine at home, which doubled their likelihood of infection. Similarly, one quarter did not have piped public water to the house, which also increased the likelihood of infection. Continued efforts to improve access to basic water and sanitation services will likely reduce the burden of infection in children for this and other intestinal infections.


Background: Systematic reviews of complex interventions can vary widely in purpose, data availability and heterogeneity, and stakeholder expectations. Rationale: This article addresses the uncertainty that systematic reviewers face in selecting methods for reviews of complex interventions. Specifically, it lays out parameters for systematic reviewers to consider when selecting analytic approaches that best answer the questions at hand and suggests analytic techniques that may be appropriate in different circumstances. Discussion: Systematic reviews of complex interventions comprising multiple questions may use multiple analytic approaches. Parameters to consider when choosing analytic methods for complex interventions include nature and timing of the decision (clinical practice guideline, policy, or other); purpose of the review; extent of existing evidence; logistic factors such as the timeline, process, and resources for deciding the scope of the review; and value of information to be obtained from choosing specific systematic review methods. Reviewers may elect to revise their analytic approach based on new or changing considerations during the course of the review but should guard against bias through transparency of reporting. © 2017 The Authors.


Purpose: Impairments in the social use of language are universal in autism spectrum disorder (ASD), but few standardized measures evaluate communication skills above the level of individual words or sentences. This study evaluated the Expression, Reception, and Recall of Narrative Instrument (ERRNI; Bishop, 2004) to determine its contribution to assessing language and communicative impairment beyond the sentence level in children with ASD. Method: A battery of assessments, including measures of cognition, language, pragmatics, severity of autism symptoms, and adaptive functioning, was administered to 74 8- to 9-year-old intellectually able children with ASD. Results: Average performance on the ERRNI was significantly poorer than on the Clinical Evaluation of Language Fundamentals-Fourth Edition (CELF-4). In addition, ERRNI scores reflecting the number and quality of relevant story components included in the participants’ narratives were significantly positively related to scores on measures of nonverbal cognitive skill, language, and everyday adaptive communication, and significantly negatively correlated with the severity of affective autism symptoms. Conclusion: Results suggest that the ERRNI reveals discourse impairments that may not be identified by measures that focus on individual words and sentences. Overall, the ERRNI provides a useful measure of communicative skill beyond the sentence level in school-aged children with ASD.


OBJECTIVE: To examine birthweight and other predictors of brachial plexus injury (BPI) among births complicated by shoulder dystocia. STUDY DESIGN: A retrospective cohort study of term births complicated by shoulder dystocia in California between 1997 and 2006. Birthweight at time of delivery was stratified into 500-g intervals. Women were further stratified by diabetes status, parity, and race/ethnicity. The perinatal outcome
of BPI was assessed. RESULTS: This study included 62,762 deliveries complicated by shoulder dystocia, of which 3168 (5 %) resulted in BPI. The association between birthweight and BPI remained significant regardless of confounders. Each increasing birthweight interval was associated with an increasing risk of BPI compared with 3000-3499-g birthweight. Race/ethnicity, diabetes, and parity were also independently associated with BPI. CONCLUSION: Increasing birthweight increases the risk of BPI among births with shoulder dystocia, independent of advanced maternal age, race, parity, gestational diabetes, or operative vaginal delivery.


Myoepithelial cells have important physical and paracrine roles in breast tissue development, maintenance, and tumor suppression. Recent molecular and immunohistochemical studies have demonstrated phenotypic alterations in ductal carcinoma in situ-associated myoepithelial cells. Although the relationship of lobular carcinoma in situ (LCIS) and myoepithelial cells was described in 1980, further characterization of LCIS-associated myoepithelial cells is lacking. We stained 27 breast specimens harboring abundant LCIS with antibodies to smooth muscle myosin heavy chain, smooth muscle actin, and calponin. Dual stains for E-cadherin/smooth muscle myosin heavy chain and CK7/p63 were also performed. In each case, the intensity and distribution of staining in LCIS-associated myoepithelial cells were compared with normal breast tissue on the same slide. In 78% of the cases, LCIS-associated myoepithelial cells demonstrated decreased staining intensity for one or more myoepithelial markers. The normal localization of myoepithelial cells (flat against the basement membrane, pattern N) was seen in 96% of LCIS, yet 85% of cases had areas with myoepithelial cell cytoplasm oriented perpendicular to the basement membrane (pattern P), and in 30% of cases, myoepithelial cells appeared focally admixed with LCIS cells (pattern C). This study characterizes detailed architectural and immunophenotypic alterations of LCIS-associated myoepithelial cells. The finding of variably diminished staining favors application of several myoepithelial immunostains in clinical practice. The interaction of LCIS with myoepithelial cells, especially in light of the perpendicular and central architectural arrangements, deserves further mechanistic investigation.


