
Our project’s purpose was to assess the acceptability of a screening and intervention program to address food insecurity (FI) in pediatric primary care. We implemented systematic FI screening during routine health supervision visits. Our positive results can help to inform implementation of routine FI screening in clinical practice. © Meharry Medical College.


Workshops are an important part of the IFPA annual meeting as they allow for discussion of specialized topics. At IFPA meeting 2016 there were twelve themed workshops, four of which are summarized in this report. These workshops addressed challenges, strengths and limitations of techniques and model systems for studying the placenta, as well as future directions for the following areas of placental research: 1) placental imaging; 2) sexual dimorphism; 3) placenta and development of other organs; 4) trophoblast cell lines. © 2017 Elsevier Ltd.


Purpose: Pinatuzumab vedotin is an antibody-drug conjugate with the potent antimicrotubule agent monomethyl auristatin E (MMAE) conjugated to an anti-CD22 antibody via a protease cleavable linker. This phase I study determined its recommended phase II dose (RP2D) and evaluated its safety, tolerability, and antitumor activity alone and with rituximab in relapsed/refractory (r/r) non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL). Experimental Design: Patients received escalating doses of pinatuzumab vedotin every 21 days. Clinical activity at the RP2D alone or with rituximab was evaluated in r/r diffuse large B-cell lymphoma (DLBCL) and r/r indolent NHL (iNHL) patients. Results: Seventy-five patients received single-agent pinatuzumab vedotin. The RP2D was 2.4 mg/kg, based on dose-limiting toxicities (DLT) of grade 4 neutropenia >7 days in 1 of 3 patients and grade 4 neutropenia <7 days in 2 of 3 patients treated at 3.2 mg/kg (maximum assessed dose). No DLTs occurred at 2.4 mg/kg. At the RP2D, neutropenia was the most common grade ≥3 adverse event. Peripheral neuropathy-related grade ≥2 adverse events most frequently resulted in treatment discontinuation. Rituximab cotreatment did not impact safety, tolerability, or pharmacokinetics of pinatuzumab vedotin. Unconjugated MMAE exposure was much lower than antibody-conjugated MMAE exposure, without accumulation with repeat dosing. At the RP2D, objective responses were observed in DLBCL (9/25) and iNHL (7/14) patients; 2 of 8 patients treated with pinatuzumab vedotin (RP2D) and rituximab had complete responses. CLL patients showed no objective responses. Conclusions: The RP2D of pinatuzumab vedotin alone and with rituximab was 2.4 mg/kg, which was well tolerated, with encouraging clinical activity in r/r NHL. © 2016 American Association for Cancer Research.

BACKGROUND: After the approval of omalizumab for severe allergic asthma, a total of 25 studies have evaluated the effectiveness of omalizumab under "real-life" conditions of heterogeneity in patients, clinicians, sites, and treatment patterns. OBJECTIVE: We conducted a meta-analysis to evaluate the effectiveness of omalizumab focusing on treatment response, lung function, quality of life, symptom control, corticosteroid use, and exacerbations and hospitalizations at 4-6, 12, and 24 months. METHODS: We searched PubMed and Embase for real-life studies on omalizumab in severe asthma published up to 2015. Three effect size types were extracted: single-point proportions; mean +/- SD of change relative to baseline as raw numbers and standardized as Cohen’s d; and changes in proportions of patients as relative risk. Random-effects meta-analyses were performed to account for within- and between-study heterogeneity. Studies were weighted by the DerSimonian and Laird method. RESULTS: Per data available at the 3 time points, omalizumab therapy was consistently associated with large proportions of patients classified as "good" to "excellent" treatment responders (Global Evaluation of Treatment Effectiveness scale); improvements in forced expiratory volume in 1 second, quality of life (Asthma-related Quality-of-Life Questionnaire scale), and asthma symptom control (Asthma Control Test scale); reductions in oral and inhaled corticosteroid (ICS) use; and reductions in exacerbations and hospitalizations. CONCLUSIONS: This meta-analysis of noncontrolled studies documents the real-life pharmacotherapeutic effectiveness of omalizumab, as add-on treatment to ICS +/- long-acting beta2-agonists agents, in improving outcomes in patients with severe allergic asthma under conditions of heterogeneity in patients, clinicians, sites, and treatment patterns. The results mirror, complement, and extend the efficacy data from randomized controlled trials.


OBJECTIVE: Extracorporeal circulation auxiliary to open-heart surgeries (ECAOHS) may exert nonphysiological stresses on periapical abscessed tissues leading to hematogenous spread of microbes. The aim of this report was to estimate risk of postoperative infectious complications in patients with periapical abscesses and undergoing ECAOHS. METHODS: A retrospective analysis of Nationwide Inpatient Sample (years 2009 and 2010) was conducted. All patients (aged 19 to 65 years) who underwent ECAOHS were selected. International Classification of Diseases-9-Clinical Modification codes were used to identify the presence of periapical abscess and infectious complications. Multivariable logistic regression models were used to examine the associations between the presence of periapical abscess and occurrence of infectious complications. RESULTS: A total of 265,235 patients underwent an ECAOH procedure. Of these, 431 patients had a periapical abscess. Septicemia developed in 16% of those with periapical abscess (compared with 4.2% in those without periapical abscess). Those with periapical abscess had higher rates of any of the infectious complications when compared with those who did not have periapical abscess (30.2% vs 11.6%, respectively). After adjustment for multiple confounders, those with periapical abscess were associated with higher odds for developing septicemia (odds ratio = 2.51, 95% confidence interval = 1.06-5.91, P = .04) and any of the infectious complications (odds ratio = 2.23, 95% confidence interval = 1.08-4.59, P = .03) when compared with those who did not have periapical abscess. CONCLUSIONS: Those with periapical abscess are associated with higher odds for infectious complications when compared with those without periapical abscess.


*Genomic alterations may improve diagnostic certainty and subsequent treatment of endometrial stromal sarcoma.*Novel JAZF1-BCORL1 mutation was identified.*Targeted therapeutics to down-stream targets may improve survival benefit in these patients.

The progress on understanding the pharmacological basis of ethanol's discriminative stimulus effects has been substantial, but appears to have plateaued in the past decade. Further, the cross-species translational efforts are clear in laboratory animals, but have been minimal in human subject studies. Research findings clearly demonstrate that ethanol produces a compound stimulus with primary activity through GABA and glutamate receptor systems, particularly ionotropic receptors, with additional contribution from serotonergic mechanisms. Further progress should capitalize on chemogenetic and optogenetic techniques in laboratory animals to identify the neural circuitry involved in mediating the discriminative stimulus effects of ethanol. These infrahuman studies can be guided by in vivo imaging of human brain circuitry mediating ethanol's subjective effects. Ultimately, identifying receptors systems, as well as where they are located within brain circuitry, will transform the use of drug discrimination procedures to help identify possible treatment or prevention strategies for alcohol use disorder.


Multiple Sclerosis (MS) is a chronic, disabling neurologic disease that has its onset in young adulthood. While the knowledge about underlying pathogenesis of MS has improved significantly over the last few decades, the exact cause still eludes us. Despite the availability of several United States Food and Drug Administration-approved disease-modifying therapies (DMT) for MS in the last two decades, the disease remains disabling for many. DMT use is limited by its partial effectiveness, significant side effects in many cases, and high cost that leads people with MS (PwMS) to look for alternative management options. Dietary intervention as a possible mode to help MS seems very appealing to PwMS; however, scientific data supporting this notion remains sparse. New information on the role of various non-MS health factors, especially vascular disease risk factors such as hypertension, hyperlipidemia, salt intake, and obesity, that may play a role in MS pathogenesis appears very intriguing as it may partly explain the heterogeneity seen in MS activity and disability. This review will highlight the emerging information on various dietary approaches that may affect MS and their possible underlying mechanism.


**BACKGROUND:** The Multinational Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oral MDV3100 in Chemotherapy-Naive Patients With Progressive Metastatic Prostate Cancer Who Have Failed Androgen Deprivation Therapy (PREVAIL) trial was unique as it included patients with visceral disease. This analysis was designed to describe outcomes for the subgroup of men from PREVAIL with specific sites of visceral disease to help clinicians understand how these patients responded to enzalutamide prior to chemotherapy. **PATIENTS AND METHODS:** Prespecified analyses examined the coprimary endpoints of radiographic progression-free survival (rPFS) and overall survival (OS) only. All other efficacy analyses were post hoc. The visceral subgroup was divided into liver or lung subsets. Patients with both liver and lung metastases were included in the liver subset. Patients with both liver and lung metastases were included in the liver subset. **RESULTS:** Of the 1717 patients in PREVAIL, 204 (12%) had visceral metastases at screening (liver only or liver/lung metastases, n = 74; lung only metastases, n = 130). In patients with liver metastases, enzalutamide was associated with an improvement in rPFS (hazard ratio [HR], 0.44; 95% confidence interval [CI], 0.22-0.90) but not OS (HR, 1.04; 95% CI, 0.57-1.87). In patients with lung metastases only, the HR for rPFS (0.14; 95% CI, 0.06-0.36) and the HR for OS (0.59; 95% CI, 0.33-1.06) favored enzalutamide over placebo. Patients with liver metastases had worse outcomes than those with lung metastases, regardless of treatment. Enzalutamide was well tolerated in patients with visceral disease. **CONCLUSIONS:** Enzalutamide is an active first-line treatment option for men with asymptomatic or mildly
symptomatic chemotherapy-naive metastatic castration-resistant prostate cancer and visceral disease. Patients with lung-only disease fared better than patients with liver disease, regardless of treatment.


The use of this material under current use conditions is supported by the existing information. This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the target material and the suitable read across analog 6-acetyl-1,1,2,4,4,7-hexamethyltetraline (CAS # 21145-77-7) show that this material is not genotoxic. Data from the suitable read across analog 6-acetyl-1,1,2,4,4,7-hexamethyltetraline (CAS # 21145-77-7) provided a MOE > 100 for the repeat dose and developmental toxicity endpoints. The reproductive and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class II material (0.009 mg/kg/day and 0.47 mg/day, respectively). Data on the target material showed that this material is below the non-reactive DST for skin sensitization and did not have the potential for phototoxicity or photoallergenicity. The environmental endpoint was completed as described in the RIFM Framework.
The use of this material under current conditions is supported by existing information. This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the suitable read across analog 2-ethylhexanol (CAS # 104-76-7) show that this material is not genotoxic. Data from the suitable read across analog isopropyl alcohol (CAS # 67-63-0) show that this material does not have skin sensitization potential. The local respiratory toxicity endpoint was completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (1.4 mg/day). The repeated dose toxicity endpoint was completed using 2-ethylhexanol (CAS # 104-76-7) and 1-heptanol, 2-propyl (CAS # 10042-59-8) as suitable read across analogs, which provided a MOE > 100. The developmental and reproductive toxicity endpoint was completed using 2-ethyl-hexanol (CAS # 104-76-7) and isobutyl alcohol (CAS # 78-83-1) as suitable read across analogs, which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.


The use of this material under current conditions is supported by existing information. This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Repeated dose toxicity was determined to have the most conservative systemic exposure derived NO[A]EL of 10 mg/kg/day. A dietary 90-day subchronic toxicity study conducted in rats resulted in a MOE of 182 while assuming 100% absorption from skin contact and inhalation. A MOE of >100 is deemed acceptable.


The use of this material under current use conditions is supported by the existing information. This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, as well as, environmental safety. Repeated dose toxicity was determined to have the most conservative systemic exposure derived NO[A]EL of 230 mg/kg/day. A gavage multigenerational continuous breeding study conducted in rats on a suitable read across analog resulted in a MOE of 12,105 while considering 22.6% absorption from skin contact and 100% from inhalation. A MOE of >100 is deemed acceptable.


The use of this material under current use conditions is supported by the existing information. This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, as well as, environmental safety. Reproductive toxicity was determined to have the most conservative systemic exposure derived NO[A]EL of 230 mg/kg/day. A gavage multigenerational continuous breeding study conducted in rats on a suitable read across analog resulted in a MOE of 12,105 while considering 22.6% absorption from skin contact and 100% from inhalation. A MOE of >100 is deemed acceptable.
The use of this material under current use conditions is supported by the existing information. This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, as well as, environmental safety. Repeated dose toxicity was determined to have the most conservative systemic exposure derived NOAEL of 37.5 mg/kg/day. A gavage 13-week subchronic toxicity study conducted in mice resulted in a MOE of 5769 while considering 38.4% absorption from skin contact and 100% from inhalation. A MOE of >100 is deemed acceptable.

The use of this material under current use conditions is supported by the existing information. This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, as well as, environmental safety. Repeated dose toxicity was determined using a suitable read across analog to have the most conservative systemic exposure derived NOAEL of 36 mg/kg/day. A dermal 90-day subchronic toxicity study conducted in rats resulted in a MOE of 2250 while considering 14.4% absorption from skin contact and 100% from inhalation. A MOE of >100 is deemed acceptable.

The use of this material under current use conditions is supported by existing information. This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization, as well as environmental safety. Data show that this material is not genotoxic. Data from the suitable read across analog 2-butyloctan-1-ol (CAS # 3913-02-8) show that this material does not have skin sensitization potential. The reproductive and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (0.03 and 1.4 mg/day, respectively). The developmental and repeat dose toxicity endpoints were completed on the target material which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.
This material was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the suitable read across analogs 2-butyloctan-1-ol (CAS # 3913-02-8) and 2-ethyl-1-hexanol (CAS # 104-76-7) show that this material is not genotoxic nor does it have skin sensitization potential. The reproductive and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (0.03 and 1.4 mg/day, respectively). The repeated dose toxicity endpoint was completed using 2-ethyl-1-hexanol (CAS # 104-76-7) and 1-heptanol, 2-propyl (CAS # 10042-59-8) as suitable read across analogs, which provided a MOE > 100. The developmental toxicity endpoint was completed using 2-ethyl-1-hexanol (CAS # 104-76-7) as a suitable read across analog, which provided a MOE > 100 The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data show that this material is not genotoxic nor does it have skin sensitization potential. The repeated dose, developmental and reproductive, and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (0.03, 0.03 mg/kg/day and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

The use of this material under current conditions is supported by existing information. This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data show that this material is not genotoxic nor does it have skin sensitization potential. The reproductive and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (0.03 and 1.4 mg/day, respectively). The developmental toxicity endpoint was completed using linalool (CAS # 78-70-6), dehydrolinalool (CAS # 29171-20-8) and cinnamic acid (CAS # 621-82-9) as suitable read across analogs, which provided a MOE > 100. The repeated dose toxicity endpoint was completed using data on the target material which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.
The use of this material under current use conditions is supported by the existing information. This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, as well as, environmental safety. Developmental toxicity was determined to have the most conservative systemic exposure derived NOAEL of 100 mg/kg/day. A gavage developmental toxicity study conducted in rats on a suitable read across analog resulted in a MOE of 3571 while considering 78.7% absorption from skin contact and 100% from inhalation. A MOE of >100 is deemed acceptable.

The use of this material under current use conditions is supported by the existing information. This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the suitable read across analog benzyl acetate (CAS # 140-11-4) show that this material is not genotoxic nor does it have skin sensitization potential and also provided a MOE > 100 for the repeated dose, developmental and reproductive, and local respiratory toxicity endpoints. The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

The use of this material under current use conditions is supported by the existing information. This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, as well as, environmental safety. Repeated dose toxicity was determined to have the most conservative systemic exposure derived NOAEL of 14.5 mg/kg/day. A dietary 2-year chronic toxicity study conducted in rats on a suitable read across analog resulted in a MOE of 1318 while considering 78.7% absorption from skin contact and 100% from inhalation. A MOE of >100 is deemed acceptable.
The use of this material under current use conditions is supported by the existing information. This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the suitable read across analog benzyl acetate (CAS # 140-11-4), show that this material is not genotoxic nor does it have skin sensitization potential. The repeated dose, developmental and reproductive, and local respiratory toxicity endpoints were completed using benzyl acetate (CAS # 140-11-4) as a suitable read across analog, which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.


The use of this material under current conditions is supported by existing information. This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data show that this material is not genotoxic. Data from the suitable read across analog linalyl phenylacetate (CAS # 7143-69-3) show that this material does not have skin sensitization potential. The repeated dose toxicity endpoint was completed using linalyl cinnamate (CAS # 78-37-5) as a suitable read across analog, which provided a MOE > 100. The developmental and reproductive toxicity endpoint was completed using linalool (CAS # 78-70-6), dehydrolinalool (CAS # 29171-20-8), benzoic acid (CAS # 65-85-0) and sodium benzoate (CAS # 532-32-1) as suitable read across analogs, which provided a MOE > 100. The local respiratory toxicity endpoint was completed using linalool (CAS # 78-70-6) and benzoic acid (CAS # 65-85-0) as suitable read across analogs, which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework along with data from the suitable read across analog linalyl cinnamate (CAS # 78-375).
A workshop was held at the National Institute for Diabetes and Digestive and Kidney Diseases with a focus on the impact of sleep and circadian disruption on energy balance and diabetes. The workshop identified a number of key principles for research in this area and a number of specific opportunities. Studies in this area would be facilitated by active collaboration between investigators in sleep/circadian research and investigators in metabolism/diabetes. There is a need to translate the elegant findings from basic research into improving the metabolic health of the American public. There is also a need for investigators studying the impact of sleep/circadian disruption in humans to move beyond measurements of insulin and glucose and conduct more in-depth phenotyping. There is also a need for the assessments of sleep and circadian rhythms as well as assessments for sleep-disordered breathing to be incorporated into all ongoing cohort studies related to diabetes risk. Studies in humans need to complement the elegant short-term laboratory-based human studies of simulated short sleep and shift work etc. with studies in subjects in the general population with these disorders. It is conceivable that chronic adaptations occur, and if so, the mechanisms by which they occur needs to be identified and understood. Particular areas of opportunity that are ready for translation are studies to address whether CPAP treatment of patients with pre-diabetes and obstructive sleep apnea (OSA) prevents or delays the onset of diabetes and whether temporal restricted feeding has the same impact on obesity rates in humans as it does in mice. © 2015 Associated Professional Sleep Societies, LLC.
Biliary adenofibroma is a rare primary hepatic neoplasm, recognized in the World Health Organization classification, although only 14 cases have been reported to date. This series includes extended follow-up from 2 of the early case reports and 4 novel cases. Clinical history and histology were reviewed in all 6 cases. Tumor DNA was analyzed for point mutations by multiplex polymerase chain reaction and copy number alterations by array comparative genomic hybridization. The patients included 4 females and 2 males presenting between 46 and 83 years of age, with tumors ranging from 7 to 16 cm in diameter. The tumors had similar morphology, with tubules and cysts lined mainly by bland to mildly atypical cuboidal epithelium embedded in fibrous stroma. Multiplex polymerase chain reaction did not identify mutations in 4 tumors tested. Three tumors tested by array comparative genomic hybridization showed chromosomal copy number alterations, including 1 with amplifications of CCND1 and ERBB2. Three patients underwent resection with no recurrence at 21, 20, and 3 years of follow-up. One patient is alive after 14 months with no resection. Two patients with margin-positive resections had local recurrence at 1 and 6 years after surgery. No patient had distant metastasis. The distinct morphology and multiple clonal cytogenetic alterations in biliary adenofibromas indicate that the lesions are neoplastic. Amplifications of CCND1 and ERBB2 are not typical of benign neoplasms, and suggest that these tumors may have the ability to behave aggressively. However, the clinical outcomes in these patients suggest the neoplasms are only slowly progressive. © 2016 Wolters Kluwer Health, Inc. All rights reserved.

Varicella zoster virus (VZV) causes varicella during acute infection and establishes latency in the sensory ganglia. Reactivation of VZV results in herpes zoster, a debilitating and painful disease. It is believed that VZV reactivates due to a decline in cell-mediated immunity; however, the roles that CD4 versus CD8 T cells play in the prevention of herpes zoster remain poorly understood. To address this question, we used a well-characterized model of VZV infection where rhesus macaques are intrabronchially infected with the homologous simian varicella virus (SVV). Latently infected rhesus macaques were thymectomized and depleted of either CD4 or CD8 T cells to induce selective senescence of each T cell subset. After T cell depletion, the animals were transferred to a new housing room to induce stress. SVV reactivation (viremia in the absence of rash) was detected in three out of six CD8-depleted and two out of six CD4-depleted animals suggesting that both CD4 and CD8 T cells play a critical role in preventing SVV reactivation. Viral loads in multiple ganglia were higher in reactivated animals compared to non-reactivated animals. In addition, reactivation results in sustained transcriptional changes in the ganglia that enriched to gene ontology and diseases terms associated with neuronal function and inflammation indicative of potential damage as a result of viral reactivation. These studies support the critical role of cellular immunity in preventing varicella virus reactivation and indicate that reactivation results in long-lasting remodeling of the ganglia transcriptome.

PURPOSE: Lateral epicondylitis is generally considered an extra-articular condition. The role of minor instability in the aetiology of lateral elbow pain has rarely been considered. The aim of this study was to evaluate the correlation of lateral ligamentous laxity with aspects of intra-articular lateral elbow pathology and investigate the role of minor instability in lateral elbow pain. METHODS: Thirty-five consecutive patients aged between 20 and 60 years with recalcitrant lateral epicondylitis who had failed conservative therapy and had no previous trauma or overt instability, were included. The presence of three signs of lateral ligamentous...
Patholaxity and five intra-articular findings were documented during arthroscopy. The relative incidence of each of these was calculated, and the correlation between patholaxity and intra-articular pathology was evaluated. RESULTS: At least one sign of lateral ligamentous laxity was observed in 48.6% of the studied cohort, and 85.7% demonstrated at least one intra-articular abnormal finding. Radial head ballottement was the most common sign of patholaxity (42.9%). Synovitis was the most common intra-articular aspect of pathology (77.1%), followed by lateral capitellar chondropathy (40.0%). A significant correlation was found between the presence of lateral ligamentous patholaxity signs and capitellar chondropathy (p = 0.0409), as well as anteromedial synovitis (p = 0.0408). CONCLUSIONS: Almost one half of patients suffering from recalcitrant lateral epicondylitis display signs of lateral ligamentous patholaxity, and over 85% demonstrate at least one intra-articular abnormality. The most frequent intra-articular findings are synovitis and lateral capitellar chondropathy, which correlate significantly with the presence of lateral ligamentous patholaxity. The fact that several patients demonstrated multiple intra-articular findings in relation to laxity provides support to a sequence of pathologic changes that may result from a symptomatic minor instability of the lateral elbow (SMILE) condition. LEVEL OF EVIDENCE: III.


To determine how the Rapid Assessment Process (RAP) can be adapted to evaluate the readiness of primary care clinics for acceptance and use of computerized clinical decision support (CDS) related to clinical management of working patients, we used a unique blend of ethnographic methods for gathering data. First, knowledge resources, which were prototypes of CDS content areas (diabetes, lower back pain, and asthma) containing evidence-based information, decision logic, scenarios and examples of use, were developed by subject matter experts. A team of RAP researchers then visited five clinic settings to identify barriers and facilitators to implementing CDS about the health of workers in general and the knowledge resources specifically. Methods included observations, semi-structured qualitative interviews and graphic elicitation interviews about the knowledge resources. We used both template and grounded hermeneutic approaches to data analysis. Preliminary results indicate that the methods succeeded in generating specific actionable recommendations for CDS design.


Americans remain at risk for potentially devastating costs for LTSS that are not covered by Medicare or private health insurance. This article proposes a legislative package to finance LTSS, offering LTSS coverage in the context of existing integrated health plans. Building on current federal demonstrations, LTSS coverage would initially be integrated with Medicare Advantage plans. The goal is to provide coverage for LTSS at little or no incremental cost within the existing health insurance system, relying on well-managed home- and community-based care to reduce the use of expensive hospital and institutional care. © 2017 American Society on Aging; all rights reserved.


Interventions to slow cognitive decline typically can do little to reverse decline. Thus, early detection methods are critical. However, tools like cognitive testing are time consuming and require costly expertise. Changes in activities of daily living such as medication adherence may herald the onset of cognitive decline before clinical standards. Here, we determine the relationship between medication adherence and cognitive function in preclinical older adults. We objectively assessed medication adherence in 38 older adults (mean
Our results demonstrate that individuals with lower cognitive function have more spread in the timing of taking their medications (P = .014) and increase the spread in the timing of taking their medications over time (P = .012). These results demonstrate that continuous monitoring of medication adherence may provide the opportunity to identify patients experiencing slow cognitive decline in the earliest stages when pharmacologic or behavioral interventions may be most effective.


Adoption of electronic health records (EHRs) has forced a transition in medical documentation, yet little is known about clinician documentation in the EHR. This study compares electronic inpatient progress notes written by residents pre- and post introduction of standardized note templates and investigates resident perceptions of EHR documentation. A total of 454 resident progress notes pre- and 610 notes post-template introduction were identified. Note length was 263 characters shorter (P = .004) and mean end time was 73 minutes later (P <.0001) with new template implementation. In subanalysis of 100 notes, the assessment and plan section was 46 words shorter with the new template (P <.01). Among survey respondents, 89% liked the new note templates, 78% stated the new templates facilitated note completion. The resident focus group revealed ambivalence toward the EHR’s contribution to note writing. Note templates resulted in shorter notes. Residents appreciate electronic note templates but are unsure if the EHR supports note writing overall. © The Author(s) 2016.


Tracheal intubation remains a life-saving procedure that is typically not difficult for experienced providers in routine conditions. Unfortunately, difficult intubation remains challenging to predict and intubation conditions may make the event life threatening. Recent technological advances aim to further improve the ease, speed, safety, and success of intubation but have not been fully investigated. Video laryngoscopy, though proven effective in the difficult airway, may result in different intubation success rates in various settings and in different providers’ hands. The rescue surgical airway remains a rarely used but critical skill, and research continues to investigate optimal techniques. This review highlights some of the new thoughts and research on these important topics. © 2017 Karlik J and Aziz M.


The following is the conference proceeding of the Second Ein Debate from the 48th Annual Meeting of the Canadian Association of Paediatric Surgeons held in Vancouver, BC, from September 22 to 24, 2016. The three main topics for debate, as prepared by the members of the CAPS Ethics Committee, are: 1. Regionalization of care: pros and cons, 2. Innovation in clinical care: ethical considerations, and 3. Surgeon well-being: caring for the caregiver. The authors of this paper, as participants in the debate, were assigned their positions at random. Therefore, the opinions they express within this summary might not reflect their own viewpoints. In the first discussion, arguments for and against the regionalization of pediatric surgical care are discussed, primarily in the context of a case of BA. In the pro argument, the evidence and lessons learned from different European countries are explored as well as different models to provide the best BA care outside of large teaching centers. In the counterargument, the author explains how regionalization of care could be detrimental for the patient, the family, the regional center, and for the health care system in general. In the debate on surgical innovation the authors define surgical innovation. They review the pertinent ethical principles, explore a model for its implementation, and the role of the institution at which the innovation is proposed. In
the third section, surgeon well-being is examined, and recent literature on surgeon resiliency and burnout both at the attending and resident level is reviewed. © 2017 Elsevier Inc.


Motivation: While existing network visualization tools enable the exploration of cancer genomics data, most biologists prefer simplified, curated pathway diagrams, such as those featured in many manuscripts from The Cancer Genome Atlas (TCGA). These pathway diagrams typically summarize how a pathway is altered in individual cancer types, including alteration frequencies for each gene. Results: To address this need, we developed the web-based tool PathwayMapper, which runs in most common web browsers. It can be used for viewing precurated cancer pathways, or as a graphical editor for creating new pathways, with the ability to overlay genomic alteration data from cBioPortal. In addition, a collaborative mode is available that allows scientists to co-operate interactively on constructing pathways, with support for concurrent modifications and built-in conflict resolution. Availability: The PathwayMapper tool is accessible at http://pathwaymapper.org and the code is available on Github (https://github.com/iVis-at-Bilkent/pathway-mapper). Contact: ivis@cs.bilkent.edu.tr. Supplementary information: Supplementary data are available at Bioinformatics online.


Study Design: This is a review of a prospective multicenter database. Objective: To investigate the relationship between preoperative disability and sagittal deformity in patients with high Oswestry Disability Index (ODI) and no sagittal malalignment, or low ODI and high sagittal malalignment. Summary of Background Data: The relationship between ODI and sagittal malalignment varies between each adult spinal deformity (ASD) patient. Methods: A prospective multicenter database of 365 patients with ASD undergoing surgical reconstruction was analyzed. Inclusion criteria entailed: age 18 years or above and the presence of spinal deformity as defined by a coronal Cobb angle ≥20 degrees, sagittal vertical axis (SVA) ≥5 cm, pelvic tilt (PT) angle ≥25 degrees, or thoracic kyphosis ≥60 degrees. Radiographic and health-related quality of life (HRQOL) variables were examined and compared, preoperatively and at 2-year postoperative follow-up. Group 1 (low disability high sagittal - LDHS) consisted of ODI<40 and SVA≥5 cm or PT≥25 degrees or pelvic incidence-lumbar lordosis≥11 degrees and group 2 (high disability low sagittal - HDLS) consisted of ODI>40 and SVA<5 cm and PT<25 degrees and pelvic incidence-lumbar lordosis<11 degrees. Results: Of 264 patients with follow-up, 58 (22.0%) patients were included in LDHS and 30 (11.4%) were included in HDLS. Both groups had similar demographics and preoperative coronal angles. HDLS had worse baseline HRQOL for all measures (P<0.05) except leg and back pain. HDLS had a higher rate of self-reported leg weakness, arthritis, depression and neurological disorder. Both groups had similar 2-year improvements in HRQOL (P>0.05), except only HDLS had a significant Scoliosis Research Society Mental improvement and a significantly higher rate of reaching minimal clinically important differences in Scoliosis Research Society Mental scores (P<0.05). Conclusions: There is an association of worse baseline HRQOL measures, weakness, arthritis, and mental disease in HDLS. Furthermore, HDLS patients demonstrated similar improvements to LDHS. However, HDLS had greater improvements in the mental domains, perhaps indicating the responsiveness of the mental disability to surgical treatment. Level of Evidence: Level III. Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

INTRODUCTION: The diagnosis and treatment of gastrointestinal stromal tumor (GIST) has emerged as a paradigm for modern cancer treatment ("precision medicine"), as it highlights the importance of matching molecular defects with specific therapies. Over the past two decades, the molecular classification and diagnostic work up of GIST has been radically transformed, accompanied by the development of molecular therapies for specific subgroups of GIST. This review summarizes the developments in the field of molecular diagnosis of GIST, particularly as they relate to optimizing medical therapy. Areas covered: Based on an extensive literature search of the molecular and clinical aspects of GIST, the authors review the most important developments in this field with an emphasis on the differential diagnosis of GIST including mutation testing, therapeutic implications of each molecular subtype, and emerging technologies relevant to the field. Expert commentary: The use of molecular diagnostics to classify GIST has been shown to be successful in optimizing patient treatment, but these methods remain under-utilized. In order to facilitate efficient and comprehensive molecular testing, the authors have developed a decision-tree to aid clinicians.


Metastatic cancer to the central nervous system is primarily deposited by hematogenous spread in various anatomically distinct regions: calvarial, pachymeningeal, leptomeningeal, and brain parenchyma. A patient’s overall clinical status and the information needed to make treatment decisions are the primary considerations in initial imaging modality selection. Contrast-enhanced MR imaging is the preferred imaging modality. Morphologic MR imaging is limited to delineating anatomic derangement of tissues. Dynamic susceptibility contrast-enhanced perfusion and diffusion-weighted physiology-based MR imaging sequences have been developed that complement morphologic MR imaging by providing additional diagnostic information.


PURPOSE OF REVIEW: In this review, we outline barriers to appropriately caring for high-risk youth with diabetes and discuss efforts in partnering with insurers through Alternative Payment Models to achieve the Triple Aim (improved health, improved care, and reduced costs) for this population. RECENT FINDINGS: Current approaches in caring for youth with diabetes who evidence a high degree of social complexity are woefully ineffective. These youth are vulnerable to repeat diabetic ketoacidosis episodes, poor glycemic control, and excessive utilization of healthcare resources. To effectively pursue the Triple Aim, an “integrator” (i.e., an entity that accepts responsibility for all components of the Triple Aim for a specified population) must be identified; however, this does not fit into current fee-for-service models. Integrators for youth with diabetes are limited, but early examples of integrator efforts are promising. We present one successful “integrator,” Novel Interventions in Children’s Healthcare (NICH), and detail this program’s efforts in partnering with insurers to serve high-risk youth with diabetes.


Hearing loss (HL) is common in childhood cancer survivors exposed to platinum chemotherapy and/or cranial radiation and can severely impact quality of life. Early detection and appropriate management can mitigate academic, speech, language, social, and psychological morbidity resulting from hearing deficits. This review is targeted as a resource for providers involved in aftercare of childhood cancers. The goal is to promote early identification of survivors at-risk for HL, appropriate evaluation and interpretation of diagnostic tests, timely referral to an audiologist when indicated, and to increase knowledge of current therapeutic options.
BACKGROUND. EGFR and Src family kinases are upregulated in head and neck squamous cell carcinoma (HNSCC). EGFR interacts with Src to activate STAT3 signaling, and dual EGFR-Src targeting is synergistic in HNSCC preclinical models. pSrc overexpression predicted resistance to the EGFR inhibitor, erlotinib, in a prior window trial. We conducted a 4-arm window trial to identify biomarkers associated with response to EGFR and/or Src inhibition. METHODS. Patients with operable stage II-IVa HNSCC were randomized to 7-21 days of neoadjuvant erlotinib, the Src inhibitor dasatinib, the combination of both, or placebo. Paired tumor specimens were collected before and after treatment. Pharmacodynamic expression of EGFR and Src pathway components was evaluated by IHC of tissue microarrays and reverse-phase protein array of tissue lysates. Candidate biomarkers were assessed for correlation with change in tumor size. RESULTS. From April 2009 to December 2012, 58 patients were randomized and 55 were treated. There was a significant decrease in tumor size in both erlotinib arms (P = 0.0014); however, no effect was seen with dasatinib alone (P = 0.24). High baseline pMAPK expression was associated with response to erlotinib (P = 0.03). High baseline pSTAT3 was associated with resistance to dasatinib (P = 0.099). CONCLUSIONS. Brief exposure to erlotinib significantly decreased tumor size in operable HNSCC, with no additive effect from dasatinib. Baseline pMAPK expression warrants further study as a response biomarker for anti-EGFR therapy. Basal expression of pSTAT3 may be independent of Src, explain therapeutic resistance, and preclude development of dasatinib in biomarker-unselected cohorts.

TRIAL REGISTRATION. NCT00779389. FUNDING. National Cancer Institute, American Cancer Society, Pennsylvania Department of Health, V Foundation for Cancer Research, Bristol-Myers Squibb, and Astellas Pharma.