BACKGROUND: Laparoscopy, specifically the bridged mesh technique, is a popular means used for ventral hernia repair. While laparoscopy has decreased the incidence of surgical site infection (SSI), hernia recurrence rates
remain unchanged. Some surgeons advocate laparoscopic primary fascial closure (PFC) with placement of intraperitoneal mesh to decrease recurrence rates. We hypothesize that in patients undergoing laparoscopic ventral hernia repair (LVHR), PFC compared to a bridged mesh repair decreases hernia recurrence rates.

**METHODS:** A multicenter, retrospective database of all ventral hernia repairs performed from 2010-2012 was accessed. Patients who underwent LVHR with mesh were reviewed. Patients who had PFC were compared to bridged repair. Primary outcome was hernia recurrence determined by clinical examination or CT scan. Secondary outcomes included SSI and seroma formation. RESULTS: A total of 1594 patients were identified. Following exclusion, a total of 196 patients were left who underwent LVHR with a mean follow-up period of 17.5 months. Ninety-seven patients underwent PFC, while 99 underwent bridged repairs. Initial comparisons between both groups was negative for any significant statistical difference in terms of recurrence, seroma formation, SSL deep/organ space SSI, reoperation, and readmission. The same initial findings held true during subgroup analysis. Propensity score analysis was then performed for recurrence, seroma, and SSI controlling for age, gender, immune status, ASA class, BMI, smoking status, and acute repair. No statistically significant differences were identified in either group. CONCLUSION: Primary fascial closure during laparoscopic hernia repairs did not result in reduced recurrence, seroma, and SSI as compared to bridge repairs in a retrospective, multi-institutional study. However, additional research is needed to further evaluate benefits to the patient in terms of pain, function, cosmesis, and overall satisfaction. Randomized, blinded, control trials should focus on these parameters in future investigations.


Ozone causes vagally mediated airway hyperreactivity and recruits inflammatory cells, including eosinophils, to lungs, where they mediate ozone-induced hyperreactivity 1 day after exposure but are paradoxically protective 3 days later. We aimed to test the role of newly divided eosinophils in ozone-induced airway hyperreactivity in sensitized and nonsensitized guinea pigs. Nonsensitized and sensitized guinea pigs were treated with 5-bromo-2-deoxyuridine (BrdU) to label newly divided cells and were exposed to air or ozone for 4 h. Later (1 or 3 days later), vagally induced bronchoconstriction was measured, and inflammatory cells were harvested from bone marrow, blood, and bronchoalveolar lavage. Ozone induced eosinophil hematopoiesis. One day after ozone, mature eosinophils dominate the inflammatory response and potentiate vagally induced bronchoconstriction. However, by 3 days, newly divided eosinophils have reached the lungs, where they inhibit ozone-induced airway hyperreactivity because depleting them with antibody to IL-5 or a TNF-alpha antagonist worsened vagally induced bronchoconstriction. In sensitized guinea pigs, both ozone-induced eosinophil hematopoiesis and subsequent recruitment of newly divided eosinophils to lungs 3 days later failed to occur. Thus mature eosinophils dominated the ozone-induced inflammatory response in sensitized guinea pigs. Depleting these mature eosinophils prevented ozone-induced airway hyperreactivity in sensitized animals. Ozone induces eosinophil hematopoiesis and recruitment to lungs, where 3 days later, newly divided eosinophils attenuate vagally mediated hyperreactivity. Ozone-induced hematopoiesis of beneficial eosinophils is blocked by a TNF-alpha antagonist or by prior sensitization. In these animals, mature eosinophils are associated with hyperreactivity. Thus interventions targeting eosinophils, although beneficial in atopic individuals, may delay resolution of airway hyperreactivity in nonatopic individuals.


OBJECTIVE: Herpes zoster (HZ) is more common in patients with rheumatoid arthritis (RA), and risk appears elevated with tofacitinib use. It is unknown whether concomitant conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) or glucocorticoids contribute to this increased risk. We aimed to evaluate whether concomitant csDMARDs or glucocorticoids contribute to increased HZ risk with tofacitinib.

METHODS: We identified HZ reports from 19 phase (P)II/PII/PIII and long-term extension tofacitinib studies in RA patients, and calculated crude IRs for all HZ (serious and non-serious; unique patients with events/100 patient-years) with 95% CIs. Within PIII studies, we described HZ rates according to concomitant csDMARD and baseline corticosteroid use. A multivariable Cox regression model was used to evaluate HZ risk factors across studies. RESULTS: Across all studies (6,192 patients; 16,839 patient-years), HZ was reported in 636 tofacitinib-treated patients: IR 4.0 (95% CI 3.7-4.4). Most HZ was non-serious (93%) and involved 1 dermatome (94%). HZ IRs varied across regions, from 2.4 (2.0-2.9) in Eastern Europe to 8.0 (6.6-9.6) and 8.4 (6.4-10.9) in Japan and Korea, respectively. Within PIII studies, HZ IRs varied by tofacitinib dose, background csDMARDs use and baseline glucocorticoids. IRs were numerically lowest for tofacitinib 5 mg BID monotherapy without glucocorticoids (IR 0.56 [0.07-2.01]) and highest for tofacitinib 10 mg BID with csDMARDs and glucocorticoids (IR 5.44 [3.72-7.68]). Age, glucocorticoids, tofacitinib dose, and enrollment within Asia were independent HZ risk factors. CONCLUSION: Patients receiving tofacitinib with glucocorticoids appear to have greater risk of developing HZ versus patients using tofacitinib monotherapy without glucocorticoids. This article is protected by copyright. All rights reserved.


The 19th annual international Targeted Therapies meeting brought together over 100 leading basic scientists and clinical researchers from around the world in the field of immunology, molecular biology and rheumatology and other specialties. During the meeting, breakout sessions were held consisting of 5 disease-specific groups with 20-40 experts assigned to each group based on clinical or scientific expertise. Specific groups included: rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, systemic lupus erythematosus, connective tissue diseases (e.g. Sjogren’s syndrome, Systemic sclerosis, vasculitis including Bechet’s and IgG4 related disease), and a basic science immunology group spanning all of the above clinical domains. In each group, experts were asked to consider and update previously identified unmet needs in 3 categorical areas: basic/translational science, clinical science and therapeutic development, and clinical care. Overall, similar primary unmet needs were identified within each disease foci, and several additional needs were identified since the time of last year’s congress. Within translational/basic science, the need for better understanding the heterogeneity within each disease was highlighted so that predictive tools for therapeutic responses can be developed. Within clinical science and therapeutic trials, a strong focus was placed upon the need to identify pre-clinical states of disease allowing prevention in those at risk. The ability to cure remains perhaps the ultimate unmet need. Further, the need to develop new and affordable therapeutics, as well as to conduct strategic trials of currently approved therapies was again highlighted. Within the clinical care realm, improved co-morbidity management and patient-centered care were identified as unmet needs. Lastly, it was strongly felt there was a need to develop a scientific infrastructure for well-characterized, longitudinal cohorts paired with biobanks and mechanisms to support data-sharing. This infrastructure could facilitate many of the unmet needs identified within each disease area.


OBJECTIVES: Rheumatoid arthritis (RA) patients are at increased risk for herpes zoster, and vaccination is recommended in >/=50-year-old patients, prior to starting biologics or tofacitinib. Tofacitinib is an oral JAK inhibitor for the treatment of RA. We evaluated its effect upon the immune response and safety of live zoster vaccine (LZV). METHODS: In this phase II, 14-week, placebo-controlled trial, patients aged >/=50 years with
active RA on background methotrexate were given LZV and randomized to receive tofacitinib 5 mg twice daily or placebo, 2-3 weeks post-vaccination. We measured humoral (varicella-zoster virus [VZV]-specific IgG via gpELISA) and cell-mediated responses (VZV-specific T-cell enumeration via ELISPOT) at baseline, 2, 6, and 14 weeks post-vaccination. Endpoints included the geometric mean fold rise (GMFR) in VZV-specific IgG levels (primary endpoint) and T-cells (spot-forming cells/106 PBMCs) at 6 weeks post-vaccination. RESULTS: 112 patients were randomized (tofacitinib, n=55; placebo, n=57). Six weeks post-vaccination, VZV-specific IgG GMFR was 2.11 for tofacitinib and 1.74 for placebo, and VZV-specific T-cell GMFR increased similarly for tofacitinib (1.50) and placebo (1.29). Serious adverse events occurred in 3 (5.5%) and 0 (0%) tofacitinib and placebo patients, respectively. One patient, lacking pre-existing VZV immunity, developed cutaneous vaccine dissemination 2 days after starting tofacitinib (16 days post-vaccination). This resolved after tofacitinib discontinuation and antiviral therapy. CONCLUSION: Patients starting tofacitinib 2-3 weeks after LZV, had similar VZV-specific humoral and cell-mediated immune responses to LZV compared with placebo-treated patients. Vaccination appeared safe in all patients but one lacking pre-existing VZV immunity. This article is protected by copyright. All rights reserved.