BACKGROUND: Recombinant bone morphogenetic proteins (BMPs) are growth factors utilized in lumbar arthrodeses. Limited data from randomized trials suggest that BMP may increase cancer risk. We sought to evaluate cancer risk and mortality following the use of BMP in lumbar arthrodesis. METHODS: Within the linked Surveillance, Epidemiology, and End Results (SEER) Program-Medicare cohort, we conducted a case-cohort study of 7,278 individuals who were >/=65 years of age and had undergone a lumbar arthrodesis from 2004 to 2011. Of these patients, 3,627 were individuals in a 5% random subcohort of Medicare enrollees in SEER areas including 191 who developed cancer, and there were 3,651 individuals outside the subcohort who developed cancer. Weighted Cox proportional-hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for cancer on the basis of exposure to BMP. RESULTS: In the SEER-Medicare subcohort, 30.7% of individuals who underwent a lumbar arthrodesis received BMP. BMP was not associated with overall cancer risk in univariate analyses (HR, 0.92 [95% CI, 0.82 to 1.02]) or after adjustment for demographic characteristics, comorbidities, hospital size, history of cancer, and calendar year (adjusted HR, 0.94 [95% CI, 0.84 to 1.05]). Individual cancer types were also not significantly elevated (p > 0.05 for all) in BMP users compared with nonusers. In addition, BMP use was not associated with a new cancer in people who had cancer prior to undergoing lumbar arthrodesis (adjusted HR, 1.04 [95% CI, 0.71 to 1.52]) or with mortality after a cancer diagnosis (adjusted HR, 1.05 [95% CI, 0.93 to 1.19]). CONCLUSIONS: In a large population of elderly U.S. adults undergoing lumbar arthrodesis, BMP use was not associated with cancer risk or mortality. LEVEL OF EVIDENCE: Therapeutic Level III. See Instructions for Authors for a complete description of levels of evidence.


Norovirus is detected in one in five diarrhoea episodes in children, yet little is known about environmental risk factors associated with this disease, especially in low-income settings. The objective of this study was to examine environmental risk factors, and spatial and seasonal patterns of norovirus diarrhoea episodes in children in León, Nicaragua. We followed a population-based cohort of children under age 5 years for norovirus diarrhoea over a 1-year period. At baseline, characteristics of each household were recorded. Households were geocoded and spatial locations of garbage dumps, rivers, and markets were collected. In bivariate analysis we observed younger children and those with animals in their households were more likely to have experienced norovirus episodes. In adjusted models, younger children remained at higher risk for norovirus episodes, but only modest associations were observed with family and environmental characteristics. We next identified symptomatic children living in the same household and within 500 m buffer zones around the household of another child infected with the same genotype. Norovirus diarrhoea episodes peaked early in the rainy season. These findings contribute to our understanding of environmental factors and norovirus infection. Copyright © Cambridge University Press 2017


In Parkinson’s disease, striatal dopamine depletion leads to plastic changes at excitatory corticostriatal and thalamostriatal synapses. The functional consequences of these responses on the expression of behavioral deficits are incompletely understood. In addition, most of the information on striatal synaptic plasticity has been obtained in models with severe striatal dopamine depletion, and less is known regarding changes during early stages of striatal denervation. Using a partial model of nigral cell loss based on intranigral injection of the proteasome inhibitor lactacystin, we demonstrate ultrastructural changes at corticostriatal synapses with a 15% increase in the length and 30% increase in the area of the postsynaptic densities at corticostriatal synapses 1 week following toxin administration. This increase was positively correlated with the performance of lactacystin-lesioned mice on the rotarod task, such that mice with a greater increase in the size of the postsynaptic density performed better on the rotarod task. We therefore propose that lengthening of the postsynaptic density at corticostriatal synapses acts as a compensatory mechanism to maintain motor function under conditions of partial dopamine depletion. The ultrastructure of thalamostriatal synapses remained unchanged following lactacystin administration. Our findings provide novel insights into the mechanisms of synaptic plasticity and behavioral compensation following partial loss of substantia nigra pars compacta neurons, such as those occurring during the early stages of Parkinson’s disease. © 2017 Elsevier Inc.
The aim of this study was to determine the influence of photoinitiator systems on physical-chemical properties of flowable composites. Conventional (CFC), composed by bisphenol-glycidyl dimethacrylate (BisGMA)+triethylene glycol dimethacrylate (TEGDMA), and self-adhesive (SAFC), composed by BisGMA+TEGDMA+bis[2-(methacryloyloxy)ethyl] phosphate (2MP), flowable composites were developed. Five photoinitiator systems were tested: camphorquinone (CQ), ethyl-4-dimethylaminobenzoate (EDMAB), diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide (TPO), phenylbis (2,4,6-trimethylbenzoyl)phosphine oxide (BAPO), CQ+EDMAB+TPO and CQ+EDMAB+BAPO. A two-peak LED was used; degree of conversion (DC) and the maximum polymerization rate (RPmax) were determined by near-infrared spectroscopy. For the yellowing degree a spectrophotometer was used. Water sorption (Wsp) was obtained after 30 days of water storage (n=5). Data were submitted to two-way analysis of variance and Tukey's test (α=0.05). BAPO presented the highest DC and RPmax values for both series. SAFCs presented lower DC and RPmax for CQ+EDMAB-based materials. Greater yellowing was observed for SAFCs compared with CFCs, except for BAPO. Greater Wsp was observed for SAFCs compared with CFCs. The photoinitiator did not influence Wsp for CFCs, but TPO and BAPO presented the highest Wsp in SAFCs. The photoinitiator system affected differently the physical-chemical properties of CFCs and SAFCs. © 2017, Associacao Brasileira de Divulgacao Cientifica. All rights reserved.
The action of calcineurin inhibition is sufficient for the activation of NCC, whereas its effect on NKCC2 is more complex and requires concomitant stimulation by AVP. © 2017 the American Physiological Society.


In high-income countries, cancer remains the commonest cause of disease-related death in adolescents and young adults (AYAs) despite survival improvements. With more than 1,000,000 new diagnoses of cancer in AYAs annually worldwide, and their number of life-years affected by cancer being greatest of all ages, the global burden of cancer in AYAs exceeds that in all other ages. In low- and middle-income countries, where the great majority of the world's 3 billion AYAs reside, the needs of those with cancer have been identified and demand attention. Unique to the age group but universal, the psychosocial challenges they face are the utmost across life’s spectrum. This lead-off article of a new series in Pediatric Blood and Cancer on AYA oncology attempts to assess the global status of this emerging discipline. The review includes the changing incidence and survival of the common cancers in AYAs—there is no other age group with a similar array of malignancies—and the specific challenges to quality and quantity of life that compromise their lives. © 2017 Wiley Periodicals, Inc.


In 1973 the Oregon Legislature passed a major revision of its civil commitment law adopting changes that mirrored those taking place across the United States. The new sections offered significant protections of the rights of individuals who are alleged to have mental illness, a limitation on the length of commitment, the adoption of both dangerousness and gravely disabled type commitment criteria and the adoption of “beyond a reasonable doubt” as the standard of proof for commitment hearings. From 1973 to the present time, the Oregon Court of Appeals adjudicated a large number of appeals emanating from civil commitment courts. This article is based on a review of 98 written Oregon Court of Appeals commitment decisions from the years 1998 through 2015 and is accompanied by a review of legislative intent in 1973. It appears that the court of appeals has significantly altered the 1973 legislative changes by moving the dangerousness criteria to imminence and the gravely disabled criteria to a focus on survival. Empirically, civil commitment has dramatically decreased in Oregon over a 40-year period and the case law, as developed by Oregon Court of Appeals, has had a significant contributing role in this reduction.


BACKGROUND: The authors present their grading scale and the outcomes of the largest cohort of top surgery published to date. Application of this grading system can help determine which patients will benefit from a subcutaneous mastectomy with free nipple graft versus a circumareolar technique, with the primary endpoint being need for aesthetic revisions. METHODS: The authors reviewed their database of transgender males who underwent bilateral mastectomy between 2006 and 2015. Data collected included age, body mass index, American Society of Anesthesiologists class, smoking, diabetes, testosterone use, months of social transition, technique used, postoperative complications, and need for revision. Two techniques were used, circumareolar incision and free nipple graft technique. RESULTS: Between 2006 and 2015, 1686 consecutive mastectomies were performed on 843 patients. Of those, 548 patients were excluded because of inadequate follow-up. Of the 295 included, 109 were treated using a circumareolar incision and 186 were treated using a free nipple graft technique. There was no statistically significant difference in complications between the two groups; however, there was a statistically significant difference in the rate of aesthetic revisions in the grade 2B circumareolar incision group (34 percent versus 8.8 percent). CONCLUSIONS: The
authors’ outcomes are comparable to the literature, and demonstrate that these procedures can safely be performed in an outpatient setting. The authors’ grading scale classifies patients and helps the surgeon select a surgical technique. The authors show a statistical difference in rates of aesthetic revisions in Fischer grade 2B patients when a circumareolar incision is selected over a free nipple graft technique. CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, III.


STUDY DESIGN.: Validation study with cross sectional and longitudinal measurements OBJECTIVE.: To translate the US National Institute of Health (NIH)-minimal dataset for clinical research on chronic low back pain into the Dutch language and to test its validity and reliability among people with chronic low back pain. SUMMARY OF BACKGROUND DATA.: The NIH developed a minimal dataset to encourage more complete and consistent reporting of clinical research and to be able to compare studies across countries in patients with low back pain. In the Netherlands, the NIH-minimal dataset has not been translated before and measurement properties are unknown. METHODS.: Cross cultural validity was tested by a formal forward-backward translation. Structural validity was tested with exploratory factor analyses (Comparative Fit Index (CFI), Tucker Lewis Index (TLI) and Root mean Square Error of Approximation (RMSEA)). Hypothesis testing was performed to compare subscales of the NIH dataset with the Pain Disability Index and the EurQol-5D (Pearson Correlation Coefficients). Internal consistency was tested with Cronbach’s α and test-retest reliability at 2 weeks was calculated in a sub-sample of patients with Intraclass Correlation Coefficients (ICC) and Weighted Kappa’s (κω). RESULTS.: In total, 452 patients were included of which 52 were included for the test-retest study. Validity: Factor analysis for structural validity pointed into the direction of a 7-factor model (Cronbach’s α=0.78). Factors and total score of the NIH-minimal dataset showed fair to good correlations with PDI (r=?=.43 to 0.70) and EQSD (r=?=.41 to −0.64). Reliability: test-retest reliability per item showed substantial agreement (κω=0.65). Test-retest reliability per factor was moderate to good (ICC?=0.71). CONCLUSION.: The Dutch Language version measurement properties of the NIH-minimal were satisfactory. Level of Evidence: N/A Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.


Summary: Cannabis use is rising in the USA. Its relationship to cannabinoid signaling in bone cells implies its use could affect bone mineral density (BMD) in the population. In a national survey of people ages 20–59, we found no association between self-reported cannabis use and BMD of the hip or spine. Introduction: Cannabis is the most widely used illegal drug in the USA, and its recreational use has recently been approved in several US states. Cannabinoids play a role in bone homeostasis. We aimed to determine the association between cannabis use and BMD in US adults. Methods: In the National Health and Nutrition Examination Survey 2007–2010, 4743 participants between 20 and 59 years old, history of cannabis use was categorized into never, former (previous use, but not in last 30 days), light (1–4 days of use in last 30 days), and heavy (≥5 days of use in last 30 days). Multivariable linear regression was used to test the association between cannabis use and DXA BMD of the proximal femur and lumbar spine with adjustment for age, sex, BMI, and race/ethnicity among other BMD determinants. Results: Sixty percent of the population reported ever using cannabis; 47% were former users, 5% were light users, and 7% were heavy users. Heavy cannabis users were more likely to be male, have a lower BMI, increased daily alcohol intake, increased tobacco pack-years, and were more likely to have used other illegal drugs (cocaine, heroin, or methamphetamines). No association
between cannabis and BMD was observed for any level of use (p ≥ 0.28). Conclusions: A history of cannabis use, although highly prevalent and related to other risk factors for low BMD, was not independently associated with BMD in this cross-sectional study of American men and women. © 2017, International Osteoporosis Foundation and National Osteoporosis Foundation.


The Bridging Hemophilia B Experiences, Results and Opportunities Into Solutions (B-HERO-S) initiative was launched in an effort to address specific gaps in the understanding of the psychosocial impact of mild-moderate-severe hemophilia B. The original Hemophilia Experiences, Results and Opportunities (HERO) qualitative study evaluated the needs of people with hemophilia A or B in multiple countries; however, a majority of participants had the more common moderate-severe hemophilia A. The B-HERO-S study was designed in collaboration with the hemophilia community to evaluate the needs of adults with hemophilia B and caregivers of children with hemophilia B, including affected women and caregivers of girls with hemophilia. The report presented here describes participant demographics and comorbidities, as well as treatment regimens and access to treatment. Bleeding symptoms were reported by 27% of mothers of children with hemophilia B who participated. Women were more likely than men to self-report arthritis and depression/anxiety as comorbidities associated with hemophilia B. More adults and children with hemophilia B were on routine treatment than on on-demand treatment, and a high percentage of adults with moderate hemophilia B received routine treatment (86%). Many adults with hemophilia B (78%) and caregivers (69%) expressed concern about access to factor in the next 5 years, and of adults with hemophilia B, women more commonly experienced issues with access to factor in the past than did men (72% vs 44%). The findings of the B-HERO-S study reveal potential unmet needs of some patients with mild-moderate hemophilia B, and the results may be leveraged to inform patient outreach by hemophilia treatment centers and education initiatives.


Increasing numbers of graduating U.S. medical students are not securing a graduate medical education (GME) position, even after participating in the National Resident Matching Program (also known as "the Match") and the Supplemental Offer and Acceptance Program. The reasons for an unsuccessful Match include increasing numbers of applicants compared with nearly unchanging numbers of available GME positions, academic problems or professionalism lapses, and a poor fit between applicants and their first-choice specialty. In this Perspective, the authors (1) examine the current Match landscape; (2) discuss the
environmental factors that affect the Match landscape such as increasing medical school enrollment without a corresponding increase in GME positions; (3) review historical data on unmatched MD students; (4) discuss medical schools’ responsibilities to unmatched students and to society; (5) explore controversial issues related to unmatched students, including graduation delays and altering the Medical Student Performance Evaluation for subsequent Match applications; and (6) outline various pathways for unmatched students to secure a GME position in the future or to pursue an alternative, nonclinical position. Finally, they share guidelines for advising unmatched students in the weeks and months following an unsuccessful Match. These recommendations aim to clarify what options exist, and are practical, for unmatched students, with the hope that further study will enable the development of best practices in this area.


Multimodality cardiovascular imaging plays a central role in caring for patients with congenital heart disease (CHD). CHD clinicians and scientists are interested not only in cardiac morphology but also in the maladaptive ventricular responses and extracellular changes predisposing to adverse outcomes in this population. Expertise in the applications, strengths, and pitfalls of these cardiovascular imaging techniques as they relate to CHD is essential. The purpose of this article is to provide an overview of cardiovascular imaging in CHD. We focus on the role of 3 widely used noninvasive imaging techniques in CHD-echocardiography, cardiac magnetic resonance imaging, and cardiac computed tomography. Consideration is given to the common goals of cardiac imaging in CHD, including assessment of structural and residual heart disease before and after surgery, quantification of ventricular volume and function, stress imaging, shunt quantification, and tissue characterization. Extracardiac imaging is highlighted as an increasingly important aspect of CHD care.


The Life Span Study (LSS) of Japanese atomic bomb survivors is comprised of a large, population-based cohort offering one of the best opportunities to study the relationship between exposure to radiation and incidence of respiratory cancers. Risks of lung, laryngeal and other cancers of the respiratory system were evaluated among 105,444 LSS subjects followed from 1958 to 2009. During this period, we identified 2,446 lung, 180 laryngeal and 115 other respiratory (trachea, mediastinum and other ill-defined sites) first primary incident cancer cases. With the addition of ten years in follow-up, radiation dose estimates were improved, smoking data was revised and migration information was updated. Based on this more updated follow-up period, we investigated the joint effects of radiation and smoking using Poisson regression methods. For nonsmokers, the sex-averaged excess relative risk per Gy (ERR/Gy) for lung cancer (at age 70 after radiation exposure at age 30) was estimated as 0.81 (95% CI: 0.51, 1.18) with a female-to-male ratio of 2.83. There was no evidence of curvature in the radiation dose-response relationship overall or by sex. Lung cancer risks increased with pack-years of smoking and decreased with time since quitting smoking at any level of radiation exposure. Similar to the previous reported study, which followed cohort members through 1999, the ERR/Gy for lung cancer was significantly higher for low-to-moderate smokers than for heavy smokers, with little evidence of any radiation-associated excess risk in heavy smokers. Of 2,446 lung cancer cases, 113 (5%) could be attributed to radiation exposure. Of the 1,165 lung cancer cases occurring among smokers, 886 (76%) could be attributed to smoking. While there was little evidence of a radiation effect for laryngeal cancer, a nonsignificantly elevated risk of other respiratory cancers was observed. However, significant smoking effects
were observed for both laryngeal (ERR per 50 pack-years = 23.57; 95% CI: 8.44, 71.05) and other respiratory cancers (ERR per 50 pack-years = 1.21; 95% CI: 0.10, 3.25).


Secreted proteins in the bone marrow microenvironment play critical roles in acute myeloid leukemia (AML). Through an ex vivo functional screen of 94 cytokines, we identified that the pro-inflammatory cytokine interleukin-1 (IL-1) elicited profound expansion of myeloid progenitors in approximately 67% of AML patients while suppressing the growth of normal progenitors. Levels of IL-1beta and IL-1 receptors were increased in AML patients, and silencing of the IL-1 receptor led to significant suppression of clonogenicity and in vivo disease progression. IL-1 promoted AML cell growth by enhancing p38MAPK phosphorylation and promoting secretion of various other growth factors and inflammatory cytokines. Treatment with p38MAPK inhibitors reversed these effects and recovered normal CD34+ cells from IL-1-mediated growth suppression. These results highlight the importance of ex vivo functional screening to identify common and actionable extrinsic pathways in genetically heterogeneous malignancies and provide impetus for clinical development of IL-1/IL1R1/p38MAPK pathway-targeted therapies in AML.


BACKGROUND: Traumatic brain injury (TBI) was deemed the ‘signature injury’ of the Iraq and Afghanistan Wars (OEF/OIF/OND). Civilians with severe TBI have increased risks of motor vehicle crashes (MVCs). Little is known about MVC risk among Veterans with TBI, many of whom incurred TBIs that were mild in severity. OBJECTIVE: To examine associations between TBI and MVC-related hospitalizations among OEF/OIF/OND Veterans who use Veterans Health Administration (VA) healthcare. METHODS: Using national VA data, we identified 277,330 Veterans who enrolled in VA within one year of deployment. MVC, TBI, and other diagnoses were identified using ICD-9-CM codes. We estimated risk of subsequent MVC hospitalization for those with, versus without, TBI using time-to-event analyses. Time-varying Cox proportional hazards models were used to compute hazard ratios (HR) and 95% confidence intervals (CI) while controlling for potential confounders, including psychiatric diagnoses. RESULTS: There were 28,551 Veterans diagnosed with TBI; 130 were subsequently hospitalized for MVC. In adjusted models, those with TBI were four times more likely to be hospitalized for MVC than those without (HR = 4.2; CI = 3.3-5.3). CONCLUSION: Veterans with TBI had substantially greater risk of MVC-related hospitalizations. These Veterans may benefit from enhanced driving safety interventions to reduce risk.


Various viscoelastic models, such as the standard linear solid, Maxwell model, and Kelvin–Voigt model, are frequently used to describe the behavior of biological materials from single cells to tissues. These models are expressed mathematically as simple differential equations, called constitutive equations, which relate the applied force (stress) to the resulting deformation (strain) of the material. Networks of these models, representing materials with heterogeneous mechanical properties, are described by systems of constitutive equations. We prove that the eigenvalues associated with such systems are all nonpositive real numbers, find bounds for them, and indicate how they can be estimated quickly and accurately. We then give formulas for the analytical solutions of the system of equations. © 2017 Springer Science+Business Media Dordrecht
Background: Women with metastatic breast cancer (MBC) have average life expectancies of about 2 years, and report high levels of disease-related symptoms including pain, fatigue, sleep disturbance, psychological distress, and functional impairment. There is growing recognition of the limitations of medical approaches to managing such symptoms. Yoga is a mind-body discipline that has demonstrated a positive impact on psychological and functional health in early stage breast cancer patients and survivors, but has not been rigorously studied in advanced cancer samples. Methods: This randomized controlled trial examines the feasibility and initial efficacy of a Mindful Yoga program, compared with a social support condition that controls for attention, on measures of disease-related symptoms such as pain and fatigue. The study will be completed by December 2017. Sixty-five women with MBC age ≥ 18 are being identified and randomized with a 2:1 allocation to Mindful Yoga or a support group control intervention. The 120-min intervention sessions take place weekly for 8 weeks. The study is conducted at an urban tertiary care academic medical center located in Durham, North Carolina. The primary feasibility outcome is attendance at intervention sessions. Efficacy outcomes include pain, fatigue, sleep quality, psychological distress, mindfulness and functional capacity at post-intervention, 3-month follow-up, and 6-month follow-up. Discussion: In this article, we present the challenges of designing a randomized controlled trial with long-term follow-up among women with MBC. These challenges include ensuring adequate recruitment including of minorities, limiting and controlling for selection bias, tailoring of the yoga intervention to address special needs, and maximizing adherence and retention. This project will provide important information regarding yoga as an intervention for women with advanced cancer, including preliminary data on the psychological and functional effects of yoga for MBC patients. This investigation will also establish rigorous methods for future research into yoga as an intervention for this population. Trial registration: ClinicalTrials.gov identifier: NCT01927081 , registered August 16, 2013 © 2017 The Author(s).
BACKGROUND Subclinical thyroid disease during pregnancy may be associated with adverse outcomes, including a lower-than-normal IQ in offspring. It is unknown whether levothyroxine treatment of women who are identified as having subclinical hypothyroidism or hypothyroxinemia during pregnancy improves cognitive function in their children.

METHODS We screened women with a singleton pregnancy before 20 weeks of gestation for subclinical hypothyroidism, defined as a thyrotropin level of 4.00 mU or more per liter and a normal free thyroxine (T4) level (0.86 to 1.90 ng per deciliter [11 to 24 pmol per liter]), and for hypothyroxinemia, defined as a normal thyrotropin level (0.08 to 3.99 mU per liter) and a low free T4 level (<0.86 ng per deciliter). In separate trials for the two conditions, women were randomly assigned to receive levothyroxine or placebo. Thyroid function was assessed monthly, and the levothyroxine dose was adjusted to attain a normal thyrotropin or free T4 level (depending on the trial), with sham adjustments for placebo. Children underwent annual developmental and behavioral testing for 5 years. The primary outcome was the IQ score at 5 years of age (or at 3 years of age if the 5-year examination was missing) or death at an age of less than 3 years.

RESULTS A total of 677 women with subclinical hypothyroidism underwent randomization at a mean of 16.7 weeks of gestation, and 526 with hypothyroxinemia at a mean of 17.8 weeks of gestation. In the subclinical hypothyroidism trial, the median IQ score of the children was 97 (95% confidence interval [CI], 94 to 99) in the levothyroxine group and 94 (95% CI, 92 to 96) in the placebo group (P = 0.71). In the hypothyroxinemia trial, the median IQ score was 94 (95% CI, 91 to 95) in the levothyroxine group and 91 (95% CI, 89 to 93) in the placebo group (P = 0.30). In each trial, IQ scores were missing for 4% of the children. There were no significant between-group differences in either trial in any other neurocognitive or pregnancy outcomes or in the incidence of adverse events, which was low in both groups.

CONCLUSIONS Treatment for subclinical hypothyroidism or hypothyroxinemia beginning between 8 and 20 weeks of gestation did not result in significantly better cognitive outcomes in children through 5 years of age than no treatment for those conditions. Copyright © 2017 Massachusetts Medical Society.
pain and infusion site reactions as the dose increased, as compared to GlucaGen. © 2016 Diabetes Technology Society.


While self-monitoring of blood glucose (SMBG) is the current standard used by people with diabetes to manage glucose levels, recent improvements in accuracy of continuous glucose monitoring (CGM) technology are making it very likely that diabetes-related treatment decisions will soon be made based on CGM values alone. Nonadjunctive use of CGM will lead to a paradigm shift in how patients manage their glucose levels and will require substantial changes in how care providers educate their patients, monitor their progress, and provide feedback to help them manage their diabetes. The approval to use CGM nonadjunctively is also a critical step in the pathway toward FDA approval of an artificial pancreas system, which is further expected to transform diabetes care for people with type 1 diabetes. In this article, we discuss how nonadjunctive CGM is expected to soon replace routine SMBG and how this new usage scenario is expected to transform health outcomes and patient care. © 2016 The Author(s).


Background: The association between various definitions of sarcopenia and hospitalization has not been evaluated in community-dwelling older men. Methods: We used data from 1,516 participants at Visit 3 of the Osteoporotic Fractures in Men (MrOS) study who also had linked Medicare Fee-For-Service Claims data available. We examined the association between several sarcopenia definitions (International Working Group, European Working Group for Sarcopenia in Older Persons, Foundation for the NIH Sarcopenia Project, Baumgartner, and Newman) and hospitalization, using two-part ("hurdle") models, adjusted for age, clinical center, functional limitations, self-reported health, comorbidity, and cognitive function. Predictors included sarcopenia status (the summary definitions and the components of slowness, weakness, and/or lean mass); outcomes included hospitalization and cumulative inpatient days/year in the 3 years following the Visit 3 exam. Results: After accounting for confounding factors, none of the summary definitions or the definition components (slowness, weakness, or low lean mass) were associated with likelihood of hospitalization, the rate ratio of inpatient days among those hospitalized, or the mean rate of inpatient days amongst all participants. Conclusions: Sarcopenia was not associated hospitalization in community-dwelling older men. These results provide further evidence that current sarcopenia definitions are unlikely to identify those who are most likely to have greater hospitalization.


The sleep electroencephalogram (EEG) is highly heritable in humans and yet little is known about the genetic basis of inter-individual differences in sleep architecture. The aim of this study was to identify associations between candidate circadian gene variants and the polysomnogram, recorded under highly controlled laboratory conditions during a baseline, overnight, 8 h sleep opportunity. A candidate gene approach was employed to analyze single-nucleotide polymorphisms from five circadian-related genes in a two-phase analysis of 84 healthy young adults (28 F; 23.21 +/- 2.97 years) of European ancestry. A common variant in Period2 (PER2) was associated with 20 min less slow-wave sleep (SWS) in carriers of the minor allele than in noncarriers, representing a 22% reduction in SWS duration. Moreover, spectral analysis in a subset of participants (n = 37) showed the same PER2 polymorphism was associated with reduced EEG power density in the low delta range (0.25-1.0 Hz) during non-REM sleep and lower slow-wave activity (0.75-4.5 Hz) in the early part of the
sleep episode. These results indicate the involvement of PER2 in the homeostatic process of sleep. Additionally, a rare variant in Melatonin Receptor 1B was associated with longer REM sleep latency, with minor allele carriers exhibiting an average of 65 min (87%) longer latency from sleep onset to REM sleep, compared to noncarriers. These findings suggest that circadian-related genes can modulate sleep architecture and the sleep EEG, including specific parameters previously implicated in the homeostatic regulation of sleep.


We extend the observed best prediction (OBP; Jiang, Nguyen, and Rao 2011) method to small area estimation when the responses are counts at the area level. We show via a simulation study that the OBP outperforms the empirical best prediction method when the underlying model is mis-specified. A bootstrap method is proposed for estimating the area-specific mean squared prediction error of the OBP conditioning on the small area mean counts. Two real data examples are considered. © 2015, Oxford University Press, American Association for Public Opinion Research, All rights reserved.


In the CNS, glutamate is both phasically and tonically released into the extracellular space and must be removed by excitatory amino acid transporters (EAATs) to prevent excitotoxic accumulation. There remains uncertainty, however, regarding the functional steady-state concentration, with estimates ranging from tens of nanomolar to tens of micromolar. Efforts to reconcile these disparate values have led to a hypothesis that the extracellular space comprises distinct compartments in which basal glutamate concentrations are maintained independently. We used electrophysiology and two-photon Ca2+ imaging to test this hypothesis in the nucleus accumbens (NAc), where it has been proposed that micromolar extracellular glutamate is necessary for normal function. We found that the average concentration of synaptic glutamate is nanomolar, in agreement with previous electrophysiological estimates. Furthermore, this held true when glutamate uptake was inhibited, indicating that extracellular glutamate is not compartmentalized by EAATs. © 2017 The Author(s)


Importance: Silent or subclinical celiac disease may result in potentially avoidable adverse health consequences.
Objectives: To review the evidence on benefits and harms of screening for celiac disease in asymptomatic adults, adolescents, and children 3 years and older for the US Preventive Services Task Force. Data Sources: Ovid MEDLINE, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews, searched to June 14, 2016. Study Selection: Randomized clinical trials and cohort or case-control studies on clinical benefits and harms of screening vs no screening for celiac disease or treatment vs no treatment for screen-detected celiac disease; studies on diagnostic accuracy of serologic tests for celiac disease. Data Extraction and Synthesis: One investigator abstracted data, a second checked data for accuracy, and 2 investigators independently assessed study quality using predefined criteria. Main Outcomes and Measures: Cancer incidence, gastrointestinal outcomes, psychological outcomes, child growth outcomes, health outcomes resulting from nutritional deficiencies, quality of life, mortality, and harms of screening. No meta-analytic pooling was done. Results: One systematic review and 3 primary studies met inclusion criteria. No trials of screening for celiac disease were identified. One recent, good-quality systematic review of 56 original studies and 12 previous systematic reviews (sample sizes of primary studies ranging from 62 to more
than 12000 participants) found IgA tissue transglutaminase was associated with high accuracy (sensitivity and specificity both >90%) for diagnosing celiac disease. IgA endomysial antibodies tests were associated with high specificity. Only 2 studies of serologic tests for celiac disease involving 62 and 158 patients were conducted in asymptomatic populations and reported lower sensitivity (57% and 71%). One fair-quality, small (n = 40) Finnish treatment trial of asymptomatic adults with screen-detected celiac disease based on positive serologic findings found initiation of a gluten-free diet associated with small improvement in gastrointestinal symptoms compared with no gluten-free diet (difference less than 1 point on a scale of 1 to 7) at 1 year, with no differences on most measures of quality of life. No withdrawals due to adverse events occurred during the trial; no other harms were reported. No studies were identified that addressed the other outcomes. Conclusions and Relevance: Although some evidence was found regarding diagnostic accuracy of tests for celiac disease, little or no evidence was identified to inform most of the key questions related to benefits and harms of screening for celiac disease in asymptomatic individuals. More research is needed to understand the effectiveness of screening and treatment for celiac disease, accuracy of screening tests in asymptomatic persons, and optimal screening strategies.


As the number of prison inmates facing end-stage chronic illness grows, more prisons across the U.S. must address the need for end-of-life care. Many will likely need to develop a plan with potentially limited resources and external support. This case study presents one long-running model of care, the Louisiana State Penitentiary Prison Hospice Program. Based on field observations and in-depth interviews with hospice staff, inmate volunteers and corrections officers, we identify five essential elements that have contributed to the long-term operation of this program: patient-centered care, an inmate volunteer model, safety and security, shared values, and teamwork. We describe key characteristics of each of these elements, discuss how they align with earlier recommendations and research, and show how their integration supports a sustained model of prison end-of-life care.


Background: Freezing of gait in Parkinson’s disease (PD) has been linked with deficits in inhibitory control, but causal mechanisms are not established. Freezing at gait initiation (start hesitation) is often accompanied by multiple anticipatory postural adjustments (APAs). If inhibition deficits contribute to freezing by interfering with ability to inhibit initial weight shifts in the wrong direction, then PD subjects should experience more episodes of multiple APAs than healthy controls (HCS) do. If inhibition deficits contribute to freezing by interfering with ability to release a previously inhibited step following multiple APAs, then step onset following multiple APAs should be delayed more in people with PD than in HCs. Methods: Older adults with PD and HC subjects rapidly initiated stepping in response to a light cue in blocks of simple (SRT) and choice (CRT) conditions. We recorded kinematics and ground reaction forces, and we administered the Stroop task to assess inhibitory control. Results: Multiple APAs were more common in CRT than SRT conditions but were equally common in HC and PD subjects. Step onsets were delayed in both conditions and further delayed in trials with multiple APAs, except for HC subjects in SRT trials. Poor Stroop performance correlated with many multiple APAs, late step onset, and rearward position of center of mass (COM) at cue presentation. Forward motion of the COM during the APA was higher in trials with multiple APAs than in trials with single APAs, especially in CRT trials and in PD subjects without self-reported freezing. Conclusion: Start hesitation is not caused by multiple APAs per se, but may be associated with difficulty recovering from multiple APAs, due to difficulty releasing a previously inhibited step.

A 6-d-old Indian-origin female rhesus macaque (Macaca mulatta) presented with bradycardia shortly after sedation with ketamine. No other cardiac abnormalities were apparent. Approximately 2 wk after the initial presentation, the macaque was again bradycardic and exhibited a regularly irregular arrhythmia on a prestudy examination. ECG, echocardiography, blood pressure measurement, Spo2 assessment, and a CBC analysis were performed. The echocardiogram and bloodwork were normal, but the infant was hypotensive at the time of echocardiogram. The ECG revealed ventricular parasystole. Ventricular parasystole is considered a benign arrhythmia caused by an ectopic pacemaker that is insulated from impulses from the sinus node. Given this abnormality, the macaque was transferred to a short-term study protocol, according to veterinary recommendation. On the final veterinary examination, a grade 3 systolic murmur and a decrease in arrhythmia frequency were noted. Gross cardiac lesions were not identified at necropsy the following day. Cardiac tissue sections were essentially normal on microscopic examination. This infant did not display signs of cardiovascular insufficiency, and a review of the medical record indicated normal growth, feed intake and activity levels. This case demonstrates the importance of appropriate screening of potential neonatal and juvenile research candidates for occult cardiovascular abnormalities. Whether the arrhythmia diagnosed in this case was truly innocuous is unclear, given the documented hypotension and the development of a systolic heart murmur.


The study verified the bond strength in simulated dental restorations of silorane- or methacrylate-based composites repaired with methacrylate-based composite. Methacrylate- (P60) or silorane-based (P90) composites were used associated with adhesive (Adper Single Bond 2). Twenty-four hemi-hourglass-shaped samples were repaired with each composite (n=12). Samples were divided according to groups: G1= P60 + Adper Single Bond 2 + P60; G2= P60 + Adper Single Bond 2 + P60 + thermocycling; G3= P90 + Adper Single Bond 2 + P60; and G4= P90 + Adper Single Bond 2 + P60 + thermocycling. G1 and G3 were submitted to tensile test 24 h after repair procedure, and G2 and G4 after submitted to 5,000 thermocycles at 5 and 55 °C for 30 s in each bath. Tensile bond strength test was accomplished in an universal testing machine at crosshead speed of 0.5 mm/min. Data (MPa) were analyzed by two-way ANOVA and Tukey’s test (5%). Sample failure pattern (adhesive, cohesive in resin or mixed) was evaluated by stereomicroscope at 30X and images were obtained in SEM. Bond strength values of methacrylate-based composite samples repaired with methacrylate-based composite (G1 and G2) were greater than for silorane-based samples (G3 and G4). Thermocycling decreased the bond strength values for both composites. All groups showed predominance of adhesive failures and no cohesive failure in composite resin was observed. In conclusion, higher bond strength values were observed in methacrylate-based resin samples and greater percentage of adhesive failures in silorane-based resin samples, both composites repaired with methacrylate-based resin.