Multiple and unpredictable numbers of actions are often required to achieve a goal. In order to organize behavior and allocate effort so that optimal behavioral policies can be selected, it is necessary to continually monitor ongoing actions. Real-time processing of information related to actions and outcomes is typically assigned to the prefrontal cortex and basal ganglia, but also depends on midbrain regions, especially the ventral tegmental area (VTA). We were interested in how individual VTA neurons, as well as networks within the VTA, encode salient events when an unpredictable number of serial actions are required to obtain a reward. We recorded from ensembles of putative dopamine and non-dopamine neurons in the VTA as animals performed multiple cued trials in a recording session where, in each trial, serial actions were randomly rewarded. While averaging population activity did not reveal a response pattern, we observed that different neurons were selectively tuned to low, medium, or high numbered actions in a trial. This preferential tuning of putative dopamine and non-dopamine VTA neurons to different subsets of actions in a trial allowed information about binned action number to be decoded from the ensemble activity. At the network level, tuning curve similarity was positively associated with action-evoked noise correlations, suggesting that action number selectivity reflects functional connectivity within these networks. Analysis of phasic responses to cue and reward revealed that the requirement to execute multiple and uncertain numbers of actions weakens both cue-evoked responses and cue-reward response correlation. The functional connectivity and ensemble coding scheme that we observe here may allow VTA neurons to cooperatively provide a real-time account of ongoing behavior. These computations may be critical to cognitive and motivational functions that have long been associated with VTA dopamine neurons.


Breast surgery is exceedingly common and may result in significant acute as well as chronic pain. Numerous options exist for the control of perioperative breast pain, including several newly described regional anesthesia techniques, but anesthesiologists have an insufficient understanding of the anatomy of the breast, the anatomic structures disrupted by the various breast surgeries, and the theoretical and experimental evidence supporting the use of the various analgesic options. In this article, we review the anatomy of the breast, common breast surgeries and their potential anatomic sources of pain, and analgesic techniques for managing perioperative pain. We performed a systematic review of the evidence for these analgesic techniques, including intercostal block, epidural administration, paravertebral block, brachial plexus block, and novel peripheral nerve blocks.

STUDY OBJECTIVE: To determine the effect of body mass index (BMI) on the relationship of the popliteal artery to the sciatic and tibial nerves in the popliteal fossa. DESIGN: Prospective, observational study. SETTING: University medical center. SUBJECTS: One hundred patients scheduled for magnetic resonance imaging scans of the knee. MEASUREMENTS: BMI was recorded and magnetic resonance imaging scans were assessed at 3 different measurement points along the femur for the distance and angle between the popliteal artery and tibial nerve, or sciatic nerve if the sciatic nerve had not bifurcated at the measurement point. MAIN RESULTS: At the distal femur, the tibial nerve was a mean of 2.9 mm from the popliteal artery. The nerve was consistently posterior to the artery; however, it was variably located medial or lateral to the artery. At the 5- and 8-cm measurement points, the nerve was 10.0 and 16.1 mm (SD, 4.1 and 5.2 mm), and 31 degrees and 44 degrees (SD, 15 degrees and 16 degrees ) lateral to the popliteal artery, respectively. Zero degree was defined as directly posterior to the artery. Increasing BMI was correlated with increasing distance between the nerve and the artery at the 5- and 8-cm measurement points (r= 0.36 P> |t|.000 and .45 P> |t|.002). CONCLUSIONS: At 5 cm proximal to the distal femoral condyles, the popliteal artery is a reliable sonographic landmark to locate the tibial nerve due to the close proximity and consistent location of the nerve 1 cm posterolateral to the artery, with only a moderate effect of BMI.


The mycobacterial cell wall is crucial to the host-pathogen interface, because it provides a barrier against antibiotics and the host immune response. In addition, cell wall lipids are mycobacterial virulence factors. The mycobacterial membrane protein large (MmpL) proteins are cell wall lipid transporters that are important for basic mycobacterial physiology and Mycobacterium tuberculosis pathogenesis. MmpL3 and MmpL11 are conserved across pathogenic and nonpathogenic mycobacteria, a feature consistent with an important role in the basic physiology of the bacterium. MmpL3 is essential and transports trehalose monomycolate to the mycobacterial surface. In this report, we characterize the role of MmpL11 in M. tuberculosis. M. tuberculosismmpL11 mutants have altered biofilms associated with lower levels of mycolic acid wax ester and long-chain triacylglycerols than those for wild-type bacteria. While the growth rate of the mmpL11 mutant is similar to that of wild-type M. tuberculosis in macrophages, the mutant exhibits impaired survival in an in vitro granuloma model. Finally, we show that the survival or recovery of the mmpL11 mutant is impaired when it is incubated under conditions of nutrient and oxygen starvation. Our results suggest that MmpL11 and its cell wall lipid substrates are important for survival in the context of adaptive immune pressure and for nonreplicating persistence, both of which are critically important aspects of M. tuberculosis pathogenicity.


NMDA receptors (NMDARs) are Ca2+ -permeant, ligand-gated ion channels activated by the excitatory neurotransmitter glutamate and have well-characterized roles in the nervous system. The expression and function of NMDARs in pancreatic beta cells, by contrast, are poorly understood. Here, we report a novel function of NMDARs in beta-cells. Using a combination of biochemistry, electrophysiology, and imaging
techniques we now show that NMDARs have a key role in mediating the effect of leptin to modulate beta-cell electrical activity by promoting AMP-activated protein kinase (AMPK)-dependent trafficking of KATP and Kv2.1 channels to the plasma membrane. Blocking NMDAR activity inhibited the ability of leptin to activate AMPK, induce KATP and Kv2.1 channel trafficking, and promote membrane hyperpolarization. Conversely, activation of NMDARs mimicked the effect of leptin, causing Ca2+ influx, AMPK activation, increased trafficking of KATP and Kv2.1 channels to the plasma membrane, and triggered membrane hyperpolarization. Moreover, leptin potentiated NMDAR currents and triggered NMDAR-dependent Ca2+ influx. Importantly, NMDAR-mediated signaling was observed in rat insulinoma 832/13 cells and in human beta-cells indicating that this pathway is conserved across species. The ability of NMDARs to regulate potassium channel surface expression and thus, beta-cell excitability provides mechanistic insight into the recently reported insulinotropic effects of NMDAR antagonists, and therefore highlights the therapeutic potential of these drugs in managing type 2 diabetes.


Background/Aim: Brain metastases commonly occur in patients with malignant skin, lung and breast cancers resulting in high morbidity and poor prognosis. Integrins containing an αv subunit are cell adhesion proteins that contribute to cancer cell migration and cancer progression. We hypothesized that high expression of αv integrin cell adhesion protein promoted metastatic phenotypes in cancer cells. Materials and Methods: Cancer cells from different origins were used and studied regarding their metastatic ability and intetumumab, anti-αv integrin mAb, sensitivity using in vitro cell migration assay and in vivo brain metastases animal models. Results: The number of brain metastases and the rate of occurrence were positively correlated with cancer cell αv integrin levels. High αv integrin-expressing cancer cells showed significantly faster cell migration rate in vitro than low αv integrin-expressing cells. Intetumumab significantly inhibited cancer cell migration in vitro regardless of αv integrin expression level. Overexpression of αv integrin in cancer cells with low αv integrin level accelerated cell migration in vitro and increased the occurrence of brain metastases in vivo. Conclusion: αv integrin promotes brain metastases in cancer cells and may mediate early steps in the metastatic cascade, such as adhesion to brain vasculature. Targeting αv integrin with intetumumab could provide clinical benefit in treating cancer patients who develop metastases.


We identified mRNA encoding the ecto-enzyme Enpp6 as a marker of newly forming oligodendrocytes, and used Enpp6 in situ hybridization to track oligodendrocyte differentiation in adult mice as they learned a motor skill (running on a wheel with unevenly spaced rungs). Within just 2.5 h of exposure to the complex wheel, production of Enpp6-expressing immature oligodendrocytes was accelerated in subcortical white matter; within 4 h, it was accelerated in motor cortex. Conditional deletion of myelin regulatory factor (Myrf) in oligodendrocyte precursors blocked formation of new Enpp6(+) oligodendrocytes and impaired learning within the same approximately 2-3 h time frame. This very early requirement for oligodendrocytes suggests a direct and active role in learning, closely linked to synaptic strengthening. Running performance of normal mice continued to improve over the following week accompanied by secondary waves of oligodendrocyte precursor proliferation and differentiation. We concluded that new oligodendrocytes contribute to both early and late stages of motor skill learning.

Radiation of the low neck can be accomplished using split field IMRT. We evaluated the effect of these treatment approaches on target coverage and thyroid and larynx doses. Using data from 14 patients with cancers of the oropharynx, we compared the following 3 strategies for radiating the low neck: (1) extended field vs extended field intensity modulated radiation therapy (EF-IMRT), (2) traditional split-field IMRT with an initial cord-junction block to 40 Gy, followed by a full-cord block to 50 Gy, and (3) traditional split-field IMRT without a cord block.