Recent updates in atherosclerotic cardiovascular disease (ASCVD) risk assessment and management guidelines have expanded the global number of statin-indicated persons, prompting clinicians to rethink conversations about initiating new statin therapy. The benefits of statins in primary prevention of ASCVD are less convincing than in secondary prevention, although higher ASCVD risk is associated with greater statin benefit. Therefore, clinicians must engage patients in a shared decision about starting new statin therapy, which should involve discussion about the risks and benefits of therapy, patient perceptions, and health status. Research has identified nonadherence to statin therapy as a factor associated with reduced clinical
benefits of statin therapy. Clinicians should be aware of patient-specific factors associated with nonadherence and implement strategies to improve adherence as indicated. Data on the impact of adherence improvement strategies and the accuracy of how we currently measure adherence are lacking. Additionally, research focusing on patient preferences and reported outcomes would greatly inform practice and improve clinician–patient relationships. © 2016, Springer Science+Business Media New York.


BACKGROUND CONTEXT: Waddell Signs (WS), introduced as a method to establish patients with substantial psychosocial components to their low back pain, carry a negative association despite no literature evaluating whether physical disease is associated with them. PURPOSE: To compare lumbar MRI findings between the patients with and without Waddell’s Signs. STUDY DESIGN: Retrospective cohort study based on prospectively collected data PATIENT SAMPLE: Thirty patients aged 35-55 with an ODI score >50 randomly selected such that there was an even distribution of patients based on number of WS OUTCOME MEASURES: ODI and SF-12 scores, number of WS, presence and severity of spinal pathology METHODS: MRIs were reviewed by three spine specialists blinded to clinical exam findings, number of WS, and patient identity. Type and severity of pathology and presence of surgical and non-surgical lesions were assessed, and findings were rank-ordered based on overall impression of the pathology. There was no external funding or potential conflicts of interest for this study. RESULTS: There were significantly more individual pathologic findings in those without WS (p=0.02). However, there was no difference in the severity of pathology based on WS (p=0.46). Furthermore, the rank ordering based on overall impression of severity showed no difference between the patients with and without WS (p=0.20). Although 100% of the patients without WS showed pathologic findings on MRI, 70% of WS patients also had significant pathology on MRI. The prevalence of spondylolisthesis, stenosis, and disc herniation was similar (p=0.41, p=0.22, and p=0.43, respectively). The prevalence and mean number of lesion amenable to surgery did not differ based on presence of WS (p=0.21 and p=0.18, respectively). CONCLUSIONS: Patients with WS present a difficult diagnostic challenge for the physician as their organic symptoms are often co-existent with emotional fear avoidance behavior. While there is more overall pathology in those without WS, a significant number of these patients appear to have comparable spinal pathology with equivalent severity, which may be contributing to patients’ symptoms and disability. Presence of these non-organic symptoms often makes us doubt these patients. However, as part of effective treatment, physicians should better understand both physical and psychological components of patient disability.


Routine entomological monitoring data are used to quantify the abundance of Ae. aegypti. The public health utility of these indicators is based on the assumption that greater mosquito abundance increases the risk of human DENV transmission, and therefore reducing exposure to the vector decreases incidence of infection. Entomological survey data from two longitudinal cohort studies in Iquitos, Peru, linked with 8,153 paired serological samples taken approximately six months apart were analyzed. Indicators of Ae. aegypti density were calculated from cross-sectional and longitudinal entomological data collected over a 12-month period for larval, pupal and adult Ae. aegypti. Log binomial models were used to estimate risk ratios (RR) to measure the association between Ae. aegypti abundance and the six-month risk of DENV seroconversion. RRs estimated using cross-sectional entomological data were compared to RRs estimated using longitudinal data. Higher cross-sectional Ae. aegypti densities were not associated with an increased risk of DENV
seroconversion. Use of longitudinal entomological data resulted in RRs ranging from 1.01 (95% CI: 1.01, 1.02) to 1.30 (95% CI: 1.17, 1.46) for adult stage density estimates and RRs ranging from 1.21 (95% CI: 1.07, 1.37) to 1.75 (95% CI: 1.23, 2.5) for categorical immature indices. Ae. aegypti densities calculated from longitudinal entomological data were associated with DENV seroconversion, whereas those measured cross-sectionally were not. Ae. aegypti indicators calculated from cross-sectional surveillance, as is common practice, have limited public health utility in detecting areas or populations at high risk of DENV infection.


Structural and functional neuroimaging studies indicate that heavy alcohol use during adolescence may be neurotoxic to the brain. This chapter reviews the neuroimaging findings in cross-sectional and longitudinal studies of adolescent heavy alcohol users. These youth exhibit reductions in prefrontal, hippocampal, and cerebellar brain volume, decreased frontoparietal, and increased frontolimbic white matter integrity, as well as alterations in blood oxygen level-dependent response during working memory, inhibitory control, verbal encoding, decision making, and reward processing—some of which appear to differ between males and females. Although some exist, additional longitudinal studies will significantly advance addiction medicine by aiding prevention scientists and treatment providers to develop neurobiologically informed ways of strengthening neural networks prior to and after the onset of heavy alcohol use, thereby promoting healthy cognitive functioning across the adolescent period.


The rostral raphe pallidus (rRPa) contains sympathetic premotor neurons controlling thermogenesis in brown adipose tissue (BAT). We sought to determine if a tonic activation of glycineA receptors (GlyAR) in the rRPa contributes to the inhibitory regulation of BAT SNA and of cardiovascular parameters in anesthetized rats. Nanoinjection of the GlyAR antagonist, strychnine (STR), into the rRPa of intact rats increased BAT sympathetic nerve activity (SNA, peak: +495%), BAT temperature (TBAT, +1.1 masculineC), expired CO2, (+0.4 %), core body temperature (TCORE, +0.2 masculineC), arterial pressure (MAP, +4 mmHg) and heart rate (HR, +57 bpm). STR into rRPa in rats with a post-dorsomedial hypothalamus transection produced similar increases in BAT thermogenic and cardiovascular parameters. Glycine (GLY) nanoinjection into the rRPa evoked a potent inhibition of the cooling-evoked increases in BAT SNA (nadir: -74 %), TBAT (-0.5 masculineC), TCORE (-0.2 masculineC), expired CO2 (-0.2 %), MAP (-9 mmHg), and HR (-22 bpm), 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 masculineC), expired CO2 (-0.3 %), MAP (-9 mmHg) and HR (-33 bpm). We conclude that a tonically active glycinergic input to the rRPa contributes to the inhibitory regulation of the discharge of BAT sympathetic premotor neurons and of BAT thermogenesis and energy expenditure.


INTRODUCTION: Progressive supranuclear palsy (PSP) is characterized by early postural instability and backward falls. The mechanisms underlying backward postural instability in PSP are not understood. The aim of this study was to test the hypothesis that postural instability in PSP is a result of dysfunction in the perception of postural verticality. METHODS: We gathered posturography data on 12 subjects with PSP to compare with 12 subjects with idiopathic Parkinson’s Disease (PD) and 12 healthy subjects. Objective tests of postural
impairment included: dynamic sensory perception tests of gravity and of surface oscillations, postural responses to surface perturbations, the sensory organization test of postural sway under altered sensory conditions and limits of stability in stance. RESULTS: Perception of toes up (but not toes down) surface tilt was reduced in subjects with PSP compared to both control subjects ($p < 0.001$ standing, $p < 0.007$ seated) and subjects with PD ($p < 0.03$ standing, $p < 0.04$ seated). Subjects with PSP, PD and normal controls accurately perceived the direction of gravity when standing on a tilting surface. Unlike PD and control subjects, subjects with PSP exerted less postural corrective torque in response to toes up surface tilts. DISCUSSION: Difficulty perceiving backward tilt of the surface or body may account for backward falls and postural impairments in patients with PSP. These observations suggest that abnormal central integration of sensory inputs for perception of body and surface orientation contributes to the pathophysiology of postural instability in PSP.


Women in areas of the Americas with endemic Aedes mosquito populations are at risk for exposure to Zika virus, which can cause fetal brain abnormalities and associated congenital microcephaly. Individual health care providers may encounter health system barriers to providing evidence-based care. We focus on Mexico and the state of Texas to highlight the role of health system factors in contraceptive access in the context of Zika and highlight efforts in Puerto Rico as an example of initiatives to improve access to contraception. In Mexico, states with the highest unmet need for contraception are low-lying coastal states. The government recently announced an investment to combat Zika but made no mention of family planning initiatives to assist women in preventing pregnancy. In Texas, the Department of State Health Services has issued recommendations to help women and men avoid mosquito bites; the issue of whether women should plan or avoid pregnancy is not addressed. Puerto Rico has the largest number of confirmed cases of Zika virus in the U.S. states and territories. Recently, the Centers for Disease Control and Prevention Foundation launched the Zika Contraception Access Network, which provides contraceptives at no cost to participating clinics in Puerto Rico. The Zika virus highlights weaknesses in health systems that make it difficult for women to use contraception if they want to delay births. Women across the globe, with or without Zika virus, need access to contraception to prevent unintended pregnancy, and health care providers require functioning health systems that offer support to ensure access is a reality.


Background: Contrast-enhanced ultrasound (CEU) limb perfusion imaging is a promising approach for evaluating peripheral artery disease (PAD). However, low signal enhancement in skeletal muscle has necessitated high-power intermittent imaging algorithms, which are not clinically feasible. We hypothesized that CEU using a combination of intermediate power and a contrast agent resistant to inertial cavitation would allow real-time limb stress perfusion imaging. Methods: In normal volunteers, CEU of the calf skeletal muscle was performed on separate days with Sonazoid, Optison, or Definity. Progressive reduction in the ultrasound pulsing interval was used to assess the balance between signal enhancement and agent destruction at escalating mechanical indices (MI, 0.1-0.4). Real-time perfusion imaging at MI 0.1-0.4 using postdestructive replenishment kinetics was performed at rest and during 25 W plantar flexion contractile exercise. Results: For Optison, limb perfusion imaging was unreliable at rest due to very low signal enhancement generated at all MIs and was possible during exercise-induced hyperemia only at MI 0.1 due to agent destruction at higher MIs. For Definity, signal intensity progressively increased with MI but was offset by microbubble destruction, which resulted in modest signal enhancement during CEU perfusion imaging and distortion of replenishment curves at MI ≥ 0.2. For Sonazoid, there strong signal enhancement at MI ≥ 0.2, with little destruction detected only at MI 0.4. Accordingly, high signal intensity and nondistorted perfusion imaging was possible
at MI 0.2-0.3 and detected an 8.0± 5.7-fold flow reserve. Conclusions: Rest-stress limb perfusion imaging in humans with real-time CEUS, which requires only seconds to perform, is possible using microbubbles with viscoelastic properties that produce strong nonlinear signal generation without destruction at intermediate acoustic pressures. © 2016 American Society of Echocardiography.


Epithelial ovarian cancer is one of the most lethal of gynecological malignancies. Due to its lack of early symptoms, detection usually occurs when the tumor is no longer confined to the ovary. We previously identified Fbxw15, a gene encoding an F-box protein in the mouse ovary, and showed that its expression is developmentally regulated. Here we report the molecular analysis of its human homologue, FBXW12 in epithelial ovarian tumors. To search for FBXW12 gene mutations, we PCR-amplified and sequenced the coding region of FBXW12, the gene’s 5′-untranslated region and the proximal promoter in each of 30 EOC tumors. Promoter methylation was determined by DNA bisulfite conversion, followed by methylation specific PCR. FBXW12 intracellular localization was identified by means of immunohistochemistry. A complete deletion of the gene’s coding region, the 5′-UTR and the proximal promoter, was observed in 3 EOC samples. Eight of the remaining 27, had a deletion of the 5′-UTR, and the proximal promoter. FBXW12 mRNA was detected in 2 of the 19 samples without deletions. The methylation specific PCR results demonstrated CpGs methylation in the FBXW12 proximal promoter. Immunohistochemistry assay revealed that within the normal ovary, FBXW12 has an oocyte specific expression, whereas in EOC samples it is present in the ovarian surface epithelium. Our results indicate that the FBXW12 gene is deleted in approximately ten percent of the EOC cases studied; such deletions comprised either the FBXW12 promoter or the mRNA-encoding region. Moreover, FBXW12 could be epigenetically silenced by CpGs methylation in some of these EOC cases.


Knowledge of brain correlates of postural control is limited by the technical difficulties in performing controlled experiments with currently available neuroimaging methods. Here we present a system that allows the measurement of anticipatory postural adjustment of human legs to be synchronized with the acquisition of functional magnetic resonance imaging data. The device is composed of Magnetic Resonance Imaging (MRI) compatible force sensors able to measure the level of force applied by both feet. We tested the device in a group of healthy young subjects and a group of elderly subjects with Parkinson’s disease using an event-related functional MRI (fMRI) experiment design. In both groups the postural behavior inside the magnetic resonance was correlated to the behavior during gait initiation outside the scanner. The system did not produce noticeable imaging artifacts in the data. Healthy young people showed brain activation patterns coherent with movement planning. Parkinson’s disease patients demonstrated an altered pattern of activation within the motor circuitry. We concluded that this force measurement system is able to index both normal and abnormal preparation for gait initiation within an fMRI experiment. © 2017 The Author(s).


OBJECTIVE: Loop electrosurgical excision procedures (LEEPs) are negative for high-grade cervical intraepithelial neoplasia (CIN 2+) after a hematoxylin and eosin-based CIN 2+ colposcopic biopsy diagnosis in 14% to 24% of cases. This may be due to diagnostic errors or biopsy-related regression of the dysplasia. Because p16 immunohistochemical staining of cervical biopsies improves diagnostic accuracy, we hypothesized that p16-
based cervical biopsy diagnoses may reduce the frequency of negative LEEPs. MATERIALS AND METHODS: We performed a retrospective cross-sectional study of all cervical LEEPs completed at our institution from 2002 to 2012. We recorded patient age, sexual history, smoking history, pathologic diagnoses (including whether the diagnosis was p16 based), the number of days from biopsy to follow-up LEEP, and clinical follow-up. This yielded 593 study subjects meeting inclusion criteria of CIN 2+ colposcopic diagnoses with follow-up LEEP and 2 years of clinical follow-up. Colposcopic biopsies and follow-up LEEPs were reviewed and p16 immunostaining was performed on all samples to provide criterion standard results. Data were analyzed by chi and regression modeling. RESULTS: Our practice employed p16 to aid cervical biopsy diagnoses by 2006. The frequency of negative LEEPs before 2006 was 12 (10%) of 126. The frequency dropped during the p16 era (2006-2012) to 23 (5%) of 467. Overall, we observed an inverse relationship between the frequency of p16 employment and the frequency of negative LEEP outcomes (R = 0.71; p < .001), independent of potential covariates. CONCLUSIONS: Our data suggest that more accurate p16-based diagnoses may reduce the frequency of unnecessary LEEPs.


Endoscopic sinus surgery is an effective intervention at improving quality of life for patients with medically refractory chronic rhinosinusitis. The evidence supporting frontal sinusotomy is limited to single institution case series. However, the data for Draf IIa frontal sinusotomy do demonstrate that most patients experience lasting frontal sinus patency on postoperative endoscopic examination and improvements in quality of life. Salvage endoscopic frontal sinus surgery via a Draf III shows high rates of neo-ostium patency and subjective improvements in symptoms at a 2-year time point in case series.


An estimated 4.5% of total US health care dollars have been devoted to mitigating chronic rhinosinusitis. The most recalcitrant of these patients undergo surgery, which fails to improve symptoms in approximately 25% of patients. Recent advances in informational, microbiomic, and genomic analysis have introduced the first set of tools that patients, physicians, politicians, and payers can apply to better forecast which patients will respond favorably to endoscopic sinus surgery. This article summarizes the forces driving the application of personalized medicine to CRS and how new advances can be applied to clinical practice.


MEK4 is an upstream kinase in MAPK signaling pathways where it phosphorylates p38 MAPK and JNK in response to mitogenic and cellular stress queues. MEK4 is overexpressed and induces metastasis in advanced prostate cancer lesions. However, the value of MEK4 as an oncology target has not been pharmacologically validated because selective chemical probes targeting MEK4 have not been developed. Despite a high level of sequence homology in the ATP-binding site, most reported MEK inhibitors are selective for MEK1/2 and display reduced potency toward other MEKS. Here, we present the first functional and binding selectivity-profiling platform of the MEK family. We applied the platform to profile a set of known kinase inhibitors and used the results to develop an in silico approach for small molecule docking against MEK proteins. The docking studies identified molecular features of the ligands and corresponding amino acids in MEK proteins responsible for high affinity binding versus those driving selectivity. WaterLOGSY and saturation transfer difference (STD) NMR spectroscopy techniques were utilized to understand the binding modes of active compounds. Further minor synthetic manipulations provide a proof of concept by showing how information gained through this platform can be utilized to perturb selectivity across the MEK family. This inhibitor-based
approach pinpoints key features governing MEK family selectivity and clarifies empirical selectivity profiles for a set of kinase inhibitors. Going forward, the platform provides a rationale for facilitating the development of MEK-selective inhibitors, particularly MEK4 selective inhibitors, and repurposing of kinase inhibitors for probing the structural selectivity of isoforms.


We conducted a study to compare a standard anterosuperolateral (ASL) portal with a percutaneous Port of Wilmington (PW) portal for repair of superior labrum anterior and posterior (SLAP) tears. We hypothesized that anchors placed through the PW portal would be less likely to penetrate the glenoid or injure the suprascapular nerve (SSN). This study used 6 matched-pair cadaveric shoulders. Two anchors were arthroscopically placed posterior to the biceps, at 11 o’clock and 10 o’clock, to simulate a SLAP repair. One set of anchors was placed through an ASL portal and the other through a PW portal. Glenoid vault penetration and distance to SSN were noted. In the ASL portal group, 8 (66.7%) of 12 anchors violated the medial cortex of the glenoid; in the penetration cases, mean distance to SSN was 6.8 mm for 11 o’clock anchors and 4.8 mm for 10 o’clock anchors. In the PW portal group, 2 (16.7%) of 12 anchors violated the medial cortex of the glenoid; in the penetration cases, distance to SSN was 20 mm for the 11 o’clock anchor and 8 mm for the 10 o’clock anchor. The risk of glenoid vault penetration during repair of SLAP tears posterior to the biceps tendon is reduced when a percutaneous posterior approach is used for anchor placement. This approach also directs the anchor away from the SSN.


BACKGROUND: Heart failure (HF) is a complex clinical syndrome associated with significant symptom burden; however, our understanding of the relationship between symptoms and physical frailty in HF is limited. OBJECTIVE: The aim of this study was to quantify associations between symptoms and physical frailty in HF. METHODS: A sample of adults with symptomatic HF were enrolled in a cross-sectional study. Physical symptoms were measured with the HF Somatic Perception Scale-Dyspnea subscale, the Epworth Sleepiness Scale, and the Brief Pain Inventory short form. Affective symptoms were measured with the Patient Health Questionnaire-9 and the Brief Symptom Inventory-Anxiety scale. Physical frailty was assessed according to the Frailty Phenotype Criteria: shrinking, weakness, slowness, physical exhaustion, and low physical activity. Comparative statistics and generalized linear modeling were used to quantify associations between symptoms and physical frailty, controlling for Seattle HF Model projected 1-year survival. RESULTS: The mean age of the sample (n = 49) was 57.4 +/- 9.7 years, 67% were male, 92% had New York Heart Association class III/IV HF, and 67% had nonischemic HF. Physically frail participants had more than twice the level of dyspnea (P < .001), 75% worse wake disturbances (P < .001), and 76% worse depressive symptoms (P = .003) compared with those who were not physically frail. There were no differences in pain or anxiety. CONCLUSIONS: Physically frail adults with HF have considerably worse dyspnea, wake disturbances, and depression. Targeting physical frailty may help identify and improve physical and affective symptoms in HF.


Local endosomal recycling at synapses is essential to maintain neurotransmission. Rab4GTPase, found on sorting endosomes, is proposed to balance the flow of vesicles among endocytic, recycling, and degradative pathways in the presynaptic compartment. Here, we report that Rab4-associated vesicles move bidirectionally in Drosophila axons but with an anterograde bias, resulting in their moderate enrichment at the synaptic region of the larval ventral ganglion. Results from FK506 binding protein (FKBP) and FKBP-
Rapamycin binding domain (FRB) conjugation assays in rat embryonic fibroblasts together with genetic analyses in Drosophila indicate that an association with Kinesin-2 (mediated by the tail domain of Kinesin-2alpha/KIF3A/KLP64D subunit) moves Rab4-associated vesicles toward the synapse. Reduction in the anterograde traffic of Rab4 causes an expansion of the volume of the synapse-bearing region in the ventral ganglion and increases the motility of Drosophila larvae. These results suggest that Rab4-dependent vesicular traffic toward the synapse plays a vital role in maintaining synaptic balance in this neuronal network.


The second iteration of the Autism Brain Imaging Data Exchange (ABIDE II) aims to enhance the scope of brain connectomics research in Autism Spectrum Disorder (ASD). Consistent with the initial ABIDE effort (ABIDE I), that released 1112 datasets in 2012, this new multisite open-data resource is an aggregate of resting state functional magnetic resonance imaging (fMRI) and corresponding structural MRI and phenotypic datasets. ABIDE II includes datasets from an additional 487 individuals with ASD and 557 controls previously collected across 16 international institutions. The combination of ABIDE I and ABIDE II provides investigators with 2156 unique cross-sectional datasets allowing selection of samples for discovery and/or replication. This sample size can also facilitate the identification of neurobiological subgroups, as well as preliminary examinations of sex differences in ASD. Additionally, ABIDE II includes a range of psychiatric variables to inform our understanding of the neural correlates of co-occurring psychopathology; 284 diffusion imaging datasets are also included. It is anticipated that these enhancements will contribute to unraveling key sources of ASD heterogeneity. © Author(s) 2017.


Motivational interviewing (MI) offers a treatment modality that can help meet the treatment needs of American Indians/Alaska Natives (AI/ANs) with substance use disorders. This report presents results from a national survey of 192 AI/AN substance abuse treatment programs with regard to their use of MI and factors related to its implementation, including program characteristics, workforce issues, clinician perceptions of MI, and how clinicians learned about MI. Sixty-six percent of programs reported having implemented the use of MI in their programs. In the final logistic regression model, the odds of implementing MI were significantly higher when programs were tribally owned (OR = 2.946; CI95 1.014, 8.564), where more than 50% of staff were Certified Alcohol and Drug Counselors (CADCs) (OR = 5.469; CI95 1.330, 22.487), and in programs in which the survey respondent perceived that MI fit well with their staff’s expertise and training (OR = 3.321; CI95 1.287, 8.569). © 2017 National Council for Behavioral Health


Age-related macular degeneration (AMD) is a leading cause of blindness in the developed world. While many AMD susceptibility variants have been identified, their influence on AMD progression has not been elucidated. Using data from two large clinical trials, Age-Related Eye Disease Study (AREDS) and AREDS2, we evaluated the effects of 34 known risk variants on disease progression. In doing so, we calculated the eye-level time-to-late-AMD and modeled them using a bivariate survival analysis approach, appropriately accounting for between-eye correlation. We then derived a genetic risk score (GRS) based on these 34 risk variants, and analyzed its effect on AMD progression. Finally, we used the AREDS data to fit prediction models of
progression based on demographic and environmental factors, eye-level AMD severity scores and the GRS and tested the models using the AREDS2 cohort. We observed that GRS was significantly associated with AMD progression in both cohorts, with a stronger effect in AREDS than in AREDS2 (AREDS: Hazard Ratio (HR) = 1.34, p=1.6x10^{-22}; AREDS2: HR=1.11, p=2.1x10^{-4}). For prediction of AMD progression, addition of GRS to the demographic/environmental risk factors considerably improved the prediction performance. However, when the baseline eye-level severity scores were included as the predictors, any other risk factors including the GRS only provided small additional predictive power. Our model for predicting the disease progression risk demonstrated satisfactory performance in both cohorts, and we recommend its use with baseline AMD severity scores plus baseline age, education level, smoking status, either with or without GRS.


Introduction: The presence of cerebrovascular pathology may increase the risk of clinical diagnosis of Alzheimer’s disease (AD). Methods: We examined excess risk of incident clinical diagnosis of AD (probable and possible AD) posed by the presence of lacunes and large infarcts beyond AD pathology using data from the Statistical Modeling of Aging and Risk of Transition study, a consortium of longitudinal cohort studies with more than 2000 autopsies. We created six mutually exclusive pathology patterns combining three levels of AD pathology (low, moderate, or high AD pathology) and two levels of vascular pathology (without lacunes and large infarcts or with lacunes and/or large infarcts). Results: The coexistence of lacunes and large infarcts results in higher likelihood of clinical diagnosis of AD only when AD pathology burden is low. Discussion: Our results reinforce the diagnostic importance of AD pathology in clinical AD. Further harmonization of assessment approaches for vascular pathologies is required. © 2016 The Alzheimer’s Association.


This study aimed to determine the impact of preoperative staging on the treatment of clinical T2N0 (cT2N0) esophageal cancer patients undergoing esophagectomy. We reviewed a retrospective cohort of 27 patients treated at a single institution between 1999 and 2011. Clinical staging was performed with computed tomography, positron emission tomography, and endoscopic ultrasound. Patients were separated into two groups: neoadjuvant therapy followed by surgery (NEOSURG) and surgery alone (SURG). There were 11 patients (41%) in the NEOSURG group and 16 patients (59%) in the SURG group. In the NEOSURG group, three of 11 patients (27%) had a pathological complete response and eight (73%) were partial or nonresponders after neoadjuvant therapy. In the SURG group, nine of 16 patients (56%) were understaged, 6 (38%) were overstaged, and 1 (6%) was correctly staged. In the entire cohort, despite being clinically node negative, 14 of 27 patients (52%) had node-positive disease (5/11 [45%] in the NEOSURG group, and 9/16 [56%] in the SURG group). Overall survival rate was not statistically significant between the two groups (P = 0.96). Many cT2N0 patients are clinically understaged and show no preoperative evidence of node-positive disease. Consequently, neoadjuvant therapy may have a beneficial role in treatment.


AIM: The aim of the study was to investigate the interchangeability and reliability of macular perfusion measurements using optical coherence tomography angiography. METHODS: A prospective cross-sectional observational study. Healthy adult Chinese subjects were recruited. Macular perfusion parameters were automatically analysed by software included in a spectral-domain optical coherence tomography system. The vessel density (VD) of the whole, parafovea, superior-hemi, inferior-hemi, fovea, temporal, superior, nasal and inferior quadrants as well as the foveal avascular zone (FAZ) and choroidal capillary VD (CCVD) were quantified. RESULTS: A total of 51 eyes in 27 subjects were included (8 men and 19 women, mean age 24+/−4 years). Significant differences in VD of all quadrants (all p<0.001) was detected between the 3x3 mm and 6x6 mm macular scan size. The biggest difference of VD between the two scan size was 5.14+/−4.03, which was not clinically meaningful. No statistically significant differences were found in FAZ or CCVD between the two different scan sizes. The mean intraclass correlation coefficient (ICC) between two measurements from the inter-rater of 20 eyes was from 0.560 to 0.893 for VD and 0.845 for FAZ. The mean ICC between two measurements from the intrarater of 20 eyes was from 0.497 to 0.870 for VD and 0.780 for FAZ. CONCLUSIONS: FAZ and CCVD are interchangeable between the 3x3 mm and 6x6 mm macular scan sizes. The VD differences between the two different scan sizes are not clinically meaningful. The macular perfusion parameters presented good but not perfect reliability, which should be acknowledged in clinical practice.


Chemotherapy for bone tumors is a major challenge because of the inability of therapeutics to penetrate dense bone mineral. We hypothesize that a nanostructured formulation with high affinity for bone could deliver drug to the tumor while minimizing off-target toxicity. Here, we evaluated the efficacy and toxicity of a novel bone-targeted, pH-sensitive liposomal formulation containing doxorubicin in an animal model of bone metastasis. Biodistribution studies with the liposome showed good uptake in tumor, but low accumulation of doxorubicin in the heart. Mice treated with the bone-targeted liposome formulation showed a 70% reduction in tumor volume, compared to 35% reduction for free doxorubicin at the same dose. Both cardiac toxicity and overall mortality were significantly lower for animals treated with the bone-targeted liposomes compared to free drug. Bone-targeted, pH-sensitive, doxorubicin containing liposomes represent a promising approach to selectively delivering doxorubicin to bone tumors while minimizing cardiac toxicity.


We encountered a patient with infantile nephrotic syndrome associated with a dense interstitial inflammatory infiltrate and prominent extramedullary hematopoiesis. Immunohistochemical analysis revealed numerous terminal deoxynucleotidyl transferase (TdT)-positive cells, which may raise concern for lymphoblastic lymphoma. Thus, we further characterized a group of pediatric kidneys with inflammation. TdT-positive nuclei were quantitated, and dual immunostains for TdT/CD79a, TdT/CD3, and TdT/CD43 were performed in a subset of cases; flow cytometry was performed in 1 case. TdT-positive nuclei were present in inflamed pediatric kidneys in 40 of 42 patients. TdT counts (average of 3 maximal high-power fields) ranged from 1 to >200, with a mean of 47. The presence and number of TdT-positive nuclei showed a strong association with
younger patient age. Extramedullary hematopoiesis was identified in 11/42 patients, all under the age of 1. The presence of extramedullary hematopoiesis did not correlate with TdT count (P=0.158). Dual immunostaining and flow cytometric analysis in 1 case showed weak expression of B-cell markers and favored normal precursor B cells. Although TdT is a common marker of lymphoblastic lymphoma, we have demonstrated that TdT-positive cells may be part of the inflammatory milieu in infant kidneys. Together with cytologic, architectural, and clinical features, these data can help to avoid misinterpretation of involvement by lymphoblastic lymphoma/leukemia. Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.


Herpes simplex virus (HSV) anterograde transport in neuronal axons is vital, allowing spread from latently-infected ganglia to epithelial tissues where viral progeny are produced in numbers allowing spread to other hosts. HSV membrane proteins gE/gI and US9 initiate the process of anterograde axonal transport ensuring that virus particles are transported from the cytoplasm into the most proximal segments of axons. These proteins do not appear to be important once HSV is inside axons. Previously we described HSV double mutants lacking both gE and US9 that failed to transport virus particles into axons. Here, we show that gE-/US9- double mutants accumulate large quantities of unenveloped and partially enveloped capsids in neuronal cytoplasm. These defects in envelopment can explain defects in axonal transport of enveloped virions. In addition, the unenveloped capsids that accumulated were frequently bound onto cytoplasmic membranes, apparently immobilized in intermediate stages of envelopment. A gE-null mutant produced enveloped virions, but these accumulated in large numbers in the neuronal cytoplasm, rather than reaching cell surfaces like wild type HSV virions. Thus, in addition to the defects in envelopment there was missorting of capsids and enveloped particles in the neuronal cytoplasm which can explain reduced anterograde transport of unenveloped capsids and enveloped virions. These mechanisms differ substantially from existing models suggesting that gE/gI and US9 function by tethering HSV particles onto kinesin microtubule motors. The defects in assembly of virus particles with gE-/US9- mutants were novel as they were neuron-specific, in keeping with observations that US9 is neuron-specific. IMPORTANCE Herpes simplex virus (HSV) and other alpha-herpesviruses such as varicella zoster virus depend upon the capacity to navigate in neuronal axons. To do this virus particles tether onto dyneins and kinesins that motor along microtubules from axon tips to neuronal cell bodies (retrograde) or from cell bodies to axon tips (anterograde). This transit in axons is essential in order for alpha-herpesviruses to establish latency in ganglia then reactivate and move back to peripheral tissues for spread to other hosts. Anterograde transport of HSV requires two membrane proteins, gE/gI and US9. Our studies describe new mechanisms for how gE/gI and US9 initiate anterograde axonal transport. HSV mutants lacking both gE and US9 fail to properly assemble enveloped virus particles in the cytoplasm which blocks anterograde transport of enveloped particles. As well, there were defects in the sorting of virus particles so that particles when formed do not enter proximal axons.


The US Multi-Society Task Force on Colorectal Cancer, with invited experts, developed a consensus statement and recommendations to assist health care providers with appropriate management of patients with biallelic mismatch repair deficiency (BMMRD) syndrome, also called constitutional mismatch repair deficiency syndrome. This position paper outlines what is known about BMMRD, the unique genetic and clinical aspects of the disease, and reviews the current management approaches to this disorder. This article represents a starting point from which diagnostic and management decisions can undergo rigorous testing for efficacy. There is a lack of strong evidence and a requirement for further research. Nevertheless, providers need direction on how to recognize and care for BMMRD patients today. In addition to identifying areas of
research, this article provides guidance for surveillance and management. The major challenge is that BMMRD is rare, limiting the ability to accumulate unbiased data and develop controlled prospective trials. The formation of effective international consortia that collaborate and share data is proposed to accelerate our understanding of this disease. Am J Gastroenterol advance online publication, 28 March 2017; doi:10.1038/ajg.2017.105.


OBJECTIVES: To examine how medical complexity modifies the relationship between enrollment in Department of Veterans Affairs (VA) home-based primary care (HBPC) and hospitalization for ambulatory care-sensitive conditions (ACSC) for veterans with diabetes mellitus and whether the effect of HBPC on hospitalizations varies according to clinical condition. DESIGN: Retrospective cohort study. SETTING: VA and non-VA hospitals. PARTICIPANTS: VA beneficiaries aged 67 and older with diabetes mellitus and enrolled in Medicare (N = 364,972). MEASUREMENTS: Instrumental variables regression models were used to estimate the effect of HBPC enrollment on hospitalization for ACSCs (defined according to the Agency for Healthcare Research and Quality Prevention Quality Indicators) overall and in subgroups stratified according to medical complexity. Models were also estimated for each ACSC to determine which conditions were most sensitive to HBPC. Distance from the veteran’s residence to the nearest HBPC site was used as the instrumental variable. RESULTS: HBPC was associated with fewer ACSC hospitalizations (odds ratio (OR) = 0.35 per person-month, 95% confidence interval (CI) = 0.30-0.42). For veterans in the highest quartile of medical complexity, HBPC enrollment was associated with fewer ACSC hospitalizations (OR = 0.43, 95% CI = 0.19-0.93), whereas for those in the lowest quartile, HBPC was associated with more ACSC hospitalizations (OR = 33.2, 95% CI = 4.6-240.1). HBPC enrollment was associated with fewer hospitalizations for a range of ACSCs. CONCLUSION: HBPC enrollment was associated with fewer hospitalizations for a range of ACSCs in veterans with diabetes mellitus but only in the most medically complex individuals. This demonstrates the importance of appropriate targeting and suggests that the effect of HBPC is attributable to its comprehensive approach rather than condition-specific interventions.