TWIST1, an epithelial-mesenchymal transition (EMT) transcription factor, is critical for oncogene-driven non-small cell lung cancer (NSCLC) tumorigenesis. Given the potential of TWIST1 as a therapeutic target, a chemical-bioinformatic approach using connectivity mapping (CMAP) analysis was used to identify TWIST1 inhibitors. Characterization of the top ranked candidates from the unbiased screen revealed that harmine, a harmala alkaloid, inhibited multiple TWIST1 functions including single-cell dissemination, suppression of normal branching in 3D epithelial culture, and proliferation of oncogene driver-defined NSCLC cells. Harmine treatment phenocopied genetic loss of TWIST1 by inducing oncogene-induced senescence or apoptosis. Mechanistic investigation revealed that harmine targeted the TWIST1 pathway through its promotion of TWIST1 protein degradation. As dimerization is critical for TWIST1 function and stability, the effect of harmine on specific TWIST1 dimers was examined. TWIST1 and its dimer partners, the E2A proteins, which were found to be required for TWIST1-mediated functions, regulated the stability of the other heterodimeric partner post-translationally. Harmine preferentially promoted degradation of the TWIST1-E2A heterodimer compared to the TWIST-TWIST1 homodimer and targeting the TWIST1-E2A heterodimer was required for harmine cytotoxicity. Finally, harmine had activity in both transgenic and patient-derived xenograft (PDX) mouse models of KRAS mutant NSCLC. These studies identified harmine as a first-in-class TWIST1 inhibitor with marked anti-tumor activity in oncogene-driven NSCLC including EGFR mutant, KRAS mutant and MET altered NSCLC. IMPLICATIONS: TWIST1 is required for oncogene-driven NSCLC tumorigenesis and EMT, thus harmine and its analogues/derivatives represent a novel therapeutic strategy to treat oncogene-driven NSCLC as well as other solid tumor malignancies.


Radiation of the low neck can be accomplished using split-field intensity-modulated radiation therapy (sf-IMRT) or extended-field intensity-modulated radiation therapy (ef-IMRT). We evaluated the effect of these treatment choices on target coverage and thyroid and larynx doses. Using data from 14 patients with cancers of the oropharynx, we compared the following 3 strategies for radiating the low neck: (1) extended-field IMRT, (2) traditional split-field IMRT with an initial cord-junction block to 40 Gy, followed by a full-cord block to 50 Gy,
and (3) split-field IMRT with a full-cord block to 50Gy. Patients were planned using each of these 3 techniques. To facilitate comparison, extended-field plans were normalized to deliver 50Gy to 95% of the neck volume. Target coverage was assessed using the dose to 95% of the neck volume (D95). Mean thyroid and larynx doses were computed. Extended-field IMRT was used as the reference arm; the mean larynx dose was 25.7 +/- 7.4Gy, and the mean thyroid dose was 28.6 +/- 2.4Gy. Split-field IMRT with 2-step blocking reduced laryngeal dose (mean larynx dose 15.2 +/- 5.1Gy) at the cost of a moderate reduction in target coverage (D95 41.4 +/- 14Gy) and much higher thyroid dose (mean thyroid dose 44.7 +/- 3.7Gy). Split-field IMRT with initial full-cord block resulted in greater laryngeal sparing (mean larynx dose 14.2 +/- 5.1Gy) and only a moderately higher thyroid dose (mean thyroid dose 31 +/- 8Gy) but resulted in a significant reduction in target coverage (D95 34.4 +/- 15Gy). Extended-field IMRT comprehensively covers the low neck and achieves acceptable thyroid and laryngeal sparing. Split-field IMRT with a full-cord block reduces laryngeal doses to less than 20Gy and spares the thyroid, at the cost of substantially reduced coverage of the low neck. Traditional 2-step split-field IMRT similarly reduces the laryngeal dose but also reduces low-neck coverage and delivers very high doses to the thyroid.


Background: Bladder dysfunction and falls are common in people with multiple sclerosis (MS), but associations between these problems are unclear. We sought to clarify the association between specific types of bladder dysfunction and prospectively recorded falls in people with MS. Methods: Fifty-one people aged 18 to 50 years with relapsing-remitting MS and mild-to-moderate disability (Expanded Disability Status Scale score ≤6.0) completed a self-report questionnaire regarding urinary incontinence, urgency, and frequency at baseline and then prospectively recorded their falls daily for 3 months using fall calendars. Participants were classified as recurrent fallers (two or more falls) or nonrecurrent fallers (fewer than 2 falls) for one regression model and then as fallers (one or more falls) or nonfallers (no falls) for another regression model. Associations between baseline bladder dysfunction and faller status were assessed using logistic regression adjusted for the potential confounders of age, sex, and disability. Results: Fifteen participants were recurrent fallers, 36 were nonrecurrent fallers, 32 were fallers, and 19 were nonfallers. After adjusting for age, sex, and disability, there was a significant association between urinary urgency with incontinence and recurrent falls in the 3 months after baseline (odds ratio, 57.57; 95% CI, 3.43-966.05; P = .005). Conclusions: Urinary urgency with incontinence is associated with recurrent falls in people with relapsing-remitting MS with mild-to-moderate disability. Further research is needed to better understand the mechanisms underlying this association and to evaluate the effect of bladder management programs on falls. © 2017 Consortium of Multiple Sclerosis Centers.


UNLABELLED: Neuroplastin (Nptn) is a member of the Ig superfamily and is expressed in two isoforms, Np55 and Np65. Np65 regulates synaptic transmission but the function of Np55 is unknown. In an N-ethyl-N-nitrosourea mutagenesis screen, we have now generated a mouse line with an Nptn mutation that causes deafness. We show that Np55 is expressed in stereocilia of outer hair cells (OHCs) but not inner hair cells and affects interactions of stereocilia with the tectorial membrane. In vivo vibrometry demonstrates that cochlear amplification is absent in Nptn mutant mice, which is consistent with the failure of OHC stereocilia to maintain stable interactions with the tectorial membrane. Hair bundles show morphological defects as the mutant mice age and while mechanotransduction currents can be evoked in early postnatal hair cells, cochlea microphonics recordings indicate that mechanotransduction is affected as the mutant mice age. We thus conclude that differential splicing leads to functional diversification of Nptn, where Np55 is essential for OHC function, while Np65 is implicated in the regulation of synaptic function. SIGNIFICANCE
STATEMENT: Amplification of input sound signals, which is needed for the auditory sense organ to detect sounds over a wide intensity range, depends on mechanical coupling of outer hair cells to the tectorial membrane. The current study shows that neuroplastin, a member of the Ig superfamily, which has previously been linked to the regulation of synaptic plasticity, is critical to maintain a stable mechanical link of outer hair cells with the tectorial membrane. In vivo recordings demonstrate that neuroplastin is essential for sound amplification and that mutation in neuroplastin leads to auditory impairment in mice.


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


PURPOSE: To measure the change of peripapillary retinal vessel density (VD) in eyes with a history of acute primary angle closure glaucoma (PACG). DESIGN: Case-control study. METHODS: Twenty-one consecutive Chinese patients with history of unilateral acute PACG were enrolled. Eyes with acute PACG constituted the case group, while the contralateral eyes without attack constituted the control. All patients underwent ophthalmic examinations including best-corrected visual acuity, intraocular pressure, and visual field (VF). Spectral-domain optical coherence tomography (SD-OCT) was used to obtain both structural OCT and OCT angiography (OCTA). Structural OCT scans provided thickness measurements of the peripapillary retinal nerve fiber layer (RNFL) and macular ganglion cell complex (GCC). OCTA was used to measure all-plexus peripapillary retinal VD. RESULTS: In unaffected eyes, a dense microvascular network surrounded the disc on all-plexus retinal OCTA. The vascular network was visibly attenuated and focal capillary dropout was evident in acute PACG eyes. The peripapillary VD in acute PACG eyes was 66.6+/−17.3% (mean+/−standard deviation), which was significantly (p<0.01) reduced compared to 87.2+/−8.6% in the unaffected eyes. In acute PACG eyes, peripapillary retina VD was positively correlated with RNFL and GCC thicknesses (p<0.001 each) and negatively correlated with VF mean deviation (p=0.002) and cup-to-disc ratio (p=0.0064). In unaffected eyes, there were no correlations between peripapillary retina VD and glaucoma-related parameters. CONCLUSIONS: In acute PACG eyes, peripapillary retinal VD decreased significantly compared with the contralateral unaffected eyes. Peripapillary retinal VD was significantly correlated with other glaucomatous changes.


Studies of the dental caries pathogen Streptococcus mutans have benefitted tremendously from its sophisticated genetic system. As part of our own efforts to further improve upon the S. mutans genetic toolbox, we previously reported the development of the first cloning-independent markerless mutagenesis (CIMM)
Lean body mass, consisting mostly of skeletal muscle, is important for healthy aging. We performed a genome-wide association study for whole body (20 cohorts of European ancestry with $n = 38,292$) and appendicular (arms and legs) lean body mass ($n = 28,330$) measured using dual energy X-ray absorptiometry or bioelectrical impedance analysis, adjusted for sex, age, height, and fat mass. Twenty-one single-nucleotide polymorphisms were significantly associated with lean body mass either genome wide ($p \leq 5 \times 10^{-8}$) or suggestively genome wide ($p \leq 2.3 \times 10^{-6}$). Replication in 63,475 (47,227 of European ancestry) individuals from 33 cohorts for whole body lean body mass and in 45,090 (42,360 of European ancestry) subjects from 25 cohorts for appendicular lean body mass was successful for five single-nucleotide polymorphisms in/near HSD17B11, VCAN, ADAMTS13, IRS1, and FTO for total lean body mass and for three single-nucleotide polymorphisms in/near VCAN, ADAMTS13, and IRS1 for appendicular lean body mass. Our findings provide new insight into the genetics of lean body mass. © 2017 The Author(s).