BACKGROUND AND OBJECTIVES: Little is known about how the patient-centered medical home (PCMH) is being implemented in residency practices. We describe both the trends in implementation of PCMH features and the influence that working with PCMH features has on resident attitudes toward their importance in 14 family medicine residencies associated with the P4 Project. METHODS: We assessed 24 residency continuity clinics annually between 2007-2011 on presence or absence of PCMH features. Annual resident surveys (n=690) assessed perceptions of importance of PCMH features using a 4-point scale (not at all important to very important). We used generalized estimating equations logistic regression to assess trends and ordinal-response proportional odds regression models to determine if resident ratings of importance were associated with working with those features during training. RESULTS: Implementation of electronic health record (EHR) features increased significantly from 2007-2011, such as email communication with patients (33% to 67%), preventive services registries (23% to 64%), chronic disease registries (63% to 82%), and population-based quality assurance (46% to 79%). Team-based care was the only process of care feature to change significantly (54% to 93%). Residents with any exposure to EHR-based features had higher odds of rating the features more important compared to those with no exposure. We observed consistently lower odds of the resident rating process of care features as more important with any exposure compared to no exposure. CONCLUSIONS: Residencies engaged in educational transformation were more successful in implementing EHR-based PCMH features, and exposure during training appears to positively influence resident ratings of importance, while exposure to process of care features are slower to implement with less influence on importance ratings.


**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 perioperative 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% CI, -26.1, -7.2). 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, -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.

---

**Ellison, D. H. (2017).**


doi:10.1056/NEJMc1700362

10.1056/NEJMc1700362#SA3

---


*Nonobstructive Coronary Artery Disease by Coronary CT Angiography Improves Risk Stratification and Allocation of Statin Therapy. JACC Cardiovasc Imaging.* doi:10.1016/j.jcmg.2016.10.022

**OBJECTIVES:** This study sought to determine prognostic value of nonobstructive coronary artery disease (CAD) for atherosclerotic cardiovascular disease (ASCVD) events and to determine whether incorporation of this information into the pooled cohort equation reclassifies recommendations for statin therapy as defined by the 2013 guidelines for cholesterol management of the American College of Cardiology and American Heart Association (ACC/AHA). **BACKGROUND:** Detection of nonobstructive CAD by coronary computed tomography angiography may improve risk stratification and permit individualized and more appropriate allocation of statin therapy. **METHODS:** This study determined the pooled hazard ratio of nonobstructive CAD for ASCVD events from published studies and incorporated this information into the ACC/AHA pooled cohort equation. The study calculated revised sex- and ethnicity-based 10-year ASCVD risk and determined
boundaries corresponding to the original 7.5% risk for ASCVD events. It also assessed reclassification for statin eligibility by incorporating the results from meta-analysis to individual patients from a separate cohort. **RESULTS:** This study included 2 studies (2,295 subjects; 66% male; prevalence of nonobstructive CAD, 47%; median follow-up, 49 months; 67 ASCVD events). The hazard ratio of nonobstructive CAD for ASCVD events was 3.2 (95% confidence interval: 1.5 to 6.7). Incorporation of this information into the pooled cohort equation resulted in reclassification toward statin eligibility in individuals with nonobstructive CAD, with an original ASCVD score of 3.0% and 5.9% or higher in African-American women and men and a score of 4.4% and 4.6% or higher in Caucasian women and men, respectively. The absence of nonobstructive CAD resulted in reclassification toward statin ineligibility if the original ASCVD score was as 10.0% and 17.9% or lower in African-American women and men and 13.7% and 14.3% or lower in Caucasian women and men, respectively. Reclassification is observed in 14% of patients. **CONCLUSIONS:** Detection of nonobstructive CAD by coronary computed tomography angiography improves risk stratification and permits individualized and more appropriate allocation of statin therapy across sex and ethnicity groups.


In the current study, we examined the role of intelligence and executive functions in the resolution of temporary syntactic ambiguity using an individual differences approach. Data were collected from 174 adolescents and adults who completed a battery of cognitive tests as well as a sentence comprehension task. The critical items for the comprehension task consisted of object/subject garden paths (e.g., While Anna dressed the baby that was small and cute played in the crib), and participants answered a comprehension question (e.g., Did Anna dress the baby?) following each one. Previous studies have shown that garden-path misinterpretations tend to persist into final interpretations. Results showed that both intelligence and processing speed interacted with ambiguity. Individuals with higher intelligence and faster processing were more likely to answer the comprehension questions correctly and, specifically, following ambiguous as opposed to unambiguous sentences. Inhibition produced a marginal effect, but the variance in inhibition was largely shared with intelligence. Conclusions focus on the role of individual differences in cognitive ability and their impact on syntactic ambiguity resolution.


Children with Smith-Lemli-Opitz syndrome (SLOS) are typically reported to have moderate to severe intellectual disability. This study aims to determine whether normal cognitive function is possible in this population and to describe clinical, biochemical and molecular characteristics of children with SLOS and normal intelligent quotient (IQ). The study included children with SLOS who underwent cognitive testing in four centers. All children with at least one IQ composite score above 80 were included in the study. Six girls, three boys with SLOS were found to have normal or low-normal IQ in a cohort of 145 children with SLOS. Major/multiple organ anomalies and low serum cholesterol levels were uncommon. No correlation with IQ and genotype was evident and no specific developmental profile were observed. Thus, normal or low-normal cognitive function is possible in SLOS. Further studies are needed to elucidate factors contributing to normal or low-normal cognitive function in children with SLOS.


Cholesterol-rich, apolipoprotein B (apoB)-containing lipoproteins are now widely accepted as the most important causal agents of atherosclerotic cardiovascular disease. Multiple unequivocal and orthogonal lines of evidence all converge on low-density lipoprotein and related particles as being the principal actors in the
genesis of atherosclerosis. Here, we review the fundamental role of atherogenic apoB-containing lipoproteins in cardiovascular disease and several other humoral and parietal factors that are required to initiate and maintain arterial degeneration. The biology of foam cells and their interactions with high-density lipoproteins, including cholesterol efflux, are also briefly reviewed. © 2017 Shapiro MD and Fazio S.


Context: The sources and biological impact of 3,30,5,50 tetraiodothyroacetic acid (TA4) are uncertain. CD34+ fibrocytes express several proteins involved in the production of thyroid hormones. They infiltrate the orbit in Graves disease (GD), an autoimmune process known as thyroid-associated ophthalmopathy. It appears that the thyrotropin receptor plays an important role in the pathogenesis of thyroid-associated ophthalmopathy. Objective: To quantify levels of TA4 in healthy participants and those with GD, determine whether fibrocytes generate this thyroid hormone analogue, and determine whether TA4 influences the actions of thyroid-stimulating hormone and thyroid-stimulating immunoglobulins in orbital fibroblasts. Design/Setting/Participants: Patients with GD and healthy donors in an academic medical center clinical practice were recruited. Main Outcome Measures: Liquid chromatography-tandem mass spectrometry, autoradiography, real-time polymerase chain reaction, hyaluronan immunoassay. Results: Serum levels of TA4 are elevated in GD. TA4 levels are positively correlated with those of thyroxine and negatively correlated with serum levels of triiodothyronine. Several cell types in culture generate TA4 from ambient thyroxine, including fibrocytes, HELA cells, human Müller stem cells, and retinal pigmented epithelial cells. Propylthiouracil inhibits TA4 generation. TA4 enhances the induction by thyrotropin and thyroid-stimulating immunoglobulins of several participants in the pathogenesis of thyroid-associated ophthalmopathy, including interleukin 6, hyaluronan synthase 1, prostaglandin endoperoxide H synthase 2, and haluronan production. Conclusion: TA4 may be ubiquitously generated in many tissues and enhances the biological impact of thyrotropin and thyroid-stimulating immunoglobulins in orbital connective tissue. These findings may identify a physiologically important determinant of extrathyroidal thyroid-stimulating hormone action. Copyright © 2017 by the Endocrine Society.


The main reason cited for the replacement of dental composite restorations is the recurrence of caries. Numerous models—both in vitro, with acid gels or bacterial biofilms, and in situ, with dental appliances—have been used to study caries formation around dental composites. The literature shows that many factors may affect caries formation, including marginal gap formation, gap size, the local chemical environment, the durability of the bonded interface, the extent of bacterial penetration, and the presence of mechanical loading. Studies have also shown that what have been called wall lesions may form independent of surface lesions, though not likely due to microleakage through very small gap spaces in the clinical situation. Gap size and mechanical loading have been shown to be related to lesion severity within in vitro models, but these results do not correspond exactly with those obtained from in situ studies using restorations in dental appliances. Though not conclusive, some in vitro models have shown that certain materials possessing antimicrobial characteristics may reduce the severity of lesion formation, suggesting possible pathways for developing new composite and adhesive materials for restorations with potentially enhanced longevity.

**BACKGROUND:** Patients with pruritus have been shown to have an increased incidence of certain subtypes of malignancy. **OBJECTIVE:** To assess predictors of malignancy in patients with chronic pruritus without prior dermatologic diagnoses. **METHODS:** Case-control study of 398 patients with chronic pruritus who developed a malignancy were compared with 8346 patients with chronic pruritus who did not develop a malignancy. Primary outcomes were odds of developing incident malignancy. **RESULTS:** Age greater than 60 years (OR 4.04, 95% CI 3.08, 5.31), male sex (OR 1.39, 95% CI 1.13, 1.71) and liver disease (OR 2.37, 95% CI 1.00, 5.65) were predictors of malignancy development in patients with chronic pruritus and non-diseased skin. In an exploratory analysis with multiple imputation via chained equations, age greater than 60 years (OR 4.13, 95% CI 3.15, 5.42), male sex (OR 1.26, 95% CI 1.02, 1.55), and current or prior smoking (OR 2.02, 95% CI 1.42, 2.88) were predictors of malignancy development in patients with chronic pruritus and non-diseased skin. **LIMITATIONS:** Potential for misclassification and detection biases. Missing data. **CONCLUSIONS AND RELEVANCE:** In patients with chronic pruritus without concomitant dermatologic diagnoses, older age, male sex, liver disease and tobacco abuse increase the odds of an underlying malignancy.


**Background:** Complaints of imbalance are common non-resolving signs in individuals with post-concussive syndrome. Yet, there is no consensus rehabilitation for non-resolving balance complaints following mild traumatic brain injury (mTBI). The heterogeneity of balance deficits and varied rates of recovery suggest varied etiologies and a need for interventions that address the underlying causes of poor balance function. Our central hypothesis is that most chronic balance deficits after mTBI result from impairments in central sensorimotor integration that may be helped by rehabilitation. Two studies are described to 1) characterize balance deficits in people with mTBI who have chronic, non-resolving balance deficits compared to healthy control subjects, and 2) determine the efficacy of an augmented vestibular rehabilitation program using auditory biofeedback to improve central sensorimotor integration, static and dynamic balance, and functional activity in patients with chronic mTBI. **Methods:** Two studies are described. Study 1 is a cross-sectional study to take place jointly at Oregon Health and Science University and the VA Portland Health Care System. The study participants will be individuals with non-resolving complaints of balance following mTBI and age- and gender-matched controls who meet all inclusion criteria. The primary outcome will be measures of central sensorimotor integration derived from a novel central sensorimotor integration test. Study 2 is a randomized controlled intervention to take place at Oregon Health & Science University. In this study, participants from Study 1 with mTBI and abnormal central sensorimotor integration will be randomized into two rehabilitation interventions. The interventions will be 6 weeks of vestibular rehabilitation 1) with or 2) without the use of an auditory biofeedback device. The primary outcome measure is the daily activity of the participants measured using an inertial sensor. **Discussion:** The results of these two studies will improve our understanding of the nature of balance deficits in people with mTBI by providing quantitative metrics of central sensorimotor integration, balance, and vestibular and ocular motor function. Study 2 will examine the potential for augmented rehabilitation interventions to improve central sensorimotor integration. **Trial registration:** This trial is registered at clinicaltrials.gov (NCT02748109). © 2017 The Author(s).


Background: The sooner people receive treatment for hearing loss (HL), the quicker they are able to recognize speech and to master hearing aid technology. Unfortunately, a majority of people with HL wait until their impairments have progressed from moderate to severe levels before seeking auditory rehabilitation. To increase the number of individuals with HL who pursue and receive auditory rehabilitation, it is necessary to improve methods for identifying and informing these people via widely accessible hearing screening procedures. Screening for HL is the first in a chain of events that must take place to increase the number of patients who enter the hearing health-care system. New methods for hearing screening should be readily accessible through a common medium (e.g., telephone or computer) and should be relatively easy and quick for people to self-administer. Purpose: The purpose of this study was to assess a digits-in-noise (DIN) hearing screening test that was delivered via personal computer. Research Design: Participants completed the Hearing Handicap Inventory for Adults (HHIA) questionnaire, audiometric testing in a sound booth, and computerized DIN testing. During the DIN test, sequences of three spoken digits were presented in noise via headphones at varying signal-to-noise ratios (SNRs). Participants entered each three-digit sequence they heard using an on-screen keypad. Study Sample: Forty adults (16 females, 24 males) participated in the study, of whom 20 had normal hearing and 20 had HL (pure-tone average [PTA] thresholds for 0.5, 1, 2, and 4 kHz .25 dB HL). Data Collection and Analysis: DIN SNR and PTA data were analyzed and compared for each ear tested. Receiver operating characteristic curves based on these data were plotted. A measure of overall accuracy of a screening test is the area under the receiver operating characteristic curve (AUC). This measures the average true positive rate across false positives at varying DIN SNR cutoffs. Larger values of the AUC indicate, on average, more accurate screening tests. HHIA responses were analyzed and compared to PTA and DIN SNR results using Pearson correlation statistics. Results: HHIA scores were positively correlated with audiometric PTA and DIN SNR results (p < 0.001 for all correlations). For an HL criterion of one or more frequencies from 0.25 to 8 kHz .25 dB HL, the AUC for the DIN test was 0.95. When a criterion of hearing level was set at one or more frequencies from 0.25 to 8 kHz .20 dB HL, the AUC for the DIN test was 0.96. Conclusions: The computer version of the DIN test demonstrated excellent sensitivity and specificity for our sample of 40 participants. AUC results (0.95) suggest that this DIN test administered via computer should be very useful for adult hearing screening.


Objective This study has investigated the influence of BisGMA, BisEMA, BisEMA 30, and two UDMA-based monomers (UDMA and Fit 852), with TEGDMA as co-monomer, on the degree of conversion, water sorption, water solubility, and optical properties of experimental dental composites. Methods Materials were formulated at 70/30 molar ratios using BisGMA, BisEMA, BisEMA 30, UDMA or FIT 852, as base monomers, combined with TEGDMA. 60 wt% of silanated-glass particles was added. Degree of conversion (DC) and polymerization kinetics were monitored using Fourier-transformed infrared spectroscopy in the near-IR range. Water sorption (Wsp) and solubility (Wsl) were assessed using mass variation after 60 days water storage. Color was evaluated using a digital spectrophotometer, applying the CIELab parameters 24 h after dry storage and 60 days after water immersion to calculate ΔE values. All data were analyzed using ANOVA and Tukey’s test (pre-set alpha = 0.05). Results The BisGMA-based co-monomer mixture presented the lowest DC (62 ± 1%), whereas BisEMA 30 had the highest DC value (95 ± 2%). The highest Wsp was observed for BisEMA 30 (12.2 ± 0.8%), and the lowest for BisEMA (0.4 ± 0.1%). BisEMA has shown the lowest Wsl (0.03 ± 0.01%) and BisEMA 30 the highest one (0.97 ± 0.1%). The ΔE values showed that BisEMA 30 (7.3 color units) and Fit 852 (3.8 color units) altered the color stability providing ΔE > 3.3, which is considered clinically unacceptable. Conclusions The chemical composition and structure of the base monomer influenced the degree of conversion, water sorption, water solubility, and color stability. Considering the overall results, it is possible...
to state that the base monomer BisEMA mixed with the co-monomer TEGDMA presented the best performance in terms of all the parameters tested. Significance The resin matrix composition might influence physical property degradation processes and color stability of dental resin composites. Formulations based on BisEMA seem most promising for materials’ development. © 2017 The Academy of Dental Materials


Multiple factors critical to the effectiveness of academic phase I cancer programs were assessed among 16 academic centers in the U.S. Successful cancer centers were defined as having broad phase I and I/II clinical trial portfolios, multiple investigator-initiated studies, and correlative science. The most significant elements were institutional philanthropic support, experienced clinical research managers, robust institutional basic research, institutional administrative efforts to reduce bureaucratic regulatory delays, phase I navigators to inform patients and physicians of new studies, and a large cancer center patient base. New programs may benefit from a separate stand-alone operation, but mature phase I programs work well when many of the activities are transferred to disease-oriented teams. The metrics may be useful as a rubric for new and established academic phase I programs. The Oncologist 2017;22:1-6.


Background. Medical decision making may be influenced by contextual factors. We evaluated whether pathologists are influenced by disease severity of recently observed cases. Methods. Pathologists independently interpreted 60 breast biopsy specimens (one slide per case; 240 total cases in the study) in a prospective randomized observational study. Pathologists interpreted the same cases in 2 phases, separated by a washout period of >6 months. Participants were not informed that the cases were identical in each phase, and the sequence was reordered randomly for each pathologist and between phases. A consensus reference diagnosis was established for each case by 3 experienced breast pathologists. Ordered logit models examined the effect the pathologists’ diagnoses on the preceding case or the 5 preceding cases had on their diagnosis for the subsequent index case. Results. Among 152 pathologists, 49 provided interpretive data in both phases I and II, 66 from only phase I, and 37 from phase II only. In phase I, pathologists were more likely to indicate a more severe diagnosis than the reference diagnosis when the preceding case was diagnosed as ductal carcinoma in situ (DCIS) or invasive cancer (proportional odds ratio [POR], 1.28; 95% confidence interval [CI], 1.15-1.42). Results were similar when considering the preceding 5 cases and for the pathologists in phase II who interpreted the same cases in a different order compared with phase I (POR, 1.17; 95% CI, 1.05-1.31). Conclusion. Physicians appear to be influenced by the severity of previously interpreted test cases. Understanding types and sources of diagnostic bias may lead to improved assessment of accuracy and better patient care. © The Author(s) 2016.


The Society of Thoracic Surgeons General Thoracic Surgery Database has grown to more than 500,000 case records. Clinical research supported by the database is increasingly used to advance patient outcomes. This research review from the General Thoracic Surgery Database in 2014 and 2015 discusses 6 recent publications and an ongoing study on longitudinal outcomes in lung cancer surgery from The Society of Thoracic Surgeons Task Force for Linked Registries and Longitudinal Follow-up. A lack of database variables specific for certain uncommon procedures limits the ability to study these operations; inclusion of clinical descriptors for selected infrequent but clinically important thoracic disorders is suggested.


Background: Aminoglycosides (AGs) and glycopeptides are antibiotics essential for treating life-threatening respiratory infections in patients with cystic fibrosis (CF). The goal of this study was to examine the effects of cumulative intravenous (IV)-AG (amikacin and/or tobramycin) and/or glycopeptide (vancomycin) dosing on hearing status in patients with CF. Methods: Hearing thresholds were measured from 0.25 to 16.0. kHz, in 81 participants with CF. Participants were categorized into two groups: normal hearing in both ears (≤ 25. dB HL for all frequency bands) or hearing loss (> 25. dB HL for any frequency band in either ear). Participants were also characterized into quartiles by their cumulative IV-AG (with or without vancomycin) exposure. Dosing was calculated using two strategies: (i) total number of lifetime doses, and (ii) total number of lifetime doses while accounting for the total doses per day. This was referred to as the “weighted” method. Results: Participants in the hearing loss group were significantly older than those in the normal-hearing group. After adjusting for gender and age at the time of hearing test, participants in the two highest-quartile exposure groups were almost 5 X more likely to have permanent sensorineural hearing loss than those in the two lowest-quartile exposure groups. There was a small group of CF patients who had normal hearing despite high exposure to IV-antibiotics. Conclusions: Cumulative IV-antibiotic dosing has a significant negative effect on hearing sensitivity in patients with CF, when controlling for age and gender effects. A trend for increasing odds of hearing loss was associated with increasing cumulative IV-antibiotic dosing. © 2017 European Cystic Fibrosis Society.

We designed a study to evaluate the use of benzodiazepines and ethanol in patients being assessed for alcohol withdrawal and compare outcomes between the two agents. This is a retrospective chart review of patients admitted to neurocritical care or neurosurgical services who were at risk for ethanol withdrawal between June 2011 and September 2015. Patients were divided into two groups based on the first medication administered for alcohol withdrawal management, either benzodiazepine (n=50) or enteral ethanol (n=50). The primary endpoint was the maximum change in Clinical Institute Withdrawal Assessment of Alcohol scale (CIWA) score within the first 24 hours. Secondary endpoints included maximum and minimum CIWA score in 5 days, length of stay, and change in Glasgow Coma Scale. Study groups differed by mortality risk, level of coma at admission, and other clinical characteristics, with the ethanol group appearing less severely ill. There was no significant difference between the two groups in the maximum change in CIWA score at 24 hours (-0.97, 95% CI: -3.21 to 1.27, p=0.39). Hospital and intensive care unit length of stay was 6.5 days and 1 day shorter for the ethanol group (p=0.03 and p=0.02, respectively). In summary, enteral ethanol was preferentially used in patients who are more likely to be capable of tolerating oral intake. We found that the change from baseline in CIWA score or other physiologic variables was not substantially different between the two agents. The overall utility of benzodiazepines and enteral ethanol remains unclear for this population and further study is needed to determine superiority.

**CONTEXT:** Guideline-discordant imaging to evaluate incident low back pain is common. **OBJECTIVE:** We compared rates of guideline-discordant imaging in patients with low back pain in two care delivery systems with differing abilities to track care through an electronic health record (EHR), and in their patients’ insurance status, to measure the association between these factors and rates of ordered low back imaging. **DESIGN:** We used data from two Kaiser Permanente (KP) Regions and from OCHIN, a community health center network. We extracted data on imaging performed after index visits for low back pain from June 1, 2011, to May 31, 2012, in these systems. Adjusted logistic regression measured associations between system-level factors and imaging rates. **MAIN OUTCOME MEASURES:** Imaging rates for incident low back pain using 2 national quality metrics: Clinical Quality Measure 0052, a measure for assessing Meaningful Use of EHRs, and the Healthcare Effectiveness Data and Information Set measure "Use of Imaging Studies for Low Back Pain.”

**RESULTS:** Among 19,503 KP patients and 2694 OCHIN patients with incident low back pain, ordered imaging was higher among men and whites but did not differ across health care systems. OCHIN’s publicly insured patients had higher rates of imaging compared with those with private or no insurance. **CONCLUSION:** Rates of ordered imaging to evaluate incident low back pain among uninsured OCHIN patients were lower than in KP overall; among insured OCHIN patients, rates were higher than in KP overall. Research is needed to establish causality and develop interventions.


Laboratory investigations of physiological processes in phytoplankton require precise control of experimental conditions. Chemostats customized to control and maintain stable pH levels (pHstats) are ideally suited for investigations of the effects of pH on phytoplankton physiology, for example in context of ocean acidification. Here we designed and constructed a simple, flexible pHstat system and demonstrated its operational capabilities under laboratory culture conditions. In particular, the system is useful for simulating natural cyclic pH variability within aquatic ecosystems, such as diel fluctuations that result from metabolic activity or tidal mixing in estuaries. The pHstat system operates in two modes: (1) static/set point pH, which maintains pH at a constant level, or (2) dynamic pH, which generates regular, sinusoidal pH fluctuations by systematically varying pH according to user-defined parameters. The pHstat is self-regulating through the use of interchangeable electronically controlled reagent or gas-mediated pH-modification manifolds, both of which feature flow regulation by solenoid valves. Although effective pH control was achieved using both liquid reagent additions and gas-mediated methods, the liquid manifold exhibited tighter control (+/-0.03pH units) of the desired pH than the gas manifold (+/-0.10pH units). The precise control provided by this pHstat system, as well as its operational flexibility will facilitate studies that examine responses by marine microbiota to fluctuations in pH in aquatic ecosystems.


**Introduction** In the USA, veterans are increasingly using and requesting complementary and alternative therapies. Our goal was to explore long-term changes in symptoms for veterans in two groups: veterans with hepatitis C (HCV) not receiving antiviral therapy (HCV-only group), and veterans with HCV who were receiving antiviral triple therapy (HCV-TT group). **Methods** This pilot study used a mixed method prospective descriptive design. Participants were asked to attend two acupuncture sessions per week for eight weeks. Quantitative data were collected at 7 time points over the course of 10 weeks using validated instruments. Semi-structured individual interviews were carried out before and after treatment. Main outcome measures were changes from baseline in physical and psychological symptoms, including fatigue, depression, quality of life,
pain, and other symptom burden. Results Although pain changes from baseline were not significant, pain disability changes were significant and varied depending on HCV treatment status. In fatigue, depression, and symptoms, we found a trend toward improvement in the HCV-only group. Qualitatively, improved mood was the most commonly reported change after acupuncture, followed by decreased pain, medication use, and fatigue, leading to improved quality of life. All veterans were pleased with their acupuncture experience and would recommend this therapy to others. Conclusions Despite the effects of a debilitating medication regimen for veterans undergoing TT, all veterans reported having a positive experience with acupuncture. We found that acupuncture is desired by veterans and can improve symptoms commonly experienced by veterans with HCV. © 2017


Rationale: While surgical resection is recommended for most patients with early stage lung cancer according to the National Comprehensive Cancer Network guidelines, stereotactic body radiotherapy is increasingly being used. Provider-patient communication regarding the risks and benefits of each approach may be a modifiable factor leading to improved patient-centered outcomes. Objectives: To qualitatively describe the experiences of patients undergoing either surgery or stereotactic body radiotherapy for early stage non-small cell lung cancer. Methods: We qualitatively evaluated and used content analysis to describe the experiences of 13 patients with early clinical stage non-small cell lung cancer before undergoing treatment in three health care systems in the Pacific Northwest, with a focus on knowledge obtained, communication, and feelings of distress. Measurements and Main Results: Although most participants reported rarely having been told about other options for treatment and could not readily recall many details about specific risks of recommended treatment, they were satisfied with their care. The patients paradoxically described clinicians as displaying caring and empathy despite not explicitly addressing their concerns and worries. We found that the communication domains that underlie shared decision making occurred infrequently, but that participants were still pleased with their role in the decision-making process. We did not find substantially different themes based on where the participant received care or the treatment selected. Conclusions: Patients were satisfied with all aspects of their care, despite reporting little knowledge about risks or other treatment options, no direct elicitation of worries from providers, and a lack of shared decision making. While the development of effective communication strategies to address these gaps is warranted, their effect on patient-centered outcomes, such as distress and decisional conflict, is unclear. Copyright © 2016 by the American Thoracic Society.


Background: Patients with Barrett’s esophagus (BE) are at increased risk of developing esophageal adenocarcinoma (EAC). The incidence of EAC is rising faster than any other cancer. Discussion: Patients with BE have a 30- to 40-fold increased risk of EAC. In the past 20 years, there have been dramatic advances in our understanding of the incidence and natural history of BE. Endoscopic treatment of BE is evolving. Even early EAC has been treated without esophagectomy and good oncologic results in the modern era. © 2017 The Society for Surgery of the Alimentary Tract

The development of human cognition results from the emergence of coordinated activity between distant brain areas. Network science, combined with non-invasive functional imaging, has generated unprecedented insights regarding the adult brain's functional organization, and promises to help elucidate the development of functional architectures supporting complex behavior. Here we review what is known about functional network development from birth until adulthood, particularly as understood through the use of resting-state functional connectivity MRI (rs-fcMRI). We attempt to synthesize rs-fcMRI findings with other functional imaging techniques, with macro-scale structural connectivity, and with knowledge regarding the development of micro-scale structure. We highlight a number of outstanding conceptual and technical barriers that need to be addressed, as well as previous developmental findings that may need to be revisited. Finally, we discuss key areas ripe for future research in order to (1) better characterize normative developmental trajectories, (2) link these trajectories to biologic mechanistic events, as well as component behaviors and (3) better understand the clinical implications and pathophysiological basis of aberrant network development. © 2017 Elsevier Inc.


BACKGROUND: The effect of IL-1 blocking therapy on mucocutaneous manifestations of Behcet's disease is incompletely understood. METHODS: Six patients with Behcet's disease and ongoing oral/genital ulcers for >/=1 month were enrolled into an adaptive, two-phase clinical trial and included in the analysis. Study duration was 6 months with extension up to 16 months. All were treated non-blinded with anakinra 100 mg subcutaneous daily with the option to escalate the dose to 200 mg in partial responders after 1 month and 300 mg after 6 months. Patients recorded the number and severity of ulcers in daily diaries. The primary outcome was remission defined as no ulcers on physical exam for two consecutive monthly visits between months 3 and 6. Secondary outcomes included the number and severity of patient-reported ulcers, patient/physician global scores, and standardized disease activity scores. RESULTS: Two of six patients achieved the primary outcome. Five of six patients had improvement in the number and severity of ulcers. Non-statistically significant improvements were seen in secondary outcomes. Over the entire study, patients reported >/=1 oral and >/=1 genital ulcer on 665 (66%) and 139 (14%) days, respectively. On anakinra 200 mg vs 100 mg, patients reported fewer days with oral ulcers (65% vs 74% of days, p = 0.01) and genital ulcers (10% vs 22% of days, p < 0.001) and milder oral ulcer severity (p < 0.001). Anakinra to 300 mg did not result in further improvements. Adverse events were notable for mild infections. CONCLUSION: Anakinra at an optimal dose of 200 mg daily had an acceptable safety profile and was partially effective in the treatment of resistant oral and genital ulcers in Behcet's disease. TRIAL REGISTRATION: Clinicaltrials.gov. NCT01441076. Registered on 24 September 2011.


PLA2G6-associated neurodegeneration (PLAN) comprises a continuum of three phenotypes with overlapping clinical and radiologic features: Infantile neuroaxonal dystrophy (INAD). Atypical neuroaxonal dystrophy (atypical NAD). PLA2G6-related dystonia-parkinsonism. INAD usually begins between ages six months and three years with psychomotor regression or delay, hypotonia, and progressive spastic tetraparesis. Many affected
Veterans who survive multiple traumatic injuries, including traumatic brain injuries (TBI), must often rely on family caregivers for ongoing care and support with reintegration. Understanding factors associated with caregiving that help or harm caregivers’ health is critical for identifying appropriate and effective interventions that support caregiver health and promote the provision of quality care to veterans. This study utilized cross-sectional data from the Family and Caregiver Experiences Study, a survey of 564 caregivers caring for veterans who served after September 11, 2001, survived TBI/polytrauma during service, and received inpatient rehabilitation care in a Veterans Affairs Polytrauma Rehabilitation Center. Structural equation modeling was used to examine the relationship between caregiver stress (i.e., veterans’ neurobehavioral problems and intensity of care required), and caregiver well-being (i.e., caregiver burden and mental health). Analyses also examined how intrapersonal, family or social, and financial resources mediate and moderate the relationship between caregiver stress and well-being. Results indicate that veterans’ neurobehavioral problems and intensity of required care were associated with more caregiver burden, and more burden was


Veterans who survive multiple traumatic injuries, including traumatic brain injuries (TBI), must often rely on family caregivers for ongoing care and support with reintegration. Understanding factors associated with caregiving that help or harm caregivers’ health is critical for identifying appropriate and effective interventions that support caregiver health and promote the provision of quality care to veterans. This study utilized cross-sectional data from the Family and Caregiver Experiences Study, a survey of 564 caregivers caring for veterans who served after September 11, 2001, survived TBI/polytrauma during service, and received inpatient rehabilitation care in a Veterans Affairs Polytrauma Rehabilitation Center. Structural equation modeling was used to examine the relationship between caregiver stress (i.e., veterans’ neurobehavioral problems and intensity of care required), and caregiver well-being (i.e., caregiver burden and mental health). Analyses also examined how intrapersonal, family or social, and financial resources mediate and moderate the relationship between caregiver stress and well-being. Results indicate that veterans’ neurobehavioral problems and intensity of required care were associated with more caregiver burden, and more burden was
associated with poor mental health. Intrapersonal and family or social resources mediated the relationship between veteran functioning and mental health. Family or social resources also moderated the relationship between care intensity and burden. The model explained a moderate amount of variability in burden (59%) and a substantial amount in mental health (75%). We conclude that caregivers of veterans with neurobehavioral problems who require intense care are at risk for burden and poor mental health. Increasing resources to bolster family or social resources may reduce risks.


Objectives: Prehospital emergency medical services (EMS) providers report anxiety as the second most common contributor to paediatric patient safety events. The objective of this study was to understand how EMS providers perceive the effect of stress and anxiety on paediatric out-of-hospital patient safety. Setting: This was a nationwide study of EMS providers from 44 of 50 (88%) US states. Participants: A total of 753 eligible EMS professionals, including emergency medical technicians, emergency department physicians and nurses (general and paediatric), and respiratory therapists who participate in out-of-hospital transports. Primary and secondary outcome measures: Outcomes included responses to: (1) clinical situations where heightened stress or anxiety was likely to contribute to safety events, (2) aspects of these clinical situations that cause stress or anxiety and (3) how stress or anxiety may lead to paediatric safety events. Results: EMS providers reported that the clinical situations where stress and anxiety were more likely to contribute to paediatric patient safety events were trauma, respiratory distress and cardiac issues. Key themes were: (1) provider sympathy or identification with children, (2) difficulty seeing an innocent child hurt and the inherent value of children and (3) insufficient exposure to paediatric emergencies. Conclusions: Caring for paediatric emergencies creates unique stresses on providers that may affect patient safety. Many of the factors reported to cause provider stress and anxiety are inherent attributes of children and therefore not modifiable. Tools that support care during stressful conditions such as cognitive aids may help to mitigate anxiety in the prehospital care of children. Further research is needed to identify opportunities for and attributes of interventions.


**BACKGROUND:** The risk of local recurrence (LR) after soft tissue sarcoma (STS) resection is higher in the setting of inadvertent positive margins (IPMs). This study assessed whether both tumor- and surgery-related factors contribute to IPMs, and whether tumor- versus surgery-related IPMs differ in LR or overall survival (OS).

METHODS: Retrospective review of a tertiary center database identified patients with IPMs following STS resection between 1989 and 2014. Of 2234 resected STSs, 309 (13%) had positive margins; 89 (4%) were IPMs. Mean follow-up was 52 months, mean tumor size was 9.2 cm, and 55% were high grade. Cases were categorized as surgery-related (67, 75%) or tumor-related (22, 25%). RESULTS: There was a significant difference in positive margin location, with the deep margin commonly involved in surgery-related IPMs (55% vs. 9%; p < 0.001). Tissue type also differed (p = 0.01), with surgery-related IPMs frequently in muscle (33%), while tumor-related IPMs favored subcutaneous tissues (41%). STSs with surgery-related IPMs were larger (p = 0.01). Histologic subtypes differed (p = 0.02), with myxofibrosarcoma and undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma predominating in tumor-related IPMs (82%). The cumulative probability of LR after IPMs, with death as a competing risk, was 28% (95% confidence interval [CI] 18-35) at 5 years and 37% (95% CI 24-45) at 10 years. Mortality was 28% (95% CI 18-38) at 5 years and 38% (26-50) at 10 years. There was no difference in LR (p = 0.91) or OS (p = 0.44) between surgery- and tumor-related IPMs. CONCLUSIONS: IPMs after STS resection results in substantial LR risk. While demonstrating distinct surgery- and tumor-related contributions, there was no between-group difference in
LR or OS. These results may aid in avoiding IPMs. LEVEL OF EVIDENCE: Therapeutic Level III, retrospective comparative study.


Women diagnosed with breast cancer within 5 years of childbirth have poorer prognosis than nulliparous or pregnant women. Weaning-induced breast involution is implicated, as the collagen-rich, immunosuppressive microenvironment of the involuting mammary gland is tumor promotional in mice. To investigate the role of mammary fibroblasts, isolated mammary PDGFRalpha+ cells from nulliparous and postweaning mice were assessed for activation phenotype and protumorigenic function. Fibroblast activation during involution was evident by increased expression of fibrillar collagens, lysyl oxidase, Tgfβ1, and Cxcl12 genes. The ability of mammary tumors to grow in an isogenic, orthotopic transplant model was increased when tumor cells were coinjected with involution-derived compared with nulliparous-derived mammary fibroblasts. Mammary tumors in the involution-fibroblast group had increased Ly6C+ monocytes at the tumor border, and decreased CD8+ T cell infiltration and tumor cell death. Ibuprofen treatment suppressed involution-fibroblast activation and tumor promotional capacity, concurrent with decreases in tumor Ly6C+ monocytes, and increases in intratumoral CD8+ T cell infiltration, granzyme levels, and tumor cell death. In total, our data identify a COX/prostaglandin E2 (PGE2)-dependent activated mammary fibroblast within the involuting mammary gland that displays protumorigenic, immunosuppressive activity, identifying fibroblasts as potential targets for the prevention and treatment of postpartum breast cancer.


Background Pyoderma gangrenosum (PG) is a rare, ulcerative cutaneous disorder. Ophthalmic involvement in PG is atypical, but can have devastating consequences. Objective We sought to characterize ocular PG to allow for earlier diagnosis and therapy. To our knowledge, this is the first systematic review summarizing this clinical variant. Methods A systematic review was conducted using PubMed and Web of Science. Data were extracted and studies were qualitatively assessed and analyzed. Results We identified all 34 cases of PG involving the eye and periorbital area, and categorized them into 4 different subtypes. Common presenting signs include ulceration, peripheral ulcerative keratitis, and decreased visual acuity. Although it is often difficult to biopsy ocular PG, histologic features are nonspecific. Combined therapy using corticosteroids and further surgical reconstruction as needed is the mainstay of treatment. Cases of the eye/orbit in particular should be treated aggressively, as these are more likely to relapse compared with cases of the periorbital area. Limitations Use of case reports, paucity of ocular PG cases, and heterogeneity of studies are limitations. Conclusion PG should be considered in the differential diagnosis of ulceration of ocular/periocular tissues. An aggressive, early, multimodal treatment strategy should be used to prevent relapse, especially in cases of the eye/orbit. © 2016 American Academy of Dermatology, Inc.


Objective For individuals with 1-2 small (<1 cm) low-risk colorectal adenomas, international guidelines range from no surveillance to offering surveillance colonoscopy in 5-10 years. We hypothesised that the risks for metachronous advanced neoplasia (AN) among patients with low-risk adenomas differ based on clinical factors distinct from those currently used. Design We pooled data from seven prospective studies to assess the risk of metachronous AN. Two groups with 1-2 small adenomas were defined based on guidelines from the UK (n=4516) or the European Union (EU)/US (n=2477). Results Absolute risk of metachronous AN ranged from a low of 2.9% to a high of 12.2%, depending on specific risk factor and guideline used. For the UK
group, the highest absolute risks for metachronous AN were found among individuals with a history of prior polyp (12.2%), villous histology (12.2%), age ≥ 70 years (10.9%), high-grade dysplasia (10.9%), any proximal adenoma (10.2%), distal and proximal adenoma (10.8%) or two adenomas (10.1%). For the EU/US group, the highest absolute risks for metachronous AN were among individuals with a history of prior polyp (11.5%) or the presence of both proximal and distal adenomas (11.0%). In multivariate analyses, strong associations for increasing age and history of prior polyps and odds of metachronous AN were observed, whereas more modest associations were shown for baseline proximal adenomas and those with villous features.

Conclusions Risks of metachronous AN among individuals with 1-2 small adenomas vary according to readily available clinical characteristics. These characteristics may be considered for recommending colonoscopy surveillance and require further investigation. © 2015 Published by the BMJ Publishing Group Limited.


Quality issue: Transfers from intensive care units to acute care units represent a complex care transition for hospitalized patients. Within our institution, variation in transfer practices resulted in unpredictable processes in which patient safety concerns were raised. Initial assessment: Key stakeholders were engaged across the institution. Patient safety (‘incident’) reports and a staff survey identified safety concerns. Choice of a solution: Using lean methodology, current transfer processes were mapped for the four adult intensive care units and waste was identified. During a summit of key stakeholders an ideal transfer process was conceived and a structured handoff tool (checklist) was developed. A daily management system (DMS) was implemented to monitor adherence. Evaluation: The primary process outcome was adherence to the standardized workflow. Audits at 4, 8, and 12 months after implementation indicated that the checklist was used for 100% of transfers. Secondary outcomes included the percentage of transfers completed within a pre-specified time window of 120 minutes, provider notification of patient arrival on the acute care unit, and staff survey responses assessing adequacy of transfer communication. Lessons learned: Prior work has shown that structuring handoffs can improve patient safety, but the novelty of this project was addressing the transfer process in its entirety, across silos of care. Factors leading to the success of this project were the involvement of key stakeholders across the entire institution early in the project development phase, employment of lean methodology, and implementation of tools to guide workflow adherence and track causes of deviation from the workflow. © The Author 2016.


Definition of normal adrenal function in critically ill patients remains controversial, despite a large body of literature. Furthermore, evaluation of adrenal function in these patients is complex. A decrease in cortisol breakdown rather than an increase in cortisol production has been suggested as the main contributor to elevated cortisol levels in critically ill patients. The concept of relative adrenal insufficiency has multiple pathophysiological flaws and is not supported by current evidence. Patients with septic shock who are pressor-dependent or refractory to fluid resuscitation should receive a short course of hydrocortisone regardless of their serum cortisol levels or their response to a Cosyntropin stimulation test (CST). Patients without septic shock who are suspected to have adrenal insufficiency should have their random cortisol levels measured. In patients with low and near normal cortisol binding proteins, a serum cortisol < 10 or 15 mcg/dL, respectively may trigger need for glucocorticoid treatment. Assays of free cortisol levels offers an advantage over total cortisol levels in patients with low-binding proteins. Most critically ill patients should
have a normal random free cortisol level of >1.8 mug/dL, although further studies are needed to define a normal range in critically ill patients based on both severity and duration of illness. A CST may be used to further evaluate adrenal function in patients without septic shock who have borderline random serum or free cortisol levels. We review the clinical presentation, diagnosis, and treatment of adrenal insufficiency in critically ill patients, and discuss the authors’ personal approach to patient management.


Emerging evidence indicates that human cytomegalovirus (HCMV) manipulates host cell signaling pathways using both proteins and noncoding RNAs. Several studies have shown that HCMV induces NF-kappaB signaling early in infection, resulting in the induction of antiviral proinflammatory cytokines with a subsequent reduction of these cytokines late in infection. The mechanism for late cytokine reduction is unknown. In this study, we show that HCMV microRNAs (miRNAs) miR-US5-1 and miR-UL112-3p target the IkappaB kinase (IKK) complex components IKKalpha and IKKbeta to limit production of proinflammatory cytokines in response to interleukin 1beta (IL-1beta) and tumor necrosis factor alpha (TNF-alpha). Transfection of miR-UL112-3p and miR-US5-1 mimics reduced endogenous IKKalpha and IKKbeta protein levels, and site-directed mutagenesis of the 3’ untranslated regions (UTRs) identified the binding sites for each miRNA. Infection with mutant viruses lacking these miRNAs resulted in increased levels of IKKalpha and IKKbeta proteins, an impaired ability to control NF-kappaB signaling at late times of lytic infection, and increased production of proinflammatory cytokines compared to wild-type virus in cell types relevant to HCMV infection in vivo. These phenotypes were rescued by preexpression of miR-US5-1 and miR-UL112-3p in infected cells or by a miR-US5-1/miR-UL112-3p double mutant virus that expresses short hairpin RNAs (shRNAs) targeting IKKalpha and IKKbeta, demonstrating the gene specificity of the miRNAs. These observations describe a mechanism through which HCMV miRNAs expressed late in the infectious cycle downregulate proinflammatory cytokine production to create a cellular proiviral environment. IMPORTANCE Human cytomegalovirus (HCMV) is a significant cause of morbidity and mortality in transplant recipients and causes hearing loss and mental retardation when acquired congenitally. Initial events during HCMV infection result in the activation of NF-kappaB signaling, which culminates in the production of IL-6, CCL5, and TNF-alpha. Several viruses have developed mechanisms to block the antiviral effects of these cytokines. We show here that two HCMV miRNAs, miR-US5-1 and miR-UL112-3p, specifically downregulate IKKalpha and IKKbeta signaling factors necessary to propagate NF-kappaB signaling and subsequent IL-6, CCL5, and TNF-alpha production. Regulation of these proinflammatory cytokines during lytic infection and during latency is critical to viral survival in the host.


INTRODUCTION: and Objectives: Left ventricular assist devices (LVADs) have been shown to cause changes in carotid artery duplex-derived flow velocity waveforms; however, possible effects on lower extremity arterial duplex (LEAD) findings have not been characterized. We sought to characterize LEAD findings in patients with LVADs to establish a basis for vascular laboratory interpretation of LEAD in patients with LVADs. METHODS: Retrospective single institution review of all patients with LEAD performed after LVAD implantation from 2003-2014. Peak systolic velocity (PSVs) of common femoral (CFA), superficial femoral (SFA), popliteal, and posterior tibial arteries (PTA) in asymptomatic extremities in patients with LVADs were compared to a control group of patients at our institution without LVADs who underwent LEAD for nonischemic indications. ABI and CFA waveform acceleration times (AT) and end diastolic velocity (EDV) were also measured. RESULTS: There were 248 LVAD patients, 29 had LEAD of at least one lower extremity (34 extremities, 22 asymptomatic, 12 symptomatic) during the study period and 136 control limbs. Mean PSVs (cm/s) in the control CFA, mid SFA, popliteal, and PTA were 137 +/- 4.8, 104.2 +/- 4.5, 65.2 +/- 2.8, and 64.6 +/- 3.2.
Mean PSVs were significantly decreased in the LVAD patients: 49.5 +/- 4.9, 40.6 +/- 3.7, 27.2 +/- 2.2 and 25.5 +/- 2.3, p < 0.001 for each comparison. Average ABI for control limbs was 0.91 +/- 0.05 compared to 1.17 +/- 0.35 in LVAD extremities (P<0.001). Mean CFA AT was 97 msec in the controls and 207 msec in LVAD patients, p < 0.001. Mean CFA EDV was 14.7 cm/s in the controls and 18.6 cm/s in the LVAD patients, P = 0.011

CONCLUSIONS: This is the first study characterizing LEAD in lower extremity arteries in LVAD patients. PSV is significantly decreased throughout lower extremity vessels, and common femoral artery acceleration time increased. Results can serve as a basis for identifying normal LEAD findings in LVAD patients.


A 55 year old male smoker presented with clinical T3N0 esophageal adenocarcinoma of the GE junction. He completed neoadjuvant chemoradiotherapy with carboplatin/paclitaxel and 5040cGy of radiation. He had limited clinical response on restaging but no evidence of metastatic disease and completed a minimally invasive three field esophagectomy. This was complicated by a chyle leak requiring thoracic duct embolization from which he recovered well. Surgical pathology showed no apparent nodal disease or metastases but a poorly differentiated primary tumor with signet-cell features. Approximately 3 months after his surgery, he developed right upper quadrant abdominal pain and elevated liver function tests and was taken for laparoscopic cholecystectomy. Gallbladder pathology demonstrated poorly differentiated adenocarcinoma with extensive lymphovascular invasion with immunohistochemistry analysis and comparison with the original surgical specimen confirming metastatic adenocarcinoma of esophageal origin. Literature review suggests that signet cell features and limited response to neoadjuvant therapy point to a more aggressive biology in esophageal cancer and increase the risk of metastatic disease, even in the setting of node negativity. © 2017 Elsevier Inc.


Arterial grafts have long-term patency superior to vein grafts but have a tendency to develop spasm that can lead to potentially life-threatening complications. A perfect antispastic protocol should include advanced surgical technique and adequate pharmacologic methods. All pharmacologic vasodilator drugs relax the vessel through specific mechanisms, and therefore, there is no perfect, single best vasodilator to prevent or treat spasm of the arterial graft against all mechanisms of contraction. One of the choices is to use a combination of pharmacologic vasodilators targeting different mechanisms of spasm to obtain the reliable and best effect.


"Frontiers in Fontan Failure" was the title of a 2015 conference sponsored by Children's Healthcare of Atlanta and Emory University School of Medicine. In what is hoped to be the first of many such gatherings, speakers and attendees gathered to discuss the problem of long-term clinical deterioration in these patients. Specific focuses included properly defining the problem and then discussing different treatment strategies, both medical and surgical. The health of the liver after Fontan palliation was a particular point of emphasis, as were quality of life and future directions.


Background: Early survey evidence suggests a reduction of disparities in insurance coverage between Latinos and non-Hispanic Whites post-Affordable Care Act (ACA). These findings may not describe the insurance status of vulnerable, low-income Latino populations served in community health centers (CHCs) over the course of this policy change. Cross-sectional surveys also may be of limited use in describing longitudinal phenomena such as changes in health insurance status. Methods: Using electronic health record (EHR) data, we compared the insurance status of N = 42,392 low-income patients served in 23 CHCs in Oregon, by race/ethnicity and language, over a period of 6 years straddling the implementation of ACA-related Medicaid expansion on January 1, 2014. Findings: Prior to 2014, Spanish-prefering Latinos were more likely to be uninsured than English-prefering Latinos and non-Hispanic Whites. Among uninsured patients who returned for at least one visit in 2014, Spanish-prefering Latinos had the largest increase in insurance coverage rates, and all three racial/ethnic/language groups had similar rates of insurance coverage. There were no racial/ethnic/language differences between those who did and did not have visit in 2014. Conclusion: Among previously uninsured low-income patients returning to Oregon CHCs, insurance disparities were eliminated after Medicaid expansion, especially in Spanish-speaking Latinos. Further study is needed to understand the elimination of insurance disparities in this cohort. © 2016 W. Montague Cobb-NMA Health Institute


Introduction: In cross-sectional survey studies, obese Latinos are less likely to be screened for elevated serum cholesterol, despite their higher risk for hyperlipidemia and coronary artery disease. This study evaluated insurance and racial/ethnic disparities in lipid screening receipt between obese Latino and non-Hispanic white patients in Oregon community health centers (CHCs) over 5 years, using electronic health record data. Methods: This retrospective cohort study evaluated obese (BMI ≥30), low-income, adult patients (aged 21-79 years) with at least one visit at an Oregon CHC during 2009-2013 (n=11,095). Odds of lipid screening in the study period (clinical data collected in 2009-2013) were measured, adjusting for age, sex, primary clinic, and comorbidities, stratified by utilization in the study period. Analysis was done in 2016. Results: Sixty percent of the study population received at least one lipid screening in 2009-2013. There were no significant differences in screening between insured Latinos and insured non-Hispanic whites, except those with more than five visits over 5 years (OR=0.75, 95% CI=0.60, 0.94). Uninsured Latinos had higher odds of screening versus insured non-Hispanic whites among the low visit strata (OR=1.65, 95% CI=1.18, 2.30). Among Latinos, Spanish preference resulted in higher screening odds versus English preference in the two- to five-visit stratum (OR=1.63, 95% CI=1.12, 2.35). Conclusions: Obese, low-income patients at CHCs underutilize cholesterol screening. However, screening differences by race/ethnicity and preferred language are minimal. Further research is necessary to understand how care delivered by CHCs may mitigate previously reported disparities in lipid screening. © 2016 American Journal of Preventive Medicine.

In a previous study, Teleaulax amphioxeia—the preferred prey of Mesodinium in the Columbia River estuary—were undetectable within intense annual blooms, suggesting blooms are prey-limited or prey are acquired outside of bloom patches. We used a novel molecular approach specifically targeting the prey (i.e., Unique Sequence Element [USE] within the ribosomal RNA 28S D2 regions of Teleaulax amphioxeia nucleus and nucleomorph) in estuarine water samples acquired autonomously with an Environmental Sample Processor integrated within a monitoring network (ESP-SATURN). This new approach allowed for both more specific detection of the prey and better constraint of sample variability. A positive correlation was observed between abundances of M. cf. major and T. amphioxeia during bloom periods. The correlation was stronger at depth (>8.2 m) and weak or non-existent in the surface, suggesting that predator-prey dynamics become uncoupled when stratification is strong. We confirmed exclusive selectivity for T. amphioxeia by M. cf. major and observed the incorporation of the prey nucleus into a 4-nuclei complex, where it remained functionally active. The specific biomarker for T. amphioxeia was also recovered in M. cf. major samples from a Namibian coastal bloom, suggesting that a specific predator-prey relationship might be widespread between M. cf. major and T. amphioxeia. This article is protected by copyright. All rights reserved.
difference between the multipotent adult progenitor cell group and placebo groups in global stroke recovery at day 90 (odds ratio 1.08 [95% CI 0.55-2.09], p=0.83). INTERPRETATION: Administration of multipotent adult progenitor cells was safe and well tolerated in patients with acute ischaemic stroke. Although no significant improvement was observed at 90 days in neurological outcomes with multipotent adult progenitor cells treatment, further clinical trials evaluating the efficacy of the intervention in an earlier time window after stroke (<36 h) are planned. FUNDING: Athersys Inc.


CATSPER-related male infertility results from abnormalities in sperm and can be either CATSPER-related nonsyndromic male infertility (NSMI) or the deafness-infertility syndrome (DIS) when associated with non-progressive prelingual sensorineural hearing loss. Males with NSMI have infertility while females have no symptoms. Males with DIS have both infertility and hearing loss, while females have only hearing loss. Routine semen analysis typically identifies abnormalities in sperm number, morphology, and motility. Otologic examination and audiologic assessment can identify hearing loss. The diagnosis of CATSPER-related NSMI is established in males by the identification of biallelic pathogenic variants in CATSPER1. The diagnosis of DIS is established in both males and females by the identification of biallelic contiguous gene deletions at chromosome 15q15.3 that includes both CATSPER2 and STRC. Treatment of manifestations: For infertile males with DIS or CATSPER-related NSMI, assisted reproductive technologies such as intracytoplasmic sperm injection are likely to be an effective fertility option. For males with DIS, treatment of hearing loss is best achieved by fitting hearing aids for amplification and special educational assistance for school-age children. Agents/circumstances to avoid: For individuals with DIS, exposure to loud noise. Evaluation of relatives at risk: For sibs at risk for DIS, audiologic testing in infancy or early childhood to enable early management of hearing loss. CATSPER-related NSMI and DIS are inherited in an autosomal recessive manner. When both parents are carriers for pathogenic variants, each child has a 25% chance of inheriting both pathogenic variants, a 50% chance of inheriting one pathogenic variant and being an asymptomatic carrier, and a 25% chance of inheriting neither pathogenic variant. Males who inherit two CATSPER1 pathogenic variants will be infertile; females who inherit two CATSPER1 pathogenic variants will have no signs/symptoms. Males who inherit two CATSPER2-STRC deletions will be fertile and deaf; females who inherit two CATSPER2-STRC deletions will be deaf. If the pathogenic variants have been identified in an affected family member, prenatal risk pregnancies is possible through laboratories offering either prenatal testing for the gene of interest or custom testing.


Parkinson’s disease (PD) is the most common cause of neurodegenerative movement disorder and the second most common cause of dementia. Genes are thought to have a stronger effect on age-at-onset of PD than on risk, yet there has been a phenomenal success in identifying risk loci but not age-at-onset modifiers. We conducted a genome-wide study for age-at-onset. We analysed familial and non-familial PD separately, per prior evidence for strong genetic effect on age-at-onset in familial PD. GWAS was conducted in 431 unrelated PD individuals with at least one affected relative (familial PD) and 1544 nonfamilial PD from the NeuroGenetics Research Consortium (NGRC); an additional 737 familial PD and 2363 non-familial PD were used for replication. In familial PD, two signals were detected and replicated robustly: one mapped to LHFPL2 on 5q14.1 (PNGRC=3E-8, PReplication=2E-5, PNGRC+Replication=1E-11), the second mapped to TPM1 on 15q22.2 (PNGRC=8E-9, PReplication=2E-4, PNGRC+Replication=9E-11). The variants that were associated with accelerated onset had low frequencies (<0.02). The LHFPL2 variant was associated with
earlier onset by 12.33 [95% CI: 6.2; 18.45] years in NGRC, 8.03 [2.95; 13.11] years in replication, and 9.79 [5.88; 13.70] years in the combined data. The TPM1 variant was associated with earlier onset by 15.30 [8.10; 22.49] years in NGRC, 9.29 [1.79; 16.79] years in replication, and 12.42 [7.23; 17.61] years in the combined data. Neither LHFPL2 nor TPM1 was associated with age-at-onset in non-familial PD. LHFPL2 (function unknown) is overexpressed in brain tumours. TPM1 encodes a highly conserved protein that regulates muscle contraction, and is a tumour-suppressor gene. © The Author 2016. Published by Oxford University Press. All rights reserved.


Zika virus (ZIKV), an emerging flavivirus, has recently spread explosively through the Western hemisphere. In addition to symptoms including fever, rash, arthralgia, and conjunctivitis, ZIKV infection of pregnant women can cause microcephaly and other developmental abnormalities in the fetus. We report herein the results of ZIKV infection of adult rhesus macaques. Following subcutaneous infection, animals developed transient plasma viremia and viruria from 1-7 days post infection (dpi) that was accompanied by the development of a rash, fever and conjunctivitis. Animals produced a robust adaptive immune response to ZIKV, although systemic cytokine response was minimal. At 7 dpi, virus was detected in peripheral nervous tissue, multiple lymphoid tissues, joints, and the uterus of the necropsied animals. Notably, viral RNA persisted in neuronal, lymphoid and joint/muscle tissues and the male and female reproductive tissues through 28 to 35 dpi. The tropism and persistence of ZIKV in the peripheral nerves and reproductive tract may provide a mechanism of subsequent neuropathogenesis and sexual transmission.


Background Imatinib, a selective BCR-ABL1 kinase inhibitor, improved the prognosis for patients with chronic myeloid leukemia (CML). We conducted efficacy and safety analyses on the basis of more than 10 years of follow-up in patients with CML who were treated with imatinib as initial therapy. Methods In this open-label, multicenter trial with crossover design, we randomly assigned patients with newly diagnosed CML in the chronic phase to receive either imatinib or interferon alfa plus cytarabine. Long-term analyses included overall survival, response to treatment, and serious adverse events. Results The median follow-up was 10.9 years. Given the high rate of crossover among patients who had been randomly assigned to receive interferon alfa plus cytarabine (65.6%) and the short duration of therapy before crossover in these patients (median, 0.8 years), the current analyses focused on patients who had been randomly assigned to receive imatinib. Among the patients in the imatinib group, the estimated overall survival rate at 10 years was 83.3%. Approximately half the patients (48.3%) who had been randomly assigned to imatinib completed study treatment with imatinib, and 82.8% had a complete cytogenetic response. Serious adverse events that were considered by the investigators to be related to imatinib were uncommon and most frequently occurred during the first year of treatment. Conclusions Almost 11 years of follow-up showed that the efficacy of imatinib persisted over time and that long-term administration of imatinib was not associated with unacceptable cumulative or late toxic effects. (Fundied by Novartis Pharmaceuticals; IRIS ClinicalTrials.gov numbers, NCT00006343 and NCT00333840.).
The recycling of vesicle membrane fused during exocytosis is essential to maintaining neurotransmission. The GTPase dynamin is involved in pinching off membrane to complete endocytosis and can be inhibited by dynasore resulting in activity-dependent depletion of release-competent synaptic vesicles. In rat brainstem slices, we examined the effects of dynasore on three different modes of glutamate release—spontaneous, evoked, and asynchronous release—at solitary tract (ST) inputs to neurons in the nucleus of the solitary tract (NTS). Intermittent bursts of stimuli to the ST interspersed with pauses in stimulation allowed examination of these three modes in each neuron continuously. Application of 100 μM dynasore rapidly increased the spontaneous EPSC (sEPSC) frequency which was followed by inhibition of both ST-evoked EPSCs (ST-EPSC) as well as asynchronous EPSCs. The onset of ST-EPSC failures was not accompanied by amplitude reduction—a pattern more consistent with conduction block than reduced probability of vesicle release. Neither result suggested that dynasore interrupted endocytosis. The dynasore response profile resembled intense presynaptic TRPV1 activation. The TRPV1 antagonist capsazepine failed to prevent dynasore increases in sEPSC frequency but did prevent the block of the ST-EPSC. In contrast, the TRPV1 antagonist JNJ 17203212 prevented both actions of dynasore in neurons with TRPV1-expressing ST inputs. In a neuron lacking TRPV1-expressing ST inputs, dynasore promptly increased sEPSC rate followed by block of ST-evoked EPSCs. Together our results suggest that dynasore actions on ST-NTS transmission are TRPV1-independent and changes in glutamatergic transmission are not consistent with changes in vesicle recycling and endocytosis.
novel scheduling strategies in outpatient ophthalmology clinics. Key findings from this study are that: 1) secondary use of EHR timestamp data in simulation models represents clinic workflow, 2) simulations provide insight into the best allocation of resources in a clinic, 3) simulations provide critical information for schedule creation and decision making by clinic managers, and 4) simulation models built from EHR data are potentially generalizable.


In the coming years, usage of Unmanned Aerial Vehicles (UAVs) is expected to grow tremendously. Maintaining security of UAVs under cyber attacks is an important yet challenging task, as these attacks are often erratic and difficult to predict. Secure estimation problems study how to estimate the states of a dynamical system from a set of noisy and maliciously corrupted sensor measurements. The fewer assumptions that an estimator makes about the attacker, the larger the set of attacks it can protect the system against. In this paper, we focus on sensor attacks on UAVs and attempt to design a secure estimator for linear time-invariant systems based on as few assumptions about the attackers as possible. We propose a computationally efficient estimator that protects the system against arbitrary and unbounded attacks, where the set of attacked sensors can also change over time. In addition, we propose to combine our secure estimator with a Kalman Filter for improved practical performance and demonstrate its effectiveness through simulations of two scenarios where an UAV is under adversarial cyber attack.


BACKGROUND: The objective of the current study was to examine social functioning among adolescents and young adults (AYAs) within the first 2 years after a cancer diagnosis and compare their scores with population norms and identify trajectories of social functioning over time and its correlates. METHODS: A multicenter, longitudinal study was conducted among 215 AYA patients with cancer aged 14 to 39 years. A total of 141 patients completed a self-report measure of social functioning within the first 4 months of diagnosis and again at 12 months and 24 months later. RESULTS: AYA patients with cancer were found to have significantly worse social functioning scores around the time of diagnosis (52.0 vs 85.1; P<.001), at the 12-month follow-up (73.1 vs 85.1; P<.001), and at the 24-month follow-up (69.2 vs 85.1; P<.001) when compared with population norms. Significant improvements in social functioning from baseline to the 12-month follow-up were observed; however, social functioning levels remained stable thereafter. Among participants, 9% demonstrated consistently high/normal social functioning, 47% demonstrated improved social functioning, 13% were found to have worsening social functioning, and 32% demonstrated consistently low social functioning. AYA patients with cancer who had consistently low social functioning were more often off treatment at the time of follow-up, reported more physical symptoms and higher levels of distress at baseline and follow-up, and perceived less social support at baseline compared with the other 3 groups. CONCLUSIONS: Although improved over time, social functioning still was found to be compromised 24 months after the primary diagnosis. Nearly one-third of these patients remain at risk of poor social functioning. Reducing physical symptoms and psychological distress and enhancing social support by interventions during the period after treatment may potentially help these young survivors to better reintegrate into society. Cancer 2017. (c) 2017 American Cancer Society.


RATIONALE: Guidelines for pulmonary nodule evaluation suggest a variety of strategies, reflecting the lack of high-quality evidence demonstrating the superiority of any one approach. It is unclear whether clinicians agree
that multiple management options are appropriate at different levels of risk and whether this impacts their
decision-making approaches with patients. OBJECTIVES: To assess clinicians’ perceptions of the
appropriateness of various diagnostic strategies, approach to decision-making, and perceived clinical
equipoise in pulmonary nodule evaluation. METHODS: We developed and administered a web-based survey
in March and April, 2014 to clinician members of the American Thoracic Society (ATS). The primary outcome
was perceived appropriateness of pulmonary nodule evaluation strategies in three clinical vignettes with
different malignancy risk. We compared responses to guideline recommendations and analyzed clinician
characteristics associated with a reported shared decision-making approach. We also assessed clinicians’
likelihood to enroll patients in hypothetical randomized trials comparing nodule evaluation strategies.
RESULTS: Of 5872 ATS members emailed, 1444 opened the email and 428 eligible clinicians participated in
the survey (response rate 30.0% among those who opened the invitation, 7% overall). The mean number of
options considered appropriate increased with pre-test probability of cancer, ranging from 1.8 (SD 1.2) for
the low-risk case to 3.5 (1.1) for the high-risk case (p<0.0001). As recommended by guidelines, the
proportion that deemed surgical resection as an appropriate option also increased with cancer risk
(p<0.0001). Half of clinicians (50.4%) reported engaging in shared decision-making with patients for
pulmonary nodule management; this was more commonly reported by clinicians with more years of
experience (p=0.01) and those who reported greater comfort in managing pulmonary nodules (p=0.005).
Although half (49.9%) deemed the evidence for pulmonary nodule evaluation to be strong, most clinicians
were willing to enroll patients in randomized trials to compare nodule management strategies in all risk
categories (low-risk: 87.6%, moderate-risk: 89.7%, high-risk: 63.0%). CONCLUSIONS: Consistent with
guideline recommendations, clinicians embrace multiple options for pulmonary nodule evaluation and many
are open to shared decision-making. Clinicians support the need for randomized clinical trials to strengthen
the evidence for nodule evaluation, which will further improve decision-making.

relationships in rhesus macaques between chronic ethanol consumption and the brain transcriptome.
Addiction Biology. doi:10.1111/adb.12501

This is the first description of the relationship between chronic ethanol self-administration and the brain
transcriptome in a non-human primate (rhesus macaque). Thirty-one male animals self-administered ethanol
on a daily basis for over 12 months. Gene transcription was quantified with RNA-Seq in the central nucleus
of the amygdala (CeA) and cortical Area 32. We constructed coexpression and cosplicing networks, and we
identified areas of preservation and areas of differentiation between regio2uuuu w ns and network types.
Correlations between intake and transcription included largely distinct gene sets and annotation categories
across brain regions and between expression and splicing; positive and negative correlations were also
associated with distinct annotation groups. Membrane, synaptic and splicing annotation categories were
over-represented in the modules (gene clusters) enriched in positive correlations (CeA); our cosplicing
analysis further identified the genes affected only at the exon inclusion level. In the CeA coexpression
network, we identified Rab6b, Cdk18 and Igsf21 among the intake-correlated hubs, while in the Area 32, we
identified a distinct hub set that included Ppp3r1 and Myev2. Overall, the data illustrate that excessive
ethanol self-administration is associated with broad expression and splicing mechanisms that involve

Ivlev, I., Hickman, E. N., McDonagh, M. S., & Eden, K. B. (2017). Use of patient decision aids increased younger
women’s reluctance to begin screening mammography: a systematic review and meta-analysis. J Gen
Intern Med, 1-10. doi:10.1007/s11606-017-4027-9

Background: As breast cancer screening guidelines have changed recently, additional investigation is needed to
understand changes in women’s behavior after using breast cancer screening patient decision aids (BCS-
PtDAs) and the potential effect on mammography utilization. This systematic review and meta-analysis
sought to evaluate the effect of BCS-PtDAs on changes in women’s intentions to undergo screening
mammography and whether women deciding to begin or discontinue screening mammography displayed
similar changes in screening intentions after using a BCS-PtD. Methods: We searched Medline, Scopus, PsycINFO, CENTRAL, Health and Psychosocial Instruments, Health Technology Assessment Database, PsycARTICLES, and cited references in eligible papers for randomized controlled trials (RCTs) and observational studies, published through August 24, 2016. The proportions of women who did and not intend to undergo screening and who were uncertain about undergoing screening mammography were pooled, using risk ratios (RR) and random effects. According to the protocol, RCTs or observational studies and any language were considered eligible for systematic review if they included data about women for which shared decision making is recommended. Results: We ultimately included six studies with screening intention data for 2040 women. Compared to usual care, the use of BCS-PtDAs in three RCTs resulted in significantly more women deciding not to undergo screening mammography (RR 1.48 [95% CI 1.04–2.13]; P = 0.03), particularly for younger (38–50 years) women (1.77 [1.34–2.34]; P < 0.001). The use of BCS-PtDAs had a non-significant effect on the intentions of older women (69–89 years) to discontinue screening. Conclusions: The use of BCS-PtDAs increased younger women’s reluctance to undergo screening for breast cancer. The implementation of such BCS-PtDAs in clinical practice would be expected to result in a 77% increase in the number of younger women (aged 38–50) who do not intend to be screened, and as a consequence, may reduce utilization of screening mammography. Registration: The protocol of this review is registered in the PROSPERO database, #CRD42016036695. © 2017 Society of General Internal Medicine


**OBJECTIVE:** To quantify hepatocellular carcinoma (HCC) perfusion and flow with the fast exchange regime-allowed Shutter-Speed model (SSM) compared to the Tofts model (TM). MATERIALS AND METHODS: In this prospective study, 25 patients with HCC underwent DCE-MRI. ROIs were placed in liver parenchyma, portal vein, aorta and HCC lesions. Signal intensities were analyzed employing dual-input TM and SSM models. ART (arterial fraction), K (trans) (contrast agent transfer rate constant from plasma to extravascular extracellular space), ve (extravascular extracellular volume fraction), kep (contrast agent intravasation rate constant), and τi (mean intracellular water molecule lifetime) were compared between liver parenchyma and HCC, and ART, K (trans), ve and kep were compared between models using Wilcoxon tests and limits of agreement. Test-retest reproducibility was assessed in 10 patients. RESULTS: ART and ve obtained with TM; ART, ve, ke and τi obtained with SSM were significantly different between liver parenchyma and HCC (p < 0.04). Parameters showed variable reproducibility (CV range 14.7–66.5% for both models). Liver K (trans) and ve; HCC ve and kep were significantly different when estimated with the two models (p < 0.03). CONCLUSION: Our results show differences when computed between the TM and the SSM. However, these differences are smaller than parameter reproducibilities and may be of limited clinical significance.


Next-generation sequencing (NGS) methods for cancer testing have been rapidly adopted by clinical laboratories. To establish analytical validation best practice guidelines for NGS gene panel testing of somatic variants, a working group was convened by the Association of Molecular Pathology with liaison representation from the College of American Pathologists. These joint consensus recommendations address NGS test development, optimization, and validation, including recommendations on panel content selection and rationale for optimization and familiarization phase conducted before test validation; utilization of reference cell lines and reference materials for evaluation of assay performance; determining of positive percentage agreement and positive predictive value for each variant type; and requirements for minimal depth of coverage and minimum number of samples that should be used to establish test performance characteristics. The recommendations emphasize the role of laboratory director in using an error-based approach that identifies
potential sources of errors that may occur throughout the analytical process and addressing these potential errors through test design, method validation, or quality controls so that no harm comes to the patient. The recommendations contained herein are intended to assist clinical laboratories with the validation and ongoing monitoring of NGS testing for detection of somatic variants and to ensure high quality of sequencing results.


Context: The premenopausal circulating lipid profile may be linked to the hormonal profile and ovarian lipid metabolism. Objective: Assess how estradiol, progesterone, and ovarian lipid metabolism contribute to the premenopausal lipid profile. Also, evaluate the acute effects of a common hormonal oral contraceptive (OC) on circulating lipids. Design: Experimental crossover with repeated measures. Setting: Academic hospitals. Patients: Eight healthy, regularly menstruating women. Interventions: Subjects underwent periodic serum sampling during a normal menstrual cycle, a standard 21 day monophasic combined hormonal OC cycle (30 microg ethinyl estradiol, 150 microg levonorgestrel/day), menopause simulated by leuprolide acetate (22.5 mg depot), and an artificial menstrual cycle achieved via transdermal estradiol (50-300 microg/day) and vaginal micronized progesterone (100-300 mg/day). Main Outcome Measures: Primary outcomes included evaluation of total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides, and the total cholesterol to HDL cholesterol ratio (TC:H ratio). To estimate the effect of estradiol, progesterone, and ovarian lipid metabolism all specimens except those from the OC cycle were analyzed. Subgroup analysis was conducted on the follicular and luteal phases. In a separate analysis, the effect of the OC was evaluated relative to the normal menstrual cycle. Results: Estradiol was significantly associated with increased HDL cholesterol throughout the menstrual cycle and in the follicular phase. Ovarian effects were associated with reduced lipids, especially during the luteal phase. The OC was associated with an increased TC:H ratio and triglycerides. Conclusions: Previously unappreciated factors including ovarian lipid metabolism may contribute to the premenopausal lipid profile.


RATIONALE: Hypothalamic-pituitary-adrenal (HPA) axis activity under different social settings in non-human primates is understudied. OBJECTIVE: The aim of this study is to evaluate the response of pituitary-adrenal hormones (adrenocorticotropic hormone (ACTH) and cortisol) to pharmacological challenges of the HPA axis in male cynomolgus macaques under different social settings. METHODS: Male cynomolgus macaques (Macaca fascicularis, n = 11) were individually (A) and socially housed (B) in alternation, over consecutive months, in an ABA design. During each experimental phase, plasma ACTH and cortisol were measured in response to low- and mild-intensity psychological stressors and following administration of saline, naloxone, ovine-corticotropin-releasing factor (oCRF), and dexamethasone. RESULTS: These data demonstrate that cortisol measured under low stress conditions is sensitive to social rank (dominance hierarchy) and distinguishes dominant from non-dominant animals during both individual and social settings. Administration of naloxone resulted in elevated circulating ACTH and cortisol, while oCRF only increased circulating cortisol. During social housing, the cortisol response to naloxone and oCRF was increased, whereas dexamethasone suppression of ACTH and cortisol remained consistent across all social settings. CONCLUSIONS: Circulating ACTH and cortisol are differentially sensitive to changes in social settings in non-human primates. Cortisol response increased during social housing and could be stimulated by both naloxone and oCRF, whereas ACTH response was generally not influenced by social setting or oCRF but was increased by naloxone. These data show differential adrenal and pituitary response to changes in social settings and a small, but consistent, effect of social dominance.
The use of non-human primates (NHPs) in studies of volitional, oral self-administration of alcohol can help address the complex interplay between stress and excessive alcohol consumption. There are aspects to brain, endocrine and behavior of NHPs, particularly macaques, that provide a critical translational link towards understanding the risks and consequences of alcohol use disorders (AUDs) in humans. These include wide individual differences in escalating daily alcohol intake, accurate measures of hypothalamic-pituitary-adrenal (HPA) axis hormonal interactions, neuroanatomical specificity of synaptic adaptations to chronic alcohol, genetic similarities to humans, and the ability to conduct in vivo brain imaging. When placed in a framework that alcohol addiction is a sequence of dysregulations in motivational circuitry associated with severity of AUD, the NHP can provide within-subject information on both risks for and consequences of repeatedly drinking to intoxication. Notably, long-term adaptations in neurocircuitry that mediate behavioral reinforcement, stress responses and executive functions are possible with NHPs. We review here the substantial progress made using NHPs to address the complex relationship between alcohol and stress as risk factors and consequences of daily drinking to intoxication. This review also highlights areas where future studies of brain and HPA axis adaptations are needed to better understand the mechanisms involved in stress leading to excessive alcohol consumption.


OBJECTIVE: Caregivers of serious juvenile offenders often hold favorable attitudes about criminality and frequently have histories of involvement in antisocial behaviors themselves. In the present study, the authors examined the long-term criminal and noncriminal outcomes for caregivers of serious juvenile offenders who had participated two decades earlier in a randomized clinical trial of multisystemic therapy (MST; Borduin et al., 1995). METHOD: Participants were 276 caregivers of serious juvenile offenders who were originally randomized to MST or individual therapy (IT). Criminal and civil suit data for caregivers were obtained during a 20.7-year follow-up when caregivers were on average 61.5 years old. RESULTS: Caregivers in the MST condition had 94% fewer felonies and 70% fewer misdemeanors than did caregivers in the IT condition. In addition, caregivers in the IT condition were sentenced to 92% more days of incarceration and had 50% more family-related civil suits. Moreover, the favorable long-term effects of MST on caregiver criminality and civil suits were mediated by improved family relations during treatment. CONCLUSION: The present study represents the only follow-up to date of caregivers in an MST clinical trial and demonstrates the broader clinical benefits of a family-based treatment for serious juvenile offenders. Implications of the findings for policymakers and researchers are discussed. (PsycINFO Database Record


BACKGROUND: Propensity scores are typically applied in retrospective cohort studies. We describe the feasibility of matching on a propensity score derived from a retrospective cohort and subsequently applied in a prospective cohort study of patients with chronic musculoskeletal pain before the start of acupuncture or usual care treatment and enrollment in a comparative effectiveness study that required patient reported pain outcomes. METHODS: We assembled a retrospective cohort study using data from 2010 to develop a propensity score for acupuncture versus usual care based on electronic healthcare record and administrative data (e.g., pharmacy) from an integrated health plan, Kaiser Permanente Northwest. The propensity score’s probabilities allowed us to match acupuncture-referred and non-referred patients prospectively in 2013-14 after a routine outpatient visit for pain. Among the matched patients, we collected patient-reported pain before treatment and during follow-up to assess the comparative effectiveness of acupuncture. We assessed
balance in patient characteristics with the post-matching c-statistic and standardized differences. RESULTS: Based on the propensity score and other characteristics (e.g., patient-reported pain), we were able to match all 173 acupuncture-referred patients to 350 non-referred (usual care) patients. We observed a residual imbalance (based on the standardized differences) for some characteristics that contributed to the score; for example, age, -0.283, and the Charlson comorbidity score, -0.264, had the largest standardized differences. The overall balance of the propensity score appeared more favorable according to the post-matching c-statistic, 0.503. CONCLUSION: The propensity score matching was feasible statistically and logistically and allowed approximate balance on patient characteristics, some of which will require adjustment in the comparative effectiveness regression model. By transporting propensity scores to new patients, healthcare systems with electronic health records can conduct comparative effectiveness cohort studies that require prospective data collection, such as patient-reported outcomes, while approximately balancing numerous patient characteristics that might confound the benefit of an intervention. The approach offers a new study design option.


Apolipoprotein E4 (E4) and type 2 diabetes are major risk factors for cognitive decline and late onset Alzheimer's disease (AD). E4-associated phenotypes and insulin resistance (IR) share several features and appear to interact in driving cognitive dysfunction. However, shared mechanisms that could explain their overlapping pathophysiology have yet to be found. We hypothesized that, compared to E3 mice, E4 mice would be more susceptible to the harmful cognitive effects of high fat diet (HFD)-induced IR due to apoE isoform-specific differences in brain metabolism. While both E3 and E4 mice fed HFD displayed impairments in peripheral metabolism and cognition, deficits in hippocampal-dependent spatial learning and memory were exaggerated in E4 mice. Combining genome-wide measures of DNA hydroxymethylation with comprehensive untargeted metabolomics, we identified novel alterations in purine metabolism, glutamate metabolism, and the pentose phosphate pathway. Finally, in E4 mice, the metabolic and cognitive deficiencies caused by HFD were rescued by switching to a low fat diet for one month, suggesting a functional role was associated with reversal of the same metabolic pathways described above. These results suggest a susceptibility of E4 carriers to metabolic impairments brought on by IR, and may guide development of novel therapies for cognitive decline and dementia.


AIMS: To test whether binge drinking, the density of familial alcoholism (FHD), and their interaction are associated with an altered developmental trajectory of impulsive choice across adolescence, and whether more lifetime drinks is associated with a greater change in impulsive choice across age. DESIGN: Alcohol-naive adolescents, with varying degrees of FHD, were recruited as part of an ongoing longitudinal study on adolescent development, and were grouped based on whether they remained non-drinkers (n = 83) or
initiated binge drinking (n = 33) during follow-up. During all visits, adolescents completed a monetary delay discounting task to measure impulsive choice. The effects of binge-drinking status, FHD, and their interaction on impulsive choice across adolescence were tested. SETTING: Developmental Brain Imaging Lab, Oregon Health & Science University, Portland, Oregon, USA. PARTICIPANTS: 116 healthy male and female adolescents (ages 10-19) completed 2-4 visits between July 2008 and May 2016. MEASUREMENTS: Discounting rates were obtained based on adolescents’ preference for immediate or delayed rewards. FHD was based on parent-reported prevalence of alcohol use disorder in the participant’s first and second degree relatives. Binge-drinking status was determined based on the number of recent binge-drinking episodes. FINDINGS: There was a significant interaction effect of binge-drinking status and FHD on impulsive choice across age (b = 1.090, p < 0.05, beta = 0.298). In adolescents who remained alcohol-naive, greater FHD was associated with a steeper decrease in discounting rates across adolescence (b = -0.633, p < 0.05, beta = -0.173); however, this effect was not present in binge-drinkers. Furthermore, total lifetime drinks predicted escalated impulsive choice (b = 0.002, p < 0.05, beta = 0.295) in binge-drinking adolescents. CONCLUSIONS: A greater degree of familial alcoholism is associated with a steeper decline in impulsive choice across adolescence, but only in those who remain alcohol-naive. Meanwhile, more lifetime drinks during adolescence is associated with increases in impulsive choice across age.


The guidance protein Semaphorin7A (Sema7A) is required for the proper development of the immune and nervous systems. Despite strong expression in the mature brain, the role of Sema7A in the adult remains poorly defined. Here we show that Sema7A utilizes different cell surface receptors to control the proliferation and differentiation of neural progenitors in the adult hippocampal dentate gyrus (DG), one of the select regions of the mature brain where neurogenesis occurs. PlexinC1 is selectively expressed in early neural progenitors in the adult mouse DG and mediates the inhibitory effects of Sema7A on progenitor proliferation. Subsequently, during differentiation of adult-born DG granule cells, Sema7A promotes dendrite growth, complexity and spine development through β1-subunit-containing integrin receptors. Our data identify Sema7A as a key regulator of adult hippocampal neurogenesis, providing an example of how differential receptor usage spatiotemporally controls and diversifies the effects of guidance cues in the adult brain.


BACKGROUND: Compressive osseointegration is as an alternative to traditional intramedullary fixation. Two- to 10-year survivorship and modes of failure have been reported; however, as a result of relatively small numbers, these studies are limited in their ability to identify risk factors for failure. QUESTIONS/PURPOSES: (1) What is survivorship free from aseptic mechanical and survivorship free from overall failure of compressive osseointegration fixation? (2) What patient factors (age, sex, body mass index [BMI], anatomic location of reconstruction, indication for reconstruction, radiation, chemotherapy) are associated with increased risk of failure? METHODS: Between 2006 and 2014, surgeons at one center treated 116 patients with 137 Compress(R) implants for lower extremity oncologic reconstructions, revision arthroplasty, and fracture nonunion or malunion. One hundred sixteen implants were available for review with a minimum of 2-year followup (mean, 4 years; range, 2-9 years). Kaplan-Meier survival plots were produced to examine survivorship and Cox regression modeling was used to generate hazard ratios (HRs) for potential risk factors for failure. Patient factors (age, sex, BMI, anatomic location of reconstruction, indication for reconstruction, radiation, chemotherapy) were obtained from chart review and an institutional database. RESULTS: Survivorship free from aseptic mechanical failure was 95% (95% confidence interval [CI], 91%-99%) at 18 months and 93% (95% CI, 86%-99%) at 4 years. Survivorship free from overall failure was 82% (95% CI, 75%-89%) at 18 months and 75% (95% CI, 66%-84%) at 4 years. Risk of overall failure was increased with
reconstruction of the proximal tibia (HR, 4.42; 95% CI 0.98-19.9) and distal femur (HR, 1.74; 95% CI 0.50-6.09) compared to the proximal femur (HR, 1; referent; p = 0.049). Risk of aseptic mechanical failure was increased with reconstruction of the proximal tibia (HR, 1; referent) and distal femur (HR, 0.37; 95% CI, 0.08-1.77) compared with the proximal femur (HR, 0, p = 0.048). Radiation was associated with increased risk of overall failure (HR, 3.85; 95% CI, 1.84-8.02; p < 0.003), but not aseptic mechanical failure. Age, sex, BMI, chemotherapy, and surgical indication were not associated with increased risk of aseptic or overall failure.

**CONCLUSIONS:** This study questions the use of age as a contraindication for the use of this technology and suggests this technology may be considered in proximal femoral reconstruction and for patients with indications other than primary oncologic reconstructions. Future research should establish long-term survivorship data to compare this approach with conventional intramedullary stems and to evaluate the potential benefits of preventing stress shielding and preserving bone stock in revision situations. LEVEL OF EVIDENCE: Level III, therapeutic study.


Methanolic and dichloromethane extracts from the leaves of Congolese Hibiscus species were characterised by chromatographic and spectroscopic techniques and their in vitro biochemical activities against ROS production were evaluated in cellular models and on an enzyme, myeloperoxidase (MPO), involved in inflammation. Hibiscus acetosella has a chemical fingerprint different from Hibiscus cannabinus and Hibiscus sabdariffa both having similar fingerprints. Major compounds were polyphenols, represented mainly by caffeoyl-hydroxycitric acid for H. acetosella and neochlorogenic acid for the two other species. All extracts displayed high cellular antioxidant activity with IC50 values ranging from 0.5 to 3 μg mL⁻¹ using lucigenin on neutrophils. Dichloromethane extracts showed more efficient effects on extracellular ROS production and MPO activity. Antioxidant and anti-inflammatory activities of caffeoyl-hydroxycitric acid were significantly higher than those of neochlorogenic acid. The bioactivities of Hibiscus species were positively correlated with their phytochemical content and could justify their use as local nutraceutical resources and medicines.


A 24-year-old woman with history of asthma was intubated emergently for acute status asthmaticus triggered by acute respiratory syncytial virus infection and treated with permissive hypercapnia. Her ventilation was complicated by auto-positive end-expiratory pressure and elevated peak airway, plateau, and central venous pressures. On hospital day 2, she was noted to have anisocoria. Imaging showed diffuse cerebral edema with central herniation. Difficult ventilation and hypercapnia directly contributed to her severe cerebral edema. Comanagement between neurologic and medical/pulmonary intensivists enabled the management of the competing treatment requirements for status asthmaticus and cerebral edema. This case highlights the importance of balancing conflicting physiologic needs and collaboration between teams.

Myanmar represents an extreme example of the difficulties in optimally allocating resources for maximum public health benefit, on the basis of limited information. At the recent Myanmar Health Forum 'Investing in Health' much of the discussion revolved around what to invest in, how health systems could be strengthened, and what research and capacity building areas the international donor community should prioritise for support. Funding for infectious disease control, particularly HIV and tuberculosis, is being channelled to the country at an unprecedented rate, but very little research has been conducted in recent years, and existing information has not yet been synthesised. This paper presents findings of the first systematic literature review on tuberculosis control and the health system in Myanmar, with the aim of informing the development of optimal research priorities and strategies. Medline and grey literature were searched for relevant papers. Inclusion criteria and analyses were structured to capture data on the Myanmar health system, healthcare delivery, financing, tuberculosis control indicators and information systems. A total of 77 papers were included in the analysis. The results indicate that there has been a large increase in the number of peer-reviewed articles published on tuberculosis in Myanmar over the past decade, although the absolute number of studies remains small. We identified several areas in which evidence to inform policy and resource allocation decisions is lacking, including research focused on rural and/or vulnerable populations, analyses of risk factors for TB and drug resistance that can inform prevention strategies and economic analyses for optimising resource allocation. The gaps in research to inform policy identified through this study may be relevant to other low resource settings with extremely limited research capacity. © 2016 The Author.


Attention-Deficit Hyperactivity Disorder (ADHD) has high heritability; however, studies of common variation account for <5% of ADHD variance. Using data from affected participants without a family history of ADHD, we sought to identify de novo variants that could account for sporadic ADHD. Considering a total of 128 families, two analyses were conducted in parallel: first, in 11 unaffected parent/affected proband trios (or quads with the addition of an unaffected sibling) we completed exome sequencing. Six de novo missense variants at highly conserved bases were identified and validated from four of the 11 families: the brain-expressed genes TBC1D9, DAGLA, QARS, CSMD2, TRPM2, and WDR83. Separately, in 117 unrelated probands with sporadic ADHD, we sequenced a panel of 26 genes implicated in intellectual disability (ID) and autism spectrum disorder (ASD) to evaluate whether variation in ASD/ID-associated genes were also present in participants with ADHD. Only one putative deleterious variant (Gln600STOP) in CHD1L was identified; this was found in a single proband. Notably, no other nonsense, splice, frameshift, or highly conserved missense variants in the 26 gene panel were identified and validated. These data suggest that de novo variant analysis in families with independently adjudicated sporadic ADHD diagnosis can identify novel genes implicated in ADHD pathogenesis. Moreover, that only one of the 128 cases (0.8%, 11 exome, and 117 MIP sequenced participants) had putative deleterious variants within our data in 26 genes related to ID and ASD suggests significant independence in the genetic pathogenesis of ADHD as compared to ASD and ID phenotypes. (c) 2017 Wiley Periodicals, Inc.


**IMPORTANCE** The US Preventive Services Task Force recommends annual lung cancer screening (LCS) with low-dose computed tomography for current and former heavy smokers aged 55 to 80 years. There is little published experience regarding implementing this recommendation in clinical practice. **OBJECTIVES** To describe organizational- and patient-level experiences with implementing an LCS program in selected Veterans Health Administration (VHA) hospitals and to estimate the number of VHA patients who may be candidates for LCS. **DESIGN, SETTING, AND PARTICIPANTS** This clinical demonstration project was conducted at 8
academic VHA hospitals among 93 033 primary care patients who were assessed on screening criteria; 2106 patients underwent LCS between July 1, 2013, and June 30, 2015. INTERVENTIONS Implementation Guide and support, full-time LCS coordinators, electronic tools, tracking database, patient education materials, and radiologic and nodule follow-up guidelines. MAIN OUTCOMES AND MEASURES Description of implementation processes; percentages of patients who agreed to undergo LCS, had positive findings on results of low-dose computed tomographic scans (nodules to be tracked or suspicious findings), were found to have lung cancer, or had incidental findings; and estimated number of VHA patients who met the criteria for LCS. RESULTS Of the 4246 patients who met the criteria for LCS, 2452 (57.7%) agreed to undergo screening and 2106 (2028 men and 78 women; mean [SD] age, 64.9 [5.1] years) underwent LCS. Wide variation in processes and patient experiences occurred among the 8 sites. Of the 2106 patients screened, 1257 (59.7%) had nodules; 1184 of these patients (56.2%) required tracking, 42 (2.0%) required further evaluation but the findings were not cancer, and 31 (1.5%) had lung cancer. A variety of incidental findings, such as emphysema, other pulmonary abnormalities, and coronary artery calcification, were noted on the scans of 857 patients (40.7%). CONCLUSIONS AND RELEVANCE It is estimated that nearly 900 000 of a population of 6.7 million VHA patients met the criteria for LCS. Implementation of LCS in the VHA will likely lead to large numbers of patients eligible for LCS and will require substantial clinical effort for both patients and staff.


Duvooglustat HCl (AT2220, 1-deoxynojirimycin) is an investigational pharmacological chaperone for the treatment of acid alpha-glucosidase (GAA) deficiency, which leads to the lysosomal storage disorder Pompe disease, which is characterized by progressive accumulation of lysosomal glycogen primarily in heart and skeletal muscles. The current standard of care is enzyme replacement therapy with recombinant human GAA (alglucosidase alfa [AA], Genzyme). Based on preclinical data, oral co-administration of duvooglustat HCl with AA increases exposure of active levels in plasma and skeletal muscles, leading to greater substrate reduction in muscle. This phase 2a study consisted of an open-label, fixed-treatment sequence that evaluated the effect of single oral doses of 50 mg, 100 mg, 250 mg, or 600 mg duvooglustat HCl on the pharmacokinetics and tissue levels of intravenously infused AA (20 mg/kg) in Pompe patients. AA alone resulted in increases in total GAA activity and protein in plasma compared to baseline. Following co-administration with duvooglustat HCl, total GAA activity and protein in plasma were further increased 1.2- to 2.8-fold compared to AA alone in all 25 Pompe patients; importantly, muscle GAA activity was increased for all co-administration treatments from day 3 biopsy specimens. No duvooglustat-related adverse events or drug-related tolerability issues were identified.


STUDY DESIGN: A retrospective review of a prospective multicenter database. OBJECTIVE: The aim of this study was to identify variables associated with extended length of stay (ExtLOS) and this impact on health-related quality of life (HRQoL) scores in adult spinal deformity (ASD) patients. SUMMARY OF BACKGROUND DATA: ASD surgery is complex and associated with complications including extLOS. Although variables contributing to extLOS have been considered, specific complications and pre-disposing factors among ASD surgical patients remain to be investigated. METHODS: INCLUSION CRITERIA: ASD surgical patients (age ≥ 18 years, scoliosis ≥ 20 degrees, sagittal vertical axis ≥ 5 cm, pelvic tilt ≥ 25 degrees, and/or thoracic kyphosis > 60 degrees) with complete demographic, radiographic, and HRQoL data at baseline, 6 weeks, and 2 years postoperative. ExtLOS was based on 75th percentile (> = 9 days). Univariate and multivariate analyses identified predictors and evaluated effects on outcomes. Repeated-measures mixed models analyzed impact of ExtLOS on HRQoL [Oswestry Disability Index; Short Form-36 physical component summary/mental
RESULTS: Three hundred eighty patients met inclusion criteria: 105 (27.6%) had extLOS (>/=9 days) and 275 (72.4%) did not. Average LOS was 8 days (range: 1-30 days). Age [odds ratio (OR) 1.04], no. of levels fused (OR 1.12), no. of infections (OR 2.29), no. of neurologic complications (OR 2.51), Charlson Comorbidity Index Score (CCI) predicted ExtLOS (OR 3.92), and no. of intraop complications predicted ExtLOS (OR 3.56). ExtLOS patients had more intracardiopulmonary (pleural effusion: 1.9% vs. 0%) and operative complications (dural tear: 13.3% vs. 5.1%; excessive blood loss: 18% vs. 5.8%) (P < 0.022). At 2 years, both groups of patients experienced an overall improvement in all HRQoL scores (P < 0.001). ExtLOS patients had significantly less overall improvement in all HRQoLs (P < 0.01) except for MCS (P = 0.17) and SRS M (P = 0.08). CONCLUSION: Extended LOS of ASD patients is affected by comorbidities (higher CCI) and number of intraoperative, but not perioperative, complications. All patients improved overall in HRQoL scores, but extended LOS patients improved less overall at 2 years in comparison. LEVEL OF EVIDENCE: 3.
STUDY DESIGN: Retrospective cohort
OBJECTIVE: To explore proximal junctional kyphosis (PJK) as a function of age

Purpose: This community project is an initiative through the University of Wisconsin Biochemical Genetics Clinic and the Wisconsin Newborn Screening Program to identify members of the Plain population who are at risk for having children with maple syrup urine disease (MSUD) or propionic acidemia (PA) or who have PA. METHODS: Because of the high prevalence of metabolic conditions in the Plain population and the importance of early intervention, a statewide outreach project was developed to provide targeted variant analysis of the common MSUD and PA pathogenic variants in this population through health-care provider distribution of blood spot testing kits. Awareness was achieved through outreach efforts with the state midwives guild and Plain population meetings. RESULTS: Eighty individuals were tested; diagnosis was confirmed for three adults with PA and one couple was identified as being at risk for having a child with PA. Genetic counseling was provided to those identified. Follow-up diagnostic testing was completed for the at-risk couple’s children; none were found to be affected. CONCLUSION: This initiative successfully provided accessible clinical testing for MSUD and PA for a high-risk population. Early identification of at-risk couples sets the foundation for early care of at-risk neonates, thereby improving future clinical outcomes. © American College of Medical Genetics and Genomics.


Purpose: This community project is an initiative through the University of Wisconsin Biochemical Genetics Clinic and the Wisconsin Newborn Screening Program to identify members of the Plain population who are at risk for having children with maple syrup urine disease (MSUD) or propionic acidemia (PA) or who have PA. METHODS: Because of the high prevalence of metabolic conditions in the Plain population and the importance of early intervention, a statewide outreach project was developed to provide targeted variant analysis of the common MSUD and PA pathogenic variants in this population through health-care provider distribution of blood spot testing kits. Awareness was achieved through outreach efforts with the state midwives guild and Plain population meetings. RESULTS: Eighty individuals were tested; diagnosis was confirmed for three adults with PA and one couple was identified as being at risk for having a child with PA. Genetic counseling was provided to those identified. Follow-up diagnostic testing was completed for the at-risk couple’s children; none were found to be affected. CONCLUSION: This initiative successfully provided accessible clinical testing for MSUD and PA for a high-risk population. Early identification of at-risk couples sets the foundation for early care of at-risk neonates, thereby improving future clinical outcomes. © American College of Medical Genetics and Genomics.


STUDY DESIGN: Retrospective cohort
OBJECTIVE: To explore proximal junctional kyphosis (PJK) as a function of age-adjusted surgical correction goals. SUMMARY OF BACKGROUND DATA: Recent adult spinal deformity (ASD) studies show that alignment targets are age-specific. Despite recognizing age and malalignment as PJK risk factors, no study has assessed the age-specific effects of alignment on PJK. METHODS: ASD patients with fusions to the pelvis were included and stratified into three groups: young adults (YA<40yo), middle aged (MA: 40-65yo), the elderly (ED>65yo). ANOVA analysis compared the groups with respect to 1-year post-operative alignments and 1-year offsets from age-specific alignment targets. RESULTS: 679 patients were enrolled (mean age=61yo, 77%F, BMI=28.1). At 1-year post-op, there was a significant decrease in PT (29 to 23 degrees), spinopelvic mismatch (PI-LL) (28 to 5 degrees), and SVA (110 to 37 mm); overall incidence of PJK was 45.1%. Stratification by age (YA, n = 28; MA, n = 389; ED, n = 262) revealed an increase in PJK incidence with age: YA = 17.9%, MA = 43.8%, and ED = 50.2% (p < 0.001). PJK patients had smaller post-operative PI-LL mismatches (ED 0.8 vs. 9.8 degrees, MA 3.1 vs. 7.3 degrees) than non-PJK patients, without any significant differences in PT or SVA. Analysis of the post-operative offsets from age-specific norms revealed that PJK patients in the two older sub-groups and in the study cohort as a whole were overcorrected as compared to non-PJK patients (PI-LL Offset: All: -5.2 vs 2.8 degrees, MA: -1 vs +4 degrees, ED: -11 vs -2 degrees; SVA Offset: All: -10 vs 7 mm, MA: -3 vs 10 mm, ED: -18 vs -6 mm). The correlation coefficients...
between PJK angles and the offsets from age-adjusted objective were small (0.320 for PI-LL, 0.114 for PT and 0.136 for SVA). CONCLUSIONS: Overall, this study suggests that PJK patients were overcorrected when compared to age-adjusted alignment goals. Certainly, elderly patients are subject to independent risk factors for PJK, making the prevention of PJK complex. However, individualized optimization of surgical alignment can improve outcomes. This emphasizes the need for surgeons to incorporate age-specific alignment targets into the standard pre-operative planning process. LEVEL OF EVIDENCE: 3.


PURPOSE OF REVIEW: Adrenal insufficiency in pregnancy, although relatively rare, has significant clinical implications on both maternal and fetal outcomes. Hypothalamo–pituitary–adrenal axis dynamics and physiological changes are complex, thus diagnosis and management of adrenal insufficiency in pregnancy remain challenging. RECENT FINDINGS: Studies consistently demonstrate a rise in total serum cortisol with pregnancy, but less data are available on free cortisol levels. Salivary cortisol values have been measured in normal pregnancy and in a few studies using healthy nonpregnant women controls. Although this adds to our current knowledge of hypothalamo–pituitary–adrenal axis changes in pregnancy, clear-cut cortisol reference ranges are yet to be established. Serum cortisol and the cosyntropin stimulation test (albeit with higher peak cortisol thresholds) are currently the diagnostic tests of choice. Hydrocortisone is the preferred glucocorticoid replacement in pregnancy as it is inactivated by placental 11-β-hydroxysteroid dehydrogenase 2; dose titration may be required, but should be individualized depending on clinical course and mode of delivery. SUMMARY: Further studies on the long-term effects of maternal glucocorticoid regimens on the fetus and potential modulators of fetal glucocorticoid sensitivity and placental 11-β-hydroxysteroid dehydrogenase 2 are needed and will be useful in guiding clinical management strategies in pregnant women with adrenal insufficiency. Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.


Products that are manufactured for use in a clinical trial, with the intent of gaining US Food and Drug Administration (FDA) approval for clinical use, must be produced under an FDA approved investigational new drug (IND) application. We describe work done toward generating reliable methodology and materials for preserving ovarian cortical tissue through a vitrification kit and reviving this tissue through a warming and recovery kit. We have described the critical steps, procedures, and environments for manufacturing products with the intent of submitting an IND. The main objective was to establish an easy-to-use kit that would ensure standardized procedures for quality tissue preservation and recovery across the 117 Oncofertility Consortium sites around the globe. These kits were developed by breaking down the components and steps of a research protocol and recombining them in a way that considers component stability and use in a clinical setting. The kits were manufactured utilizing current good manufacturing practice (cGMP) requirements and environment, along with current good laboratory practices (cGLP) techniques. Components of the kit were tested for sterility and endotoxicity, and morphological endpoint release criteria were established. We worked with the intended down-stream users of these kits for development of the kit instructions. Our intention is to test these initial kits, developed and manufactured here, for submission of an IND and to begin clinical testing for preserving the ovarian tissue that may be used for future restoration of fertility and/or hormone function in women who have gonadal dysgenesis from gonadotoxic treatment regimens or disease.

This study aims to describe patterns of injury mechanism among patients treated at a tertiary trauma center in Mumbai to identify opportunities for targeted injury prevention strategies. Data were collected from an institutional trauma registry, and all patients presenting with life- or limb-threatening injuries over a 16-month period were included. Univariate and bivariate analyses were performed for demographic characteristics, injury mechanisms, and clinical outcomes. A total of 1,115 patients were treated during the study period, and the in-hospital mortality rate was 32% in this severely injured cohort. More than one half of patients were suffered transportation injuries (58%). Of victims of transportation injuries, 45% were victims of railway injuries and 28% were pedestrians struck by motor vehicles. Mortality was highest among victims of railway injuries (42%) and pedestrians struck by automobiles (38%). Although injury prevention is a major public health concern worldwide, it is important to understand local patterns of injury to guide targeted prevention strategies. This study highlights the utility of trauma registries in collecting crucial injury surveillance data. In this context, a focus on pedestrian safety and railway injury prevention is warranted. © 2017 Taylor & Francis Group, LLC and The University of Tennessee.


Several distinct melanoma syndromes have been defined, and genetic tests are available for the associated causative genes. Guidelines for melanoma genetic testing have been published as an informal “rule of twos and threes,” but these guidelines apply to CDKN2A testing and are not intended for the more recently described non-CDKN2A melanoma syndromes. In order to develop an approach for the full spectrum of hereditary melanoma patients, we have separated melanoma syndromes into two types: “melanoma dominant” and “melanoma subordinate.” Syndromes in which melanoma is a predominant cancer type are considered melanoma dominant, although other cancers, such as mesothelioma or pancreatic cancers, may also be observed. These syndromes are associated with defects in CDKN2A, CDK4, BAP1, MITF, and POT1. Melanoma-subordinate syndromes have an increased but lower risk of melanoma than that of other cancer(s) seen in the syndrome, such as breast and ovarian cancer or Cowden syndrome. Many of these melanoma-subordinate syndromes are associated with well-established predisposition genes (e.g., BRCA1/2, PTEN). It is likely that these predisposition genes are responsible for the increased susceptibility to melanoma as well but with lower penetrance than that observed for the dominant cancer(s) in those syndromes. In this review, we describe our extension of the “rule of twos and threes” for melanoma genetic testing. This algorithm incorporates an understanding of the spectrum of cancers and genes seen in association with melanoma to create a more comprehensive and tailored approach to genetic testing. © 2017 The Author(s)


Plasma kynurenine/tryptophan (KT) ratio, a marker of adaptive immune defects, strongly predicts mortality during treated HIV disease in Ugandans compared to U.S.-based populations. Here, KT ratio, and T cell and plasma biomarkers of immune activation were measured among 535 HIV-infected Ugandans prior to ART initiation and at month 6 of viral suppression. Month 6 KT ratio (aHR=2.74), sCD14 (aHR=2.32), IL-6 (aHR=2.34), and D dimer (aHR=1.95) were associated with mortality occurring >/=6 months after ART initiation, KT ratio
remained significantly predictive of mortality even after adjustment for the additional biomarkers, suggesting an independent contribution to clinical outcomes in resource-limited settings.


Vestibulodynia is a form of provoked vulvodynia characterized by profound tenderness, hyperinnervation, and frequently inflammation within well-defined areas of the human vestibule. Previous experiments in animal models show that inflammatory hypersensitivity and hyperinnervation occur in concert with establishment of a local renin-angiotensin system (RAS). Moreover, mechanical hypersensitivity and sensory axon sprouting are prevented by blocking effects of angiotensin II on angiotensin II receptor type 2 (AT2) receptors. This case-control study assessed whether a RAS contributes to hyperinnervation observed in human vestibulodynia. Vestibular biopsies from asymptomatic controls or patients' nontender areas showed moderate innervation and small numbers of inflammatory cells. In women with vestibulodynia, tender areas contained increased numbers of mechanoreceptive nociceptor axons, T-cells, macrophages, and B-cells, whereas mast cells were unchanged. RAS proteins were increased because of greater numbers of T cells and B cells expressing angiotensinogen, and increased renin-expressing T cells and macrophages. Chymase, which converts angiotensin I to angiotensin II, was present in constant numbers of mast cells. To determine if tender vestibular tissue generates angiotensin II that promotes axon sprouting, we conditioned culture medium with vestibular tissue. Rat sensory neurons cultured in control-conditioned medium showed normal axon outgrowth, whereas those in tender tissue-conditioned medium showed enhanced sprouting that was prevented by adding an AT2 antagonist or angiotensin II neutralizing antibody. Hypersensitivity in provoked vestibulodynia is therefore characterized by abnormal mechanonociceptor axon proliferation, which is attributable to inflammatory cell-derived angiotensin II (or a closely related peptide) acting on neuronal AT2 receptors. Accordingly, reducing inflammation or blocking AT2 represent rational strategies to mitigate this common pain syndrome. Perspective: This study provides evidence that local inflammation leads to angiotensin II formation, which acts on the AT2 to induce nociceptor axon sprouting in vulvodynia. Preventing inflammation and blocking AT2 therefore present potential pharmacological strategies for reducing vestibular pain. © 2016 American Pain Society.


OBJECTIVE: In 2013, the Accreditation Council of Graduate Medical Education (ACGME) updated requirements for training in community pediatrics and advocacy in pediatric residency programs. In light of this update, the aim of this study was to better understand how community pediatrics is being taught and evaluated in pediatric residency programs in the US. METHODS: Cross-sectional exploratory study using a web-based survey of pediatric residency program directors in September 2014. Questions focused on teaching and evaluation of 10 community pediatrics competencies. RESULTS: Of 85 programs (43% response rate), 30% offered a separate training track and/or 6-block individualized curriculum in community pediatrics or advocacy. More than 75% required all residents to learn 7 of 10 competencies queried. Respondents in urban settings were more likely to teach care of special populations (P = 0.02) and public speaking (P < 0.01). Larger programs were more likely to teach (P = 0.04) and evaluate (P = 0.02) community-based research. Experiential learning and classroom-based didactics were the most frequent teaching methodologies. Many programs used multiple teaching methodologies for all competencies. Observation was the most frequent evaluation technique used; portfolio review and written reflection were also commonly reported. CONCLUSION: Our findings demonstrate a strong emphasis on community pediatrics and advocacy teaching among responding US pediatric residency programs. Although respondents reported a variety of teaching and evaluation methods, there were few statistically significant differences between programs.


We investigate the relationship between the unemployment rate and characteristics of applicants for Social Security Disability Insurance using administrative records of the universe of applicants between 1991 and 2008. As the unemployment rate rises, applications shift to those with higher work capacity who are rejected early in the eligibility determination process and have higher pre-application earnings and employment. However, post-application earnings and employment of denied applicants are slightly negatively related to the unemployment rate, suggesting that both compositional changes toward applications with higher work capacity and adverse economic conditions affect their employment and earnings. © 2017 Walter de Gruyter GmbH, Berlin/Boston 2017.


The placenta is a vital organ necessary for healthy fetal development. Placental insufficiency creates an in utero environment where the fetus is at risk of insufficient oxygen or nutrient exchange. This is primarily caused by impairment of either maternal or fetal circulation or vascular thrombosis such as placental infarction. As a result of placental dysfunction, affected fetuses may be growth restricted, neurologically impaired, and at risk of increased morbidity and mortality. In a cohort of 4 pregnant Rhesus macaques, we describe antenatal detection of naturally occurring intrauterine growth restriction (IUGR) and aberrant fetal neurodevelopment in 1 animal. Abnormal growth parameters were detected by Doppler ultrasound, and vascular insufficiency in the intervillous space was characterized by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). Furthermore, placental oxygen reserve was shown to be reduced compared to control animals by measurements of placental water T2*. To characterize the effects of IUGR on fetal brain development, T2 and diffusion anisotropy images of the fetal brain were acquired in utero. Reduced brain volume and cerebral cortical surface area were apparent macroscopically. Microstructural abnormalities within the developing white matter and cerebral cortex were also observed through analysis of water diffusion anisotropy. After delivery by cesarean section, pathological examination confirmed placental insufficiency with hypoxia. These findings exemplify how DCE-MRI and T2*-based measurements of blood oxygenation within the placenta can provide noninvasive imaging methods for assessing in vivo placental health to potentially identify pregnancies affected by placental insufficiency and abnormal fetal neurodevelopment prior to the onset of fetal and neonatal distress.


PUF60 encodes a nucleic acid-binding protein, a component of multimeric complexes regulating RNA splicing and transcription. In 2013, patients with microdeletions of chromosome 8q24.3 including PUF60 were found to have developmental delay, microcephaly, craniofacial, renal and cardiac defects. Very similar phenotypes have been described in six patients with variants in PUF60, suggesting that it underlies the syndrome. We report 12 additional patients with PUF60 variants who were ascertained using exome sequencing: six through the Deciphering Developmental Disorders Study and six through similar projects. Detailed phenotypic
analysis of all patients was undertaken. All 12 patients had de novo heterozygous PUF60 variants on exome analysis, each confirmed by Sanger sequencing: four frameshift variants resulting in premature stop codons, three missense variants that clustered within the RNA recognition motif of PUF60 and five essential splice-site (ESS) variant. Analysis of cDNA from a fibroblast cell line derived from one of the patients with an ESS variant revealed aberrant splicing. The consistent feature was developmental delay and most patients had short stature. The phenotypic variability was striking; however, we observed similarities including spinal segmentation anomalies, congenital heart disease, ocular colobomata, hand anomalies and (in two patients) unilateral renal agenesis/horseshoe kidney. Characteristic facial features included micrognathia, a thin upper lip and long philtrum, narrow almond-shaped palpebral fissures, synophrys, flared eyebrows and facial hypertrichosis. Heterozygote loss-of-function variants in PUF60 cause a phenotype comprising growth/developmental delay and craniofacial, cardiac, renal, ocular and spinal anomalies, adding to disorders of human development resulting from aberrant RNA processing/spliceosomal function. European Journal of Human Genetics advance online publication, 22 March 2017; doi:10.1038/ejhg.2017.27.


OBJECTIVE: To survey newborn clinicians in the United States regarding the frequency of intramuscular (IM) vitamin K refusal by a parent, reasons for refusal, and approaches of clinicians to refusals. METHODS: An electronic survey was administered to the clinician site representative (nursery director or designee knowledgeable about site-specific nursery policies) at all newborn nurseries in the Better Outcomes through Research for Newborns (BORN) network of newborn nurseries. RESULTS: Of 92 BORN sites, 85 (92%) respondents completed the survey. Frequency of IM vitamin K refusal during the past 5 years was reported as increased by 52% of respondents, unchanged by 42%, and 6% did not know. Reported frequencies of refusal of IM vitamin K was weekly (9%), a few times a month (31%), once a month (13%), once every 3 to 4 months (20%), once or twice a year (26%), or never (1%). The overall distribution of the reported frequencies of refusal differed among regions in the United States (higher in the West and the South; P < .05). Reported reasons for refusal by parents included perceptions of parents that the injection was unnecessary, lack of knowledge about vitamin K deficiency bleeding, and concern about preservatives. Approaches to refusal included attempts to educate parents, enlisting support from community clinicians, a state mandate, and prescription of oral vitamin K. CONCLUSIONS: Respondents from a national sample of newborn nursery clinicians reported an increase in refusal of IM vitamin K in the past 5 years with regional variation. Approaches to refusals need further investigation to determine effectiveness.


N-methyl-D-aspartate receptors (NMDARs) are heterotetrameric ion channels assembled as diheteromeric or triheteromeric complexes. Here, we report structures of the triheteromeric GluN1/GluN2A/GluN2B receptor in the absence or presence of the GluN2B-specific allosteric modulator Ro 25-6981 (Ro), determined by cryogenic electron microscopy (cryo-EM). In the absence of Ro, the GluN2A and GluN2B amino terminal domains (ATD) adopt “closed” and “open” clefts, respectively. Upon binding Ro, the GluN2B ATD clamshell transitions from an open to a closed conformation. Consistent with a predominance of the GluN2A subunit in ion channel gating, the GluN2A subunit interacts more extensively with GluN1 subunits throughout the receptor, in comparison with the GluN2B subunit. Differences in the conformation of the pseudo 2-fold related GluN1 subunits further reflect receptor asymmetry. The triheteromeric NMDAR structures provide the first view of the most common NMDA receptor assembly and show how incorporation of two different GluN2 subunits modifies receptor symmetry and subunit interactions, allowing each subunit to uniquely influence receptor structure and function, thus increasing receptor complexity. © 2017 American Association for the Advancement of Science.

Maternal obesity prior to and during pregnancy has been associated with an increased incidence of childhood asthma. As diets rich in saturated fat are linked to obesity and inflammation, we created a murine model to investigate the effect of maternal high-fat diet (HFD) on adult offspring airway hyperreactivity (AHR), a cardinal feature of asthma. Balb/cByJ dams were fed a HFD (60% fat Calories) or normal-fat diet (NFD) (10% fat Calories) from 8 weeks prior to first breeding through their pregnancies. Pups were weaned to either a HFD or NFD (at 4 weeks of age). AHR was measured in the 10-week-old offspring following inhaled methacholine challenge by end-inflation technique. Bronchial alveolar lavage fluid (BALF) was analyzed for cell count, total protein, and IL-6. Offspring of HFD dams weaned to NFD had increased AHR compared to offspring of NFD dams weaned to NFD Offspring of HFD dams that remained on HFDs had increased AHR compared to offspring of NFD dams weaned to HFDs. Offspring of HFD dams had higher BALF cell counts, higher neutrophil percentage, greater total protein, and IL-6 in the BALF. These results demonstrate that a maternal diet high in saturated fat through pregnancy and lactation plays a key role in programming adult offspring AHR.


Deficits in social communication, particularly pragmatic language, are characteristic of individuals with autism spectrum disorder (ASD). Speech disfluencies may serve pragmatic functions such as cueing speaking problems. Previous studies have found that speakers with ASD differ from typically developing (TD) speakers in the types and patterns of disfluencies they produce, but fail to provide sufficiently detailed characterizations of the methods used to categorize and quantify disfluency, making cross-study comparison difficult. In this study we propose a simple schema for classifying major disfluency types, and use this schema in an exploratory analysis of differences in disfluency rates and patterns among children with ASD compared to TD and language impaired (SLI) groups. 115 children ages 4±8 participated in the study (ASD = 51; SLI = 20; TD = 44), completing a battery of experimental tasks and assessments. Measures of morphological and syntactic complexity, as well as word and disfluency counts, were derived from transcripts of the Autism Diagnostic Observation Schedule (ADOS). High inter-annotator agreement was obtained with the use of the proposed schema. Analyses showed ASD children produced a higher ratio of content to filler disfluencies than TD children. Relative frequencies of repetitions, revisions, and false starts did not differ significantly between groups. TD children also produced more cued disfluencies than ASD children. © 2017 MacFarlane et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.


In urethane/alpha-chloralose anesthetized rats, electrical stimulation of cervical vagal afferent fibers inhibited the increases in brown adipose tissue sympathetic nerve activity and brown adipose tissue thermogenesis evoked by cold exposure, by nanoinjection of the GABAA receptor antagonist, bicuculline, in the dorsomedial hypothalamus, and by nanoinjection of N-methyl-D-aspartate in the rostral raphe pallidus. Vagus nerve stimulation-evoked inhibition of brown adipose tissue sympathetic nerve activity was prevented by blockade of ionotropic glutamate receptors in the termination site of vagal afferents in the nucleus of the solitary tract, and by nanoinjection of GABAA receptor antagonists in the rostral raphe pallidus. In
conclusion, the brown adipose tissue sympathoinhibitory effect of cervical afferent vagal nerve stimulation is mediated by glutamatergic activation of second-order sensory neurons in the nucleus of the solitary tract and by a GABAergic inhibition of brown adipose tissue sympathetic premotor neurons in the rostral raphe pallidus, but does not require GABAergic inhibition of the brown adipose tissue sympathoexcitatory neurons in the dorsomedial hypothalamus.


The major histocompatibility complex I (MHC1) pathway, which canonically functions in innate immune viral antigen presentation and detection, is functionally pleiotropic in the central nervous system (CNS). Alternative roles include developmental synapse pruning, regulation of synaptic plasticity, and inhibition of neuronal insulin signaling; all processes altered during brain aging. Upregulation of MHC1 components with aging has been reported; however, no systematic examination of MHC1 cellular localization, expression, and regulation across CNS regions, life span, and sexes has been reported. In the mouse, MHC1 is expressed by neurons and microglia, and MHC1 components and receptors (H2-K1, H2-D1, ?2M, LlrB3, Klra2, CD247) display markedly different expression profiles across the hippocampus, cortex, cerebellum, brainstem, and retina. MHC1 components, receptors, associated inflammatory transcripts (Il1?, Il1?, Il6, Tnf?), and TAP (transporter associated with antigen processing) components are induced with aging and to a greater degree in female than male mice across CNS regions. H2-K1 and H2-D1 expression is associated with differential CG and non-CG promoter methylation across CNS regions, ages, and between sexes, and concomitant increased expression of proinflammatory genes. Meta-analysis of human brain aging data also demonstrates age-related increases in MHC1. Induction of MHC1 signaling could contribute to altered synapse regulation and impaired synaptic plasticity with aging. © The Author 2016.


Genome sequencing has revolutionized the diagnosis of genetic diseases. Close collaborations between basic scientists and clinical genomicists are now needed to link genetic variants with disease causation. To facilitate such collaborations, we recommend prioritizing clinically relevant genes for functional studies, developing reference variant-phenotype databases, adopting phenotype description standards, and promoting data sharing.


Survival implications of nontuberculous mycobacterial pulmonary disease (NTM-PD) and NTM pulmonary isolation without disease (NTM-PI) are unclear. To study deaths associated with NTM-PD and NTM-PI and differences in survival between them, we conducted a population-based cohort study of persons with microbiologically defined NTM-PD or NTM-PI diagnosed during 2001-2013 in Ontario, Canada. We used propensity score matching and Cox proportional hazards models to compare survival. Among 9,681 NTMPD patients and
10,936 NTM-PI patients, 87% and 91%, respectively, were successfully matched with unexposed controls. Both NTM-PD and NTM-PI were associated with higher rates of death for all species combined and for most individual species. Compared with NTM-PI, NTM-PD was associated with higher death rates for all species combined, Mycobacterium avium complex, and M. xenopi. NTM-PD and NTM-PI were significantly associated with death, NTMPD more so than NTM-PI. © 2017, Centers for Disease Control and Prevention (CDC). All rights reserved.


Although Diagnostic and Statistical Manual of Mental Disorders–Fifth edition requires that attention-deficit/hyperactivity disorder (ADHD) symptoms are apparent across settings, assessed by multiple informants, there remains no standardized approach to integration of multiple sources in adult ADHD diagnosis. The goal of the study was to evaluate informant effects on adult ADHD symptom ratings. Participants were 406 adults, ages 18 to 37, and identified second reporters, recruited from the community, and completing a comprehensive diagnostic and cognitive assessment, including a clinician-administered diagnostic interview and self- and other-report questionnaires of ADHD symptoms. Structural equation modeling indicated good fit for a trifactor model of ADHD, including general ADHD, specific inattention and hyperactivity–impulsivity, and self- and other-perspective factors. Yet there were a number of symptoms on the specific hyperactive–impulsive and self-factors that exhibited nonsignificant loadings. Significant differential item functioning across self-ratings and informant ratings was also noted. The external validation indices of laboratory executive function and diagnostic team-rated impairment was significantly correlated with the specific inattentive factor. While executive function was marginally significantly correlated with the other perspective factor, impairment was associated with the self-perspective factor. Overall, inattentive symptoms may be more sensitive measures of adult ADHD, and other and self-ratings may provide different information in relation to external criteria. © 2016, © The Author(s) 2016.


Background: Bariatric centers frequently provide preoperative educational programs to inform patients about the risks and benefits of weight loss surgery. However, most programs are conducted in English, which may create barriers to effective treatment and access to care for non-English speaking populations. To address this concern, we instituted a comprehensive Spanish-language education program consisting of preoperative information and group nutrition classes conducted entirely in, and supported with Spanish-language materials. Objectives: The primary aim was to examine the effect of this intervention on Spanish-speaking patients’ decision to undergo surgery in a pilot study. Setting: University Hospital/Community Health Center, United States. Methods: Three cohorts of patients seeking bariatric surgery between January 1, 2011 and March 31, 2012 were identified: 1) primary English speakers attending English-language programs (“English-English”); 2) primary Spanish speakers attending Spanish-language programs (“Spanish-Spanish”); and 3) primary Spanish speakers attending English-speaking programs with the assistance of a Spanish-to-English translator (“Spanish-English”). Results: 26% of the English-English cohort ultimately underwent surgery compared with only 12% of the Spanish-Spanish cohort (P = .009). Compared with the English-English group, time to surgery was 35 days longer for the Spanish-Spanish and 185 days longer for the Spanish-English group (both P < .001). Conclusion: Spanish-speaking patients were less likely to undergo bariatric surgery regardless of the language in which educational sessions are provided. For those choosing surgery, providing Spanish-language sessions can shorten time to surgery. A barrier to effective obesity treatment may exist for Spanish speakers, which may be only partially overcome by providing support in Spanish. © 2017.

STUDY DESIGN: An analysis of the State Inpatient Database of North Carolina, 2005 to 2012, and the Nationwide Inpatient Sample, including all inpatient lumbar fusion admissions from nonfederal hospitals. OBJECTIVE: The aim of the study was to examine the influence of a major commercial policy change that restricted lumbar fusion for certain indications and to forecast the potential impact if the policy were adopted nationally.

SUMMARY OF BACKGROUND DATA: Few studies have examined the effects of recent changes in commercial coverage policies that restrict the use of lumbar fusion. METHODS: We included adults undergoing elective lumbar fusion or re-fusion operations in North Carolina. We aggregated data into a monthly time series to report changes in the rates and volume of lumbar fusion operations for disc herniation or degeneration, spinal stenosis, spondylolisthesis, or revision fusions. Time series regression models were used to test for significant changes in the use of fusion operation following a major commercial coverage policy change initiated on January 1, 2011. RESULTS: There was a substantial decline in the use of lumbar fusion for disc herniation or degeneration following the policy change on January 1, 2011. Overall rates of elective lumbar fusion operations in North Carolina (per 100,000 residents) increased from 103.2 in 2005 to 120.4 in 2009, before declining to 101.9 by 2012. The population rate (per 100,000 residents) of fusion among those under age 65 increased from 89.5 in 2005 to 101.2 in 2009, followed by a sharp decline to 76.8 by 2012. There was no acceleration in the already increasing rate of fusion for spinal stenosis, spondylolisthesis, or revision procedures, but there was a coincident increase in decompression without fusion. CONCLUSION: This commercial insurance policy change had its intended effect of reducing fusion operations for indications with less evidence of effectiveness without changing rates for other indications or resulting in an overall reduction in spine surgery. Nevertheless, broader adoption of the policy could significantly reduce the national rates of fusion operations and associated costs. LEVEL OF EVIDENCE: 3.


In primate retina, the midget, parasol, and small bistratified cell populations form the large majority of ganglion cells. In addition, there is a variety of low-density wide-field ganglion cell types that are less well characterized. Here we studied retinal ganglion cells in the common marmoset, Callithrix jaccus, using particle-mediated gene transfer. Ganglion cells were transfected with an expression plasmid for the postsynaptic density 95-green fluorescent protein. The retinas were processed with established immunohistochemical markers for bipolar and/or amacrine cells to determine ganglion cell dendritic stratification. In total over 500 ganglion cells were classified based on their dendritic field size, morphology, and stratification in the inner plexiform layer. Over 17 types were distinguished, including midget, parasol, broad thorny, small bistratified, large bistratified, recursive bistratified, recursive monostratified, narrow thorny, smooth monostratified, large sparse, giant sparse (melanopsin) ganglion cells, and a group that may contain several as yet uncharacterized types. Assuming each characterized type forms a hexagonal mosaic, the midget and parasol cells account for over 80% of all ganglion cells in the central retina but only ~50% of cells in the peripheral (>2mm) retina. We conclude that the fovea is dominated by midget and parasol cells, but outside the fovea the ganglion cell diversity in marmoset is likely as great as that reported for nonprimate retinas. Taken together, the ganglion cell types in marmoset retina resemble those described previously in macaque retina with respect to morphology, stratification, and change in proportion across the retina. © 2016 Wiley Periodicals, Inc.

A 69-year-old woman presented with symptoms of presumed cardiac involvement of idiopathic retroperitoneal fibrosis, otherwise known as Ormond disease. Distinct pericoronary tissue proliferations were depicted at cardiac magnetic resonance (MR) imaging and coronary computed tomographic (CT) angiography. On images, the coronary manifestation was termed the "mistletoe sign." The presence of the mistletoe sign on cardiac MR and coronary CT angiographic images is probably rare, but it might be a characteristic manifestation of retroperitoneal fibrosis. With the increasing number of noninvasive cardiac imaging tests performed worldwide, the recognition of the mistletoe sign could be helpful in diagnosing retroperitoneal fibrosis. © 2016 RSNA.


Chronic neutrophilic leukemia (CNL) is a distinct myeloproliferative neoplasm with a high prevalence (>$80%) of mutations in the colony-stimulating factor 3 receptor (CSF3R). These mutations activate the receptor, leading to the proliferation of neutrophils that are a hallmark of CNL. Recently, the World Health Organization guidelines have been updated to include CSF3R mutations as part of the diagnostic criteria for CNL. Because of the high prevalence of CSF3R mutations in CNL, it is tempting to think of this disease as being solely driven by this genetic lesion. However, recent additional genomic characterization demonstrates that CNL has much in common with other chronic myeloid malignancies at the genetic level, such as the clinically related diagnosis atypical chronic myeloid leukemia. These commonalities include mutations in SETBP1, spliceosome proteins (SRSF2, U2AF1), and epigenetic modifiers (TET2, ASXL1). Some of these same mutations also have been characterized as frequent events in clonal hematopoiesis of indeterminate potential, suggesting a more complex disease evolution than was previously understood and raising the possibility that an age-related clonal process of preleukemic cells could precede the development of CNL. The order of acquisition of CSF3R mutations relative to mutations in SETBP1, epigenetic modifiers, or the spliceosome has been determined only in isolated case reports; thus, further work is needed to understand the impact of mutation chronology on the clonal evolution and progression of CNL. Understanding the complete landscape and chronology of genomic events in CNL will help in the development of improved therapeutic strategies for this patient population. © 2017 by The American Society of Hematology.


Objective: Title 42 of the Code of Federal Regulations Part 2 (42 CFR Part 2) controls the release of patient information about treatment for substance use disorders. In 2016, the Substance Abuse and Mental Health Services Administration (SAMHSA) released a proposed rule to update the regulations, reduce provider burdens, and facilitate information exchange. Oregon’s Medicaid program (Oregon Health Plan) altered the financing and structure of medical, dental, and behavioral care to promote greater integration and coordination. A qualitative analysis examined the perceived impact of 42 CFR Part 2 on care coordination and integration. Methods: Interviews with 76 stakeholders (114 interviews) conducted in 2012-2015 probed the processes of integrating behavioral health into primary care settings in Oregon and assessed issues associated with adherence to 42 CFR Part 2. Results: Respondents expressed concerns that the regulations caused legal confusion, inhibited communication and information sharing, and required updating. Addiction treatment directors noted the challenges of obtaining patient consent to share information with primary care providers. Conclusions: The confidentiality regulations were perceived as a barrier to care coordination and integration. The Oregon Health Authority, therefore, requested regulatory changes. SAMSHA’s proposed revisions permit a general consent to an entire health care team and allow inclusion of substance use disorder information within health information exchanges, but they mandate data segmentation of diagnostic and procedure codes related to substance use disorders and restrict access only to parties with authorized consent, possibly adding barriers to the coordination and integration of addiction treatment with primary care.
Acoustic neuroma (AN) management involves surgery, radiation, or observation. Previous studies have demonstrated that patient race and insurance status impact in-hospital morbidity/mortality following surgery; however, the nationwide impact of these demographics on the receipt of each treatment modality has not been examined. The National Cancer Data Base (NCDB) from 2004 to 2013 identified AN patients. Multivariate analysis adjusted for several variables within each treatment modality, including patient age, race, sex, income, primary payer for care, tumor size, and medical comorbidities. Patients who were African-American (OR=0.7; 95%CI=0.5-0.9; p=0.01), elderly (minimum age 65) (OR=0.4; 95%CI=0.4-0.6; p<0.0001), on Medicare (OR=0.6; 95% CI=0.4-0.7; p=0.0005), or treated at a community hospital (OR=0.4; 95%CI=0.2-0.7; p=0.007) were less likely to receive surgery. Patients on Medicaid (OR=1.2; 95%CI=0.8-1.8; p=0.04) or treated at an integrated network (OR=1.2; 95%CI=0.9-1.6; p=0.0004) were more likely to receive surgery. Patients who were elderly (OR=2.2; 95%CI=1.7-2.9; p<0.0001) or treated in a comprehensive cancer center (OR=1.5; 95%CI=1.3-1.9; p=0.02) were more likely and Medicaid patients (OR=0.8; 95%CI=0.5-1.2; p=0.04) were less likely to receive radiation. Patients who were elderly (OR=2.2; 95%CI=1.7-2.7; p<0.0001), African-American (OR=1.5; 95%CI=1.1-2.0; p=0.01), on Medicare (OR=1.8; 95%CI=1.4-2.3; p=0.0003), or treated in a community hospital (OR=3.0; 95%CI=1.6-5.6; p=0.0007) were more likely to receive observation. Patients on Medicaid (OR=0.8; 95%CI=0.5-1.2; p=0.04) or treated in an integrated network (OR=0.8; 95%CI=0.6-1.0; p=0.0001) were less likely to receive observation. African-American race, elderly age, and community hospital treatment triaged towards observation/away from surgery; age also triaged towards radiation. Conversely, integrated networks triaged towards surgery/away from observation; comprehensive cancer centers triaged towards radiation. Medicaid insurance triaged towards surgery/away from radiation/observation; this may be detrimental since lack of private insurance is a known risk factor for increased in-hospital postoperative morbidity.
Randomized Optimal Platelet and Plasma Ratio (PROPPR) trial, excluding patients who died within 24 hours and/or were on pre-injury anticoagulants. Patient characteristics, adverse outcomes, and parameters of platelet function (PF) and coagulation (thromboelastography; TEG) were compared from admission to 72 hours between VTE (n=83) and non-VTE (n=475) patients. p<0.05 indicated significance. RESULTS: Despite similar patient demographics, VTE patients exhibited hypercoagulable TEG parameters and enhanced PF at admission (p<0.05). Both groups exhibited hypocoagulable TEG parameters, platelet dysfunction and suppressed clot lysis (low LY30) 2HR following admission (p<0.05). VTE patients exhibited delayed coagulation recovery (a significant change compared to 2HR) of K (48 vs 24HR), alpha-angle (no recovery), MA (24 vs 12HR) and LY30 (48hrs vs 12HR). PF recovery mediated by arachidonic acid (72 vs 4HR), adenosine-5’-diphosphate (72 vs 12HR), and collagen (48 vs 12HR) were delayed in VTE patients. VTE patients had lower mortality (4% vs 13%, p<0.05), but less hospital free days (0 (0-8) vs 10 (0-20), p<0.05) and higher complication rates (p<0.05). CONCLUSIONS: Recovery from platelet dysfunction and coagulopathy following severe trauma were delayed in VTE patients. Suppressed clot lysis and compensatory mechanisms associated with altered coagulation that may potentiate VTE formation require further investigation.


BACKGROUND: The treatment of early-stage esophageal cancer and high-grade dysplasia of the esophagus has changed significantly in recent years. Many early tumors that were traditionally treated with esophagectomy can now be resected with endoscopic therapy alone. These new endoscopic modalities can offer similar survival outcomes without the associated morbidity of a major operation. However, a number of these cases may still require surgical intervention as the best treatment option. METHODS: The current scientific literature, national and international guidelines were reviewed for recommendations regarding optimal treatment of early esophageal malignancy. RESULTS: The primary advantage of surgery over endoscopic treatment lies in the reduced risk of recurrence as well as the ability to assess harvested lymph nodes for regional disease. We recommend that esophageal tumors that have invaded into the submucosa (T1b) or beyond should be treated with an esophagectomy. In addition, dysplastic lesions and cancers that demonstrate poorly differentiated pathology or lymphovascular or perineural invasion should be surgically resected. Finally, large tumors, multifocal lesions, tumors within a long segment of Barrett’s esophagus, tumors adjacent to a hiatal hernia, tumors that cannot be resected enbloc with endoscopic techniques should also be treated with an esophagectomy. CONCLUSIONS: When performed at high-volume centers in experienced hands, esophagectomy can have consistently good outcomes for high-grade dysplasia and early esophageal cancers, and should be considered as a treatment option.


Objective: The aim of this study was to describe deployed National Guard members’ and their families’ perceptions of their experience with family reintegration, and the causes and conditions of challenges reintegration presents after deployment. Methods: A total of 26 National Guard members and 19 family members participated in individual (n = 22), couples (n = 6), or focus group (n = 17) interviews. In-depth interviews were used to assess needs and maximize input from military families regarding deployment-related experiences and reintegration issues. Qualitative coding and analysis of data were completed using NVivo. Results: Finding their way back in is the key process that the military members must complete to successfully reestablish their desired social connections with the family and reclaim their place within the family. Several conditions shape the degree of challenges with reintegration that veterans and their family will encounter. These include preparation for deployment, length and type of deployment, communication during deployment, and finally, awareness of how deployment changes the military member and the family. Conclusion: Support resources dedicated to providing National Guard members and their families with assistance in preparing for deployments and educating them about the importance of communication during deployment should be maintained and expanded. Broader educational efforts that increase
awareness of what to expect regarding how deployment changes the military member and the family are needed. © Association of Military Surgeons of the U.S. All rights reserved.


Rupture of fetal membranes can initiate parturition at both term and preterm. Collagen is the crucial factor determining the tensile strength of the membranes. Toward the end of gestation, a feed-forward regeneration of cortisol via 11beta-hydroxysteroid dehydrogenase 1 exists in fetal membranes. It remains undetermined whether cortisol contributes to collagen reduction in fetal membranes. Here we have examined whether cortisol accumulation is a causative factor for collagen reduction in human amnion fibroblasts, the major source of collagens in the membranes. Cortisol had no effect on collagen 1A1 (COL1A1) and 1A2 (COL1A2) mRNA abundance but decreased their protein abundance. The latter effect was affected by neither mRNA transcription inhibitor nor protein translation inhibitor. Mechanistic studies revealed that the reduction in COL1A1 but not COL1A2 protein by cortisol was blocked by lysosome inhibitor chloroquine or siRNA-mediated knock-down of ATG7, an essential protein for autophagy, while the proteasome inhibitors MG132 and bortezomib were ineffective. Further analysis showed that cortisol dose-dependently increased the ratio of LC3II/LC3I, a marker of lysosome activation, an effect blocked by the glucocorticoid receptor (GR) antagonist RU486 and siRNA-mediated knock-down of GR. Consistently, cortisol decreased COL1A1 and COL1A2 protein abundance in amnion tissue explants, and decreased COL1A1 and COL1A2 protein abundance was observed at parturition in the amnion tissue. Conclusively, cortisol regeneration in fetal membranes may contribute to rupture of fetal membranes at parturition by reducing collagen protein abundance. Lysosome-mediated autophagy accounts for the reduction in COL1A1 by cortisol but the mechanism underlying the reduction in COL1A2 awaits further investigation.


Although cardiac malformations at birth are typically associated with genetic anomalies, blood flow dynamics also play a crucial role in heart formation. However, the relationship between blood flow patterns in the early embryo and later cardiovascular malformation has not been determined. We used the chicken embryo model to quantify the extent to which anomalous blood flow patterns predict cardiac defects that resemble those in humans and found that restricting either the inflow to the heart or the outflow led to reproducible abnormalities with a dose-response type relationship between blood flow stimuli and the expression of cardiac phenotypes. Constricting the outflow tract by 10-35% led predominantly to ventricular septal defects, whereas constricting by 35-60% most often led to double outlet right ventricle. Ligation of the vitelline vein caused mostly pharyngeal arch artery malformations. We show that both cardiac inflow reduction and graded outflow constriction strongly influence the development of specific and persistent abnormal cardiac structure and function. Moreover, the hemodynamic associated cardiac defects recapitulate those caused by genetic disorders. Thus our data demonstrate the importance of investigating embryonic blood flow conditions to understand the root causes of congenital heart disease as a prerequisite to future prevention and treatment. New & Noteworthy Congenital heart defects result from genetic anomalies, teratogen exposure, and altered blood flow during embryonic development. We show here a novel “dose-response” type relationship between the level of blood flow alteration and manifestation of specific cardiac phenotypes. We speculate that abnormal blood flow may frequently underlie congenital heart defects. © 2017 the American Physiological Society.

Introduction. The three types of priapism are stuttering, arterial (high-flow, nonischemic), and venoocclusive (low-flow, ischemic). These are usually distinct entities and rarely occur in the same patient. T-shunts and other distal shunts are frequently combined with tunneling, but a seldom recognized potential complication is conversion to a high-flow state. Case Presentation. We describe 2 cases of men who presented with low-flow priapism episodes that were treated using T-shunts with tunneling that resulted with both men having recurrent erections shortly after surgery that were found to be consistent with high-flow states. Case 1 was a 33-year-old male with sickle cell anemia and case 2 was a 24-year-old male with idiopathic thrombocytopenic purpura. In both cases the men were observed over several weeks and both men returned to normal erectile function. Conclusions. Historically, proximal shunts were performed only in cases when distal shunts failed and carry a higher risk of serious complications. T-shunts and other distal shunts combined with tunneling are being used more frequently in place of proximal shunts. These cases illustrate how postoperative erections after T-shunts with tunneling can signify a conversion from low-flow to high-flow states and could potentially be misdiagnosed as an operative failure.


A group of informatics experts in simulation, biomedical informatics, patient safety, medical education, and human factors gathered at Corbett, Oregon on April 30 and May 1, 2015. Their objective: to create a consensus statement on best practices for the use of electronic health record (EHR) simulations in education and training, to improve patient safety, and to outline a strategy for future EHR simulation work. A qualitative approach was utilized to analyze data from the conference and generate recommendations in five major categories: (1) Safety, (2) Education and Training, (3) People and Organizations, (4) Usability and Design, and (5) Sociotechnical Aspects.


In the last decade, an increasing number of cardiac conditions have been shown to have a genetic basis. Cardiovascular genetic counseling has emerged as a subspecialty aiming to identify unaffected at-risk individuals. An important sector of this at-risk population also includes expectant mothers, in whom unique clinical challenges may arise. Genetic counselors, especially those in cardiovascular and prenatal settings, have an opportunity to identify and assist women who may benefit from cardiovascular care during pregnancy. This paper provides basic management and genetic evaluation principles for affected women, as well as guidance on identifying those who are at risk. We provide considerations for cardiac surveillance in pregnancy and the post-partum period. Finally, key psychosocial issues that appraise how to best provide support to at risk women as they make informed decisions are discussed. We propose that a team approach including cardiology, maternal fetal medicine, and genetic counseling best serves this patient population. Ongoing questions addressing an evidence based approach to cardiovascular genetic conditions in pregnancy still remain. Thus, well-designed research protocols are essential to mark progress in this area. © 2017 National Society of Genetic Counselors, Inc.

OBJECTIVES: In the United States, emergency medicine researchers hold proportionately fewer federal career development awards than researchers in other specialties. Others hypothesize this deficit may partly be attributed to lack of mentors, departmental resources, and qualified applicants. Our objectives were to examine the association between departmental and institutional resources and career development awards and to describe the barriers to conducting research and obtaining grants in emergency medicine. METHODS: We conducted an online, cross-sectional survey study of Vice Chairs for Research and Research Directors at academic emergency departments in the United States in January-February 2016. Participants provided quantitative information regarding their department’s demographics, available research resources, number of funded independent investigators, and number of career development awards. They were also asked about the perceived adequacy of departmental and institutional resources and perceived barriers to research and grant success. Data were analyzed using descriptive statistics and multivariable linear regression, as appropriate. RESULTS: Of 178 eligible participants, 103 (58%) completed the survey. Most departments reported some infrastructure for research and grant submission, including research coordinator(s) (n=75/99; 76%, 95%CI 66-84%), research associates (69/99; 70%, 95%CI 60-79%), and administrative/secretarial research support (79/101; 78%, 95%CI 69-86%). The majority of departments (56/103; 49%, 95%CI 44-64%) had no R01-funded researchers, and only 15 (15%, 95%CI 8-23%) had three or more R01-funded researchers. The most frequently reported challenge to junior faculty applying for grants was low motivation for applying (62/103; 60%, 95%CI 50-70%), followed closely by insufficient mentorship (50/103; 49%, 95%CI 39-59%) and discouragement from low funding rates (50/103; 49%, 95%CI 39-59%). In the multivariable model, only the number of departmental R-level funded researchers was associated with the number of departmental career development awards (coefficient 0.75 95%CI 0.39, 1.11; R2 =0.57). CONCLUSIONS: While more multiple departmental and institutional resources correlated with a greater number of funded career development awards, the single greatest predictor was the number of R-level funded researchers in the department. Low motivation and insufficient mentorship were the most frequently reported barriers to junior faculty applying for career development awards. Further studies are needed to describe junior faculty perspectives on these issues and to explore strategies for overcoming these barriers. This article is protected by copyright. All rights reserved.


A predisposing factor for development of the hyperglycaemic state of gestational diabetes mellitus (GDM) is obesity. We previously showed that increasing maternal obesity is associated with significant reductions in placental mitochondrial respiration. MicroRNA (miR)-143 has been previously shown to regulate the metabolic switch from oxidative phosphorylation to aerobic glycolysis in cancer tissues. We hypothesized that mitochondrial respiration is reduced and aerobic glycolysis is up-regulated via changes in miR-143 expression in the placenta of women with GDM. Placental tissue was collected at term from women with A1GDM (controlled by diet), A2GDM (controlled by medication) and body mass index (BMI)-matched controls (CTRL). miR-143 expression was measured by RT-PCR. Expression of mitochondrial complexes, transcription factors peroxisome proliferator-activated receptor-γ co-activator 1α (PGC1α) and peroxisome proliferator-activated receptor γ (PPARγ), components of mammalian target of rapamycin (mTOR) signalling, glucose transporter GLUT1 and glycolytic enzymes [hexokinase-2 (HK-2), phosphofructokinase (PFK) and lactate dehydrogenase (LDH)] were measured by Western blot. Trophoblast respiration was measured by XF24 Analyser. Expression of miR-143, mitochondrial complexes, and PPARγ and PGC1α, which act downstream of miR-143, were significantly decreased in A2GDM placenta compared with A1GDM and CTRL (P < 0.01). Placental hPL (human placental lactogen) levels, expression of glycolytic enzymes, GLUT1 and mTOR signalling were also
significantly increased by more than 2-fold in A2GDM compared with A1GDM and CTRL (P < 0.05). There was a 50% reduction in mitochondrial respiration in trophoblast cells isolated from A2GDM placentae. Overexpression of miR-143 was able to increase mitochondrial respiration, increase protein expression of mitochondrial complexes and decrease expression of glycolytic enzymes by 40% compared with A2GDM. Down-regulation of miR-143 mediates the metabolic switch from oxidative phosphorylation to aerobic glycolysis in placenta of women with A2GDM. © 2016 The Author(s).


The literature on the contribution of kerosene lighting to indoor air particulate concentrations is sparse. In rural Uganda, kitchens are almost universally located outside the main home, and kerosene is often used for lighting. In this study, we obtained longitudinal measures of particulate matter 2.5 microns or smaller in size (PM2.5) from living rooms and kitchens of 88 households in rural Uganda. Linear mixed effects models with a random intercept for household were used to test the hypotheses that primary reported lighting source and kitchen location (indoor vs. outdoor) is associated with PM2.5 levels. During initial testing, households reported using the following sources of lighting: open wick kerosene (19.3%), hurricane kerosene (45.5%), battery powered (33.0%), and solar (1.1%) lamps. During follow-up testing these proportions changed to 29.5%, 35.2%, 18.2%, and 9.1%, respectively. Average ambient, living room, and kitchen PM2.5 levels were 20.2, 35.2, and 270.0 μg/m³. Living rooms using open wick kerosene lamps had the highest PM2.5 levels (55.3 μg/m³ ) compared to those using solar lighting (19.4 μg/m³; open wick vs. solar, p = 0.01). 27.6% of homes using open wick kerosene lamps met World Health Organization indoor air quality standards compared to 75.0% in homes using solar lighting. This article is protected by copyright. All rights reserved.


We have provided 3-D and 4D mapping of speech and language function based upon the results of direct cortical stimulation and event-related modulation of electrocorticography signals. Patients estimated to have right-hemispheric language dominance were excluded. Thus, 100 patients who underwent two-stage epilepsy surgery with chronic electrocorticography recording were studied. An older group consisted of 84 patients at least 10 years of age (7367 artefact-free non-epileptic electrodes), whereas a younger group included 16 children younger than age 10 (1438 electrodes). The probability of symptoms transiently induced by electrical stimulation was delineated on a 3D average surface image. The electrocorticography amplitude changes of high-gamma (70-110 Hz) and beta (15-30 Hz) activities during an auditory-naming task were animated on the average surface image in a 4D manner. Thereby, high-gamma augmentation and beta attenuation were treated as summary measures of cortical activation. Stimulation data indicated the causal relationship between (i) superior-temporal gyrus of either hemisphere and auditory hallucination; (ii) left superior-/middle-temporal gyri and receptive aphasia; (iii) widespread temporal/frontal lobe regions of the left hemisphere and expressive aphasia; and (iv) bilateral precentral/left posterior superior-frontal regions and speech arrest. On electrocorticography analysis, high-gamma augmentation involved the bilateral superior-temporal and precentral gyri immediately following question onset; at the same time, high-gamma activity was attenuated in the left orbitofrontal gyrus. High-gamma activity was augmented in the left temporal/frontal lobe regions, as well as left inferior-parietal and cingulate regions, maximally around question offset, with high-gamma augmentation in the left pars orbitalis inferior-frontal, middle-frontal, and inferior-parietal regions preceded by high-gamma attenuation in the contralateral homotopic regions. Immediately before verbal response, high-gamma augmentation involved the posterior superior-frontal and
pre/postcentral regions, bilaterally. Beta-attenuation was spatially and temporally correlated with high-gamma augmentation in general but with exceptions. The younger and older groups shared similar spatial-temporal profiles of high-gamma and beta modulation; except, the younger group failed to show left-dominant activation in the rostral middle-frontal and pars orbitalis inferior-frontal regions around stimulus offset. The human brain may rapidly and alternately activate and deactivate cortical areas advantageous or obtrusive to function directed toward speech and language at a given moment. Increased left-dominant activation in the anterior frontal structures in the older age group may reflect developmental consolidation of the language system. The results of our functional mapping may be useful in predicting, across not only space but also time and patient age, sites specific to language function for presurgical evaluation of focal epilepsy.


BACKGROUND: Data on second-line treatment options for pediatric patients with immune thrombocytopenia (ITP) are limited. Thrombopoietin receptor agonists (TPO-RA) provide a nonimmunosuppressive option for children who require an increased platelet count. PROCEDURE: We performed a multicenter retrospective study of pediatric ITP patients followed at ITP Consortium of North America (ICON) sites to characterize TPO-RA use. RESULTS: Seventy-nine children had a total of 87 treatments (28 eltrombopag, 43 romiplostim, and eight trialed on both). The majority had primary ITP (82%) and most (60.8%) had chronic ITP. However, 22% had persistent ITP and 18% had newly diagnosed ITP. During the first 3 months of treatment, 89% achieved a platelet count >/= 50 x 10(9) /l (86% romiplostim, 81% eltrombopag, P = 0.26) at least once in the absence of rescue therapy. The average time to a response was 6.4 weeks for romiplostim and 7.0 weeks for eltrombopag (P = 0.83). Only 40% of patients demonstrated a stable response with consistent dosing over time. An intermittent response with constant dose titration was seen in 15%, and an initial response that waned to no response was seen in 13%. Significant adverse events were minimal with the exception of two patients with thrombotic events and one who developed a neutralizing antibody. CONCLUSIONS: Our results demonstrate that TPO-RA agents are being used in children with ITP of varying duration and severity. The response was similar to clinical trials, but the sustainability of response varied. Future studies need to focus on the ideal timing and rationale for these medications in pediatric patients.


IMPORTANCE Despite a large rural US population, there are potential differences between rural and urban regions in the processes and outcomes following trauma. OBJECTIVES To describe and evaluate rural vs urban processes of care, injury severity, and mortality among injured patients served by 9-1-1 emergency medical services (EMS). DESIGN, SETTING, AND PARTICIPANTS This was a preplanned secondary analysis of a prospective cohort enrolled from January 1 through December 31, 2011, and followed up through hospitalization. The study included 44 EMS agencies transporting to 28 hospitals in 2 rural and 5 urban counties in Oregon and Washington. A population-based, consecutive sample of 67 047 injured children and adults served by EMS (1971 rural and 65 076 urban) was enrolled. Among the 53 487 patients transported by EMS, a stratified probability sample of 17 633 patients (1438 rural and 16 195 urban) was created to track hospital outcomes (78.9% with in-hospital follow-up). Data analysis was performed from June 12, 2015, to
May 20, 2016. EXPOSURES Rural was defined at the county level by 60 minutes or more driving proximity to the nearest level I or II trauma center and/or rural designation in the Centers for Medicare & Medicaid Services ambulance fee schedule by zip code. MAIN OUTCOMES AND MEASURES Mortality (out-of-hospital and in-hospital), need for early critical resources, and transfer rates. RESULTS Of the 53,487 injured patients transported by EMS (17,633 patients in the probability sample), 27,535 were women (51.5%); mean (SD) age was 51.6 (26.1) years. Rural vs urban sensitivity of field triage for identifying patients requiring early critical resources was 65.2% vs 80.5%, and only 29.4% of rural patients needing critical resources were initially transported to major trauma centers vs 88.7% of urban patients. After accounting for transfers, 39.8% of rural patients requiring critical resources were cared for in major trauma centers vs 88.7% of urban patients. Overall mortality did not differ between rural and urban regions (1.44% vs 0.89%; P = .09); however, 89.6% of rural deaths occurred within 24 hours compared with 64% of urban deaths. CONCLUSIONS AND RELEVANCE Most high-risk trauma patients injured in rural areas were cared for outside of major trauma centers and most rural trauma deaths occurred early, although overall mortality did not differ between regions. There are opportunities for improved timeliness and access to major trauma care among patients injured in rural regions. © 2017 American Medical Association. All rights reserved.


BACKGROUND: A rhabdomyolysis protocol (RP) with mannitol and bicarbonate to prevent acute renal dysfunction (ARD, creatinine >2.0 mg/dL) remains controversial. METHODS: Patients with creatine kinase (CK) greater than 2,000 U/L over a 10-year period were identified. Shock, Injury Severity Score, massive transfusion, intravenous contrast exposure, and RP use were evaluated. RP was initiated for a CK greater than 10,000 U/L (first half of the study) or greater than 20,000 U/L (second half). Multivariable analyses were used to identify predictors of ARD and the independent effect of the RP. RESULTS: Seventy-seven patients were identified, 24 (31%) developed ARD, and 4 (5%) required hemodialysis. After controlling for other risk factors, peak CK greater than 10,000 U/L (odds ratio 8.6, P = .016) and failure to implement RP (odds ratio 5.7, P = .030) were independent predictors of ARD. Among patients with CK greater than 10,000, ARD developed in 26% of patients with the RP versus 70% without it (P = .008). CONCLUSION: Reduced ARD was noted with RP. A prospective controlled study is still warranted.


Serum proteomics analysis may lead to the discovery of novel osteoporosis biomarkers. The Osteoporotic Fractures in Men Study (MrOS) comprises men >/=65 in the US who have had repeated BMD measures and have been followed for incident fracture. High-throughput quantitative proteomic analysis was performed on baseline fasting serum samples from non-Hispanic white men using a multi-dimensional approach coupling liquid chromatography, ion-mobility separation, and mass spectrometry (LC-IMS-MS). We followed the participants for a mean of 4.6 years for changes in femoral neck bone mineral density (BMD) and for incident hip fracture. Change in BMD was determined from mixed effects regression models taking age and weight into account. Participants were categorized into three groups: BMD maintenance (no decline; estimated change >/= 0 g/cm2, n = 453); expected loss (estimated change 0 to 1 SD below the estimated mean change, -0.034
Nutritional excess of vitamin A, a precursor for retinoic acid (RA), causes premature epiphyseal fusion, craniosynostosis, and light-dependent retinopathy. Similarly, homozygous loss-of-function mutations in CYP26B1, one of the major RA-metabolizing enzymes, cause advanced bone age, premature epiphyseal fusion, and craniosynostosis. In this paper, a patient with markedly accelerated skeletal and dental development, retinal scarring, and autism-spectrum disease is presented and the role of retinoic acid in longitudinal bone growth and skeletal maturation is reviewed. Genetic studies were carried out using SNP array and exome sequencing. RA isomers were measured in the patient, family members, and in 18 age-matched healthy children using high-performance liquid chromatography coupled to tandem mass spectrometry. A genomic SNP array identified a novel 8.3 megabase microdeletion on chromosome 10q23.2-23.33. The 79 deleted genes included CYP26A1 and C1, both major RA-metabolizing enzymes. Exome sequencing did not detect any variants that were predicted to be deleterious in the remaining alleles of these genes or other known retinoic acid-metabolizing enzymes. The patient exhibited elevated plasma total RA (16.5 vs. 12.6+/-.1.5 nM, mean+/-.SD, subject vs. controls) and 13-cisRA (10.7 nM vs. 6.1+/-.1.1). The findings support the hypothesis that elevated RA concentrations accelerate bone and dental maturation in humans. CYP26A1 and C1 haploinsufficiency may contribute to the elevated retinoic acid concentrations and clinical findings of the patient, although this phenotype has not been reported in other patients with similar deletions, suggesting that other unknown genetic or environmental factors may also contribute.


Cognitive impairments, uncontrolled drinking, and neuropathological cortical changes characterize alcohol use disorder. Dysfunction of the orbitofrontal cortex (OFC), a critical cortical sub-region that controls learning, decision-making, and prediction of reward outcomes, contributes to executive cognitive function deficits in alcoholics. 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 as compared to controls. Bath application of alcohol reduced evoked firing in neurons from control 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 alcoholics as a risk factor for relapse, and alcoholics 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 non-human 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 if targeting these novel targets reduces excessive and harmful levels of alcohol drinking.


Between January 1, 2012 and December 31, 2014, there was a large population (N = 200) of insanity acquittees placed on conditional release (CR) in the state of Oregon. This article looks at the demographic and system characteristics of this large group of individuals. The authors then focus on the initial housing placement and what happens to individuals after their release in relation to their housing placement. In Oregon, insanity acquittees are either conditionally released directly by the court or placed in the hospital prior to potential CR by a supervising board. In general, once CR occurs, individuals tend to stay in their initial placement without moving to less structured levels of care, raising concerns about transinstitutionalization. This is especially true for individuals released to the most structured living arrangement (secure residential treatment facility). Those individuals who are conditionally released to less structured settings have a higher rate of revocation back to the hospital. Those individuals who do move to less structured levels of care usually have longer hospital stays and start off in more structured levels of care to start their CR. Copyright (c) 2016 John Wiley & Sons, Ltd.


Background: Over the past 15 years of war, eligible U.S. military members donated organs overseas in Germany. Our hypothesis was that outcomes at a military treatment facility were comparable to a civilian cohort. Methods: Military donors were matched 1:3 with a donor cohort from the U.S. United Network for Organ Sharing. Data were compared using univariate and multivariate analysis. Significance set at p < 0.05. Results: Forty military organ donors were compared with 116 civilian matched donors. The military cohort conversion rate was 75.5% and recovered more organs per donor (4.6 vs. 4.0, p = 0.02) with more transplants (4.2 vs 3.5, p = 0.01). Multivariate analysis controlling for sex, age, and type of organ donation showed no difference in odds of total organs donated in the military versus civilian cohort (odds ratio 2.1, 95% CI 0.87-5.24, p = 0.10). Conclusions: Organ donation at a military treatment facility overseas can be accomplished successfully. © 2017.


INTRODUCTION: To determine the factors used to make the decision between vasovasostomy (VV) and vasoepididymostomy (VE) by leaders performing microsurgical vasectomy reversal using a questionnaire. MATERIALS AND METHODS: An online questionnaire was sent to all members of the Society for the Study of Male Reproduction (SSMR), a male reproduction subspecialty society of the AUA, using the SurveyMonkey platform. RESULTS: Sixty-seven surgeons responded to the questionnaire (27% of SSMR members). Of which
72% of members performed less than 50 vasectomy reversals per year. Also, 71% of members stated that less than 20% of their vasectomy reversals are vasoepididymostomies. When evaluating epididymal fluid at the time of reversal, 87% would perform a VE for pasty fluid, 66% with creamy fluid without sperm heads and 55% with no or scant fluid. With respect to banking sperm, 36% take sperm or testicular tissue at the time of VE while 37% sometimes take sperm mostly depending on the couple’s preference. The Berger end-to-side with intussusception VE technique is used by the majority of members (78%). The presence of intact sperm or sperm parts determined the location in the epididymis for anastomosis for 55% and 19% of members respectively. Postoperative semen testing after a VE is evaluated first between 6 weeks to 3 months for 64%. The procedure is considered a failure between 6 to 12 months for 34% and 12 to 18 months for another 48% if no sperm is seen on semen analysis. CONCLUSIONS: Most members perform a VE with pasty fluid or creamy fluid without sperm heads. Three out of four members are using the Berger end-to-side intussusception technique to perform their VE. More studies are needed to determine the optimal circumstances to perform a VE as there is significant variation in responses even among members of the SSMR.


BACKGROUND AND AIMS: Sitosterolemia displays high plasma total sterols [high plant sterols (PS) + normal to high total cholesterol (TC)] with normal to moderately elevated low-density lipoprotein (LDL) levels. High LDL, intermediate-density lipoprotein (IDL) and very low-density lipoprotein (VLDL) particles, low high-density lipoprotein (HDL), and increased non-HDL and the ratios of TC and triglycerides (TG) to HDL can increase the risk for atherosclerosis. Ezetimibe (EZE) can reduce plasma PS and TC levels in sitosterolemia, but its effect on lipoprotein subclasses has not been previously reported. METHODS: Sitosterolemia patients (n = 8) were taken off EZE for 14 weeks (OFF EZE) and placed on EZE (10 mg/d) for 14 weeks (ON EZE). Serum lipids were measured enzymatically and lipoprotein subclasses were assessed by polyacrylamide gel electrophoresis. RESULTS: EZE reduced (p < 0.05) total sterols (-12.5 +/- 4.1%) and LDL-sterol (-22.7 +/- 5.7%) and its sterol mass of large VLDL (-24.4 +/- 4.5%), VLDL remnants (-21.1 +/- 7.9%) and large IDL (-22.4 +/- 7.2%) compared to OFF EZE. EZE did not affect large LDL subclasses or mean LDL particle size (273.8 +/- 0.6 vs. 274.6 +/- 0.3 A). EZE increased HDL-sterol (25.5 +/- 8.0%, p = 0.008) including intermediate (34 +/- 14%, p = 0.02) and large (33 +/- 16%, p = 0.06) HDL. EZE reduced non-HDL-sterol (-21.8 +/- 5.0%), total sterols/HDL (-28.2 +/- 5.5%) and TG/HDL (-27.4 +/- 6.5, all p < 0.01). CONCLUSIONS: EZE improves VLDL and HDL subfraction distribution, thereby reducing the atherogenic lipid profile, thus providing potential clinical benefit in sitosterolemia beyond TC and PS reduction.


While much investment has gone into developing interprofessional education (IPE) curriculum for healthcare professional students, many of these efforts have focused on classroom rather than clinical environments. Implementing robust IPE experiences into clinical training is often complicated by obstacles such as differing rotating schedules and differing curricular requirements. The Combined Medical-Physician Assistant Student Rural Rotation (Med-PARR) at the Oregon Health and Science University takes a practical approach to these challenges. Med-PARR students participate in focused IPE activities that overlay, or ‘float’, on top of each trainee’s profession-specific curricular requirements. Through critical reflection, goal setting, and a community-based project, students get the opportunity to critically reflect on their interprofessional roles while participating in their rural clinical settings. The practical approach of the Med-PARR can serve as a model for other institutions seeking to solve similar logistical issues in their own rural and community clinical IPE implementation efforts.

With its ease of availability during adolescence, sweetened ethanol ('alcopops') is consumed within many contexts. We asked here whether genetically based differences in social motivation are associated with how the adolescent social environment impacts voluntary ethanol intake. Mice with previously described differences in sociability (BALB/c, C57BL/6J, FVB/NJ and MSM/MsJ strains) were weaned into isolation or same-sex pairs (postnatal day, PD, 21), and then given continuous access to two fluids on PDs 34–45: one containing water and the other containing an ascending series of saccharin-sweetened ethanol (3–6–10%). Prior to the introduction of ethanol (PDs 30–33), increased water and food intake was detected in some of the isolation-reared groups, and controls indicated that isolated mice also consumed more 'saccharin-only' solution. Voluntary drinking of 'ethanol-only' was also higher in a subset of the isolated groups on PDs 46–49. However, sweetened ethanol intake was increased in all isolated strain × sex combinations irrespective of genotype. Surprisingly, blood ethanol concentration (BEC) was not different between these isolate and socially housed groups 4 h into the dark phase. Using lickometer-based measures of intake in FVB mice, we identified that a predominance of increased drinking during isolation transpired outside of the typical circadian consumption peak, occurring ≈8.5 h into the dark phase, with an associated difference in BEC. These findings collectively indicate that isolate housing leads to increased consumption of rewarding substances in adolescent mice independent of their genotype, and that for ethanol this may be because of when individuals drink during the circadian cycle. © 2016 John Wiley & Sons Ltd and International Behavioural and Neural Genetics Society


We investigated how subjects with cerebellar ataxia (CA) adapt their postural stability and alignment to a slow and small tilt of the support surface allowing for online postural corrections. Eight subjects with CA and eight age- and gender-matched healthy control subjects participated in the study. Subjects stood eyes closed for 1 min after which the support surface was tilted 5 degrees toes-up at a ramp velocity of 1 degrees /s. The toes-up position was held for 2.5 min after which the surface rotated back down to level with identical tilt characteristics. As reflected by the large number of falls, subjects with CA had marked difficulty adapting their posture to the up-moving incline in contrast to control subjects. Subjects with CA who lost their balance had faster trunk velocity and excessive backward trunk reorientation beginning within the first second after onset of the tilting surface. In contrast, the down-moving tilt to level did not result in instability in CA subjects. These results suggest that instability and falls associated with CA derive from an inability to maintain trunk orientation to vertical while standing on a slow-moving or unstable surface. This study underscores the importance of the cerebellum in the online sensory control of the upper body orientation during small amplitude and slow velocity movements of the support surface.


Rationale: Primary care providers (PCPs) frequently encounter sleep complaints, especially in regions with limited specialty care access. Objectives: The U.S. Department of Veterans Affairs Extension for Community Healthcare Outcomes (VA-ECHO) program (based on Project ECHO) has successfully provided rural PCP education in subspecialty areas, including hepatitis C. We describe the feasibility of an ECHO program for sleep medicine. Methods: ECHO creates a virtual learning community through video-teleconferencing, combining didactics with individualized clinical care review. We invited multidisciplinary providers to attend up to 10 stand-alone, 1-hour sessions. Invitees completed a needs assessment, which guided curriculum
development. After program completion, we examined participant characteristics and self-reported changes in practice and comfort with managing sleep complaints. We surveyed participation barriers among invitees with low/no attendance. Measurements and Main Results: Of the 39 program participants, 38% worked in rural healthcare. Participants included nurse practitioners (26%), registered nurses (21%), and physicians (15%). Seventeen (44%) completed the summative program evaluation. Respondents anticipated practice change from the program, especially in patient education about sleep disorders (93% of respondents). Respondents reported improved comfort managing sleep complaints, especially sleep-disordered breathing, insomnia, and sleep in post-traumatic stress disorder (80% of respondents each). A follow-up survey of program invitees who attended zero to two sessions reported scheduled conflicts (62%) and lack of protected time (52%) as major participation barriers. Conclusions: Participants in a pilot sleep medicine VA-ECHO program report practice change and increased comfort managing common sleep complaints. Future work is needed to identify objective measures of return on investment and address participation barriers. © Copyright 2017 by the American Thoracic Society.


BACKGROUND CONTEXT: Adult spinal deformity (ASD) represents a constellation of complex mal-alignments affecting the spinal column. Corrective surgical procedures aimed at improving ASD can be equally challenging, and commonly require multiple index procedures and potential revisions prior to definitive management. There is a paucity of data comparing the outcomes of same-day (simultaneous) and two-day (staged) procedures for long spinal-fusions for ASD. Utilizing a large patient cohort with surgeon and patient-reported outcomes will be particularly useful in determining the utility and effect of staging long spine fusions for ASD. PURPOSE: Compare intra-operative, peri-operative, and two-year outcomes of staged and simultaneous procedures correcting ASD. STUDY DESIGN/SETTING: Retrospective analysis of a prospective multi-center database. PATIENT SAMPLE: 142 patients (71 Staged, 71 Simultaneous). OUTCOME MEASURES: Primary: intra- and peri-op (6 wk) complication rates. Secondary: 2 year thoracolumbar and spine-pelvic radiographic parameters, 2 year Health Related Quality of Life changes (Oswestry Disability Index and SF-36), and 2 year complication rates METHODS: Inclusion criteria included ASD patients >/=18yrs with 6-wk and 2 year follow-up. Propensity score matching identified similar patients undergoing staged (STA) or simultaneous (SIM) long spine fusions based on Surgical Invasiveness, Pelvic Tilt, and SVA. Complications, HRQLs (SRS22r, SF-36, ODI), and patient characteristics were compared across and within treatment groups at follow-up with ANOVA and paired t-tests at 3 surgical stages: intra-op, peri-op (6wk), and post-op (>6wk). RESULTS: 142 patients were included (71 STA, 71 SIM). Matching staged and simultaneous groups based on degree of deformity and surgical invasiveness created two groups similar in overall correction of the surgery. STA patients underwent more ALIF and LLIF interbody procedures while SIM patients had longer fusions. Charlson Comorbidity Index and revision status were similar between groups (p>0.05). There were significantly more complications causing reoperation in STA procedures (STA: 47% SIM: 8%, p=0.021). STA had a greater number of peri-op complications requiring a return to the OR (STA: 9.9% SIM: 1.4% p=0.029). There was no difference in intra-op complications, mortality, or peri-op infection or wound complications (p>0.05). At 2 year follow-up, incidence of revision surgery was higher in STA (STA: 21.1% SIM: 8.5%, p=0.033). CONCLUSION: Staged spinal fusions which add ALIFs and LLIFs to the procedure, compared to similar-correction simultaneous procedures, result in similar intra-operative complication incidence, but significantly higher rates of peri- and post-op complications leading to revision. Functional outcomes, radiographic parameters, and mortality were similar. This will aid surgeons in their determination of optimal treatment for such complex procedures.


The surgical critically ill patient is subject to a variable and complex metabolic response, which has detrimental effects on immunity, wound healing, and preservation of lean body muscle. The concept of nutrition support has
evolved into nutrition therapy, whereby the primary objectives are to prevent oxidative cell injury, modulate the immune response, and attenuate the metabolic response. This review outlines the metabolic response to critical illness, describes nutritional risk; reviews the evidence for the role, dose, and timing of enteral and parenteral nutrition, and reviews the evidence for immunonutrition in the surgical intensive care unit. © 2017 Elsevier Inc.


Pump thrombosis is a dire sequela after left ventricular assist device (LVAD) implantation. Treatment comprises antiplatelet agents, anticoagulants, thrombolytic agents, and pump exchange. Although pump exchange is the definitive therapy, it is also the most invasive, often exposing patients to the risks of repeat sternotomy and cardiopulmonary bypass. In some cases, patients experience left ventricular recovery after LVAD implantation. The optimal strategy surrounding the management of LVADS in patients who have experienced ventricular recovery is unknown; techniques range from total system explantation to partial pump resection. Here, we describe a novel means of LVAD deactivation in a 65-year-old man with recurrent pump thrombosis, via percutaneous outflow graft closure in the cardiac catheterization laboratory. We also review the existing literature on surgical and percutaneous LVAD deactivation techniques. © 2017 by the Texas Heart Institute, Houston.


Liver disease is a common sequela of heart failure and can range from mild reversible liver injury to hepatic fibrosis and, in its most severe form, cardiac cirrhosis. Hepatic fibrosis and cirrhosis due to chronic heart failure have important implications for prognosis, medication management, mechanical circulatory support, and heart transplantation. This article reviews the current understanding of liver disease in heart failure and provides a framework for approaching liver disease in the advanced heart failure population.


HIV testing is an essential part of treatment and prevention. Using population-based data from 1664 adults across eight villages in rural Uganda, we assessed individuals’ perception of the norm for HIV testing uptake in their village and compared it to the actual uptake norm. In addition, we examined how perception of the norm was associated with personal testing while adjusting for other factors. Although the majority of people had been tested for HIV across all villages, slightly more than half of men and women erroneously thought that the majority in their village had never been tested. They underestimated the prevalence of HIV testing uptake by 42 percentage points (s.d. = 17 percentage points), on average. Among men, perceiving that HIV testing was not normative was associated with never testing for HIV (AOR = 2.6; 95% CI 1.7–4.0, p < 0.001). Results suggest an opportunity for interventions to emphasize the commonness of HIV testing uptake. © 2017 Springer Science+Business Media New York

Rare and low frequency variants are not well covered in most germline genotyping arrays and are understudied in relation to epithelial ovarian cancer (EOC) risk. To address this gap, we used genotyping arrays targeting rarer protein-coding variation in 8,165 EOC cases and 11,619 controls from the international Ovarian Cancer Association Consortium (OCAC). Pooled association analyses were conducted at the variant and gene level for 98,543 variants directly genotyped through two exome genotyping projects. Only common variants that represent or are in strong linkage disequilibrium (LD) with previously identified signals at established loci reached traditional thresholds for exome-wide significance (P < 5.0 × 10^-7). One of the most significant signals (Pal histologies = 1.01 × 10^-13; Pserous = 3.54 × 10^-14) occurred at 3q25.31 for rs62273959, an missense variant mapping to the LEKR1 gene that is in LD (r^2=0.90) with a previously identified ‘best hit’ (rs7651446) mapping to an intron of TIPARP. Suggestive associations (5.0 × 10^-5 ≥ P ≥ 5.0 × 10^-7) were detected for rare and low-frequency variants at 16 novel loci. Four rare missense variants were identified (ACTBL2 rs73757391 (S11.2), BTD rs200337373 (3p25.1), KRT13 rs150321809 (17q21.2) and MC2R rs104894658 (18p11.21)), but only MC2R rs104894668 had a large effect size (OR=9.66). Genes most strongly associated with EOC risk included ACTBL2 (PAML=3.23 × 10^-5; PSKAT-o=9.23 × 10^-4) and KRT13 (PAML=1.67 × 10^-4; PSKAT-o=1.07 × 10^-5), reaffirming variant-level analysis. In summary, this large study identified several rare and low-frequency variants and genes that may contribute to EOC susceptibility, albeit with possible small effects. Future studies that integrate epidemiology, sequencing, and functional assays are needed to further unravel the unexplained heritability and biology of this disease. © The Author 2016. Published by Oxford University Press. All rights reserved.


People with Parkinson's disease exhibit debilitating gait impairments, including gait slowness, increased step variability, and poor postural control. A widespread supraspinal locomotor network including the cortex, cerebellum, basal ganglia, and brain stem contributes to the control of human locomotion, and altered activity of these structures underlies gait dysfunction due to Parkinson's disease.


**Background:** Bowel dysfunction, including both slow transit constipation and defecatory dysfunction, is a frequent and often troubling nonmotor manifestation of Parkinson's disease (PD). A variety of agents are employed for the treatment of constipation in PD, but dissatisfaction with available treatment approaches is common. Relamorelin is a synthetic ghrelin agonist that has demonstrated prokinetic properties within the gastrointestinal tract. Methods: We carried out a multi-center, randomized, double-blind, placebo-controlled study of relamorelin in patients with PD experiencing chronic, inadequately controlled constipation. Results: Only 18 of an intended 56 subjects completed the trial, in part because of the unexpected occurrence of multiple partially complete bowel movements in constipated PD patients, which made many subjects ineligible for participation. Conclusions: Although recruitment goals were not met, which precluded demonstration of any potential