Rhabdomyosarcoma (RMS) is the most frequent soft tissue sarcoma in children that shares many features of developing skeletal muscle. TBX2, a T-box family member, is highly upregulated in tumor cells of both major RMS subtypes where it functions as an oncogene. TBX2 is a repressor that is often overexpressed in cancer cells and functions in bypassing cell growth control, including the repression of the cell cycle regulators p14 and p21. We have found that TBX2 directly represses the tumor-suppressor phosphatase and tensin homolog (PTEN) in both RMS and normal muscle. Exogenous expression of TBX2 in normal muscle cells downregulates PTEN, and depletion or interference with TBX2 in RMS cells upregulates PTEN. Human RMS tumors show high levels of TBX2 and correspondingly low levels of PTEN. The expression of PTEN in clinical RMS samples is relatively uncharacterized, and we establish that suppression of PTEN is a frequent event in both subtypes of RMS. TBX2 represses PTEN by directly binding to the promoter and recruiting the histone deacetylase, HDAC1. RMS cells have high levels of activated AKT owing to the deregulation of phosphoinositide-3 kinase (PI3K) signaling, and depletion or interference with TBX2, which upregulates PTEN, results in a reduction of phospho-AKT. We have also found that the highly related T-box family member TBX3 does not repress PTEN in the muscle lineage. This work suggests that TBX2 is a central component of the PTEN/PI3K/AKT signaling pathway deregulation in RMS cells and that targeting TBX2 in RMS tumors may offer a novel therapeutic approach for RMS.


Lean body mass, consisting mostly of skeletal muscle, is important for healthy aging. We performed a genome-wide association study for whole body (20 cohorts of European ancestry with $n = 38,292$) and appendicular (arms and legs) lean body mass ($n = 28,330$) measured using dual energy X-ray absorptiometry or bioelectrical impedance analysis, adjusted for sex, age, height, and fat mass. Twenty-one single-nucleotide polymorphisms were significantly associated with lean body mass either genome wide ($p \leq 5 \times 10^{-8}$) or suggestively genome wide ($p \leq 2.3 \times 10^{-6}$). Replication in 63,475 (47,227 of European ancestry) individuals from 33 cohorts for whole body lean body mass and in 45,090 (42,360 of European ancestry) subjects from 25 cohorts for appendicular lean body mass was successful for five single-nucleotide polymorphisms in/near HSD17B11, VCAN, ADAMTS13, IRS1, and FTO for total lean body mass and for three single-nucleotide polymorphisms in/near VCAN, ADAMTS13, and IRS1 for appendicular lean body mass. Our findings provide new insight into the genetics of lean body mass. © 2017 The Author(s).
The weighted ensemble (WE) methodology orchestrates quasi-independent parallel simulations run with intermittent communication that can enhance sampling of rare events such as protein conformational changes, folding, and binding. The WE strategy can achieve superlinear scaling—the unbiased estimation of key observables such as rate constants and equilibrium state populations to greater precision than would be possible with ordinary parallel simulation. WE software can be used to control any dynamics engine, such as standard molecular dynamics and cell-modeling packages. This article reviews the theoretical basis of WE and goes on to describe successful applications to a number of complex biological processes—protein conformational transitions, (un)binding, and assembly processes, as well as cell-scale processes in systems biology. We furthermore discuss the challenges that need to be overcome in the next phase of WE methodological development. Overall, the combined advances in WE methodology and software have enabled the simulation of long-timescale processes that would otherwise not be practical on typical computing resources using standard simulation.


BACKGROUND: To validate and further improve the stratification of intermediate risk prostate cancer into favorable and unfavorable subgroups for patients undergoing radical prostatectomy. MATERIALS AND METHODS: The SEARCH database was queried for patients undergoing radical prostatectomy without adjuvant radiotherapy. UIR disease was defined as any patient with at least one unfavorable risk factor (URF), including primary Gleason pattern 4, 50% of more biopsy cores containing cancer, or multiple National Comprehensive Cancer Network IR factors. RESULTS: One thousand five hundred eighty-six patients with IR prostate cancer comprised the study cohort. Median follow-up was 62 months. Patients classified as UIR were significantly more likely to have pathologic high-risk features, such as Gleason score 8-10, pT3-4 disease, or lymph node metastases, than FIR patients (P < 0.001). Furthermore, UIR patients had significantly higher rates of PSA-relapse (PSA, hazard ratio [HR] = 1.89, P < 0.001) and distant metastasis (DM, HR = 2.92, P = 0.001), but no difference in prostate cancer-specific mortality (PCSM) or all-cause mortality in multivariable analysis. On secondary analysis, patients with >/=2 URF had significantly worse PSA-RFS, DM, and PCSM than those with 0 or 1 URF. Moreover, 40% of patients with >/=2 URF had high-risk pathologic features. CONCLUSIONS: Patients with UIR prostate cancer are at increased risk of PSA relapse, DM, and pathologic upstaging following prostatectomy. However, increased risk of PCSM was only detected in those with >/=2 URF. This suggests that further refinement of the UIR subgroup may improve risk stratification. Prostate Prostate 77:154-163, 2017. (c) 2016 Wiley Periodicals, Inc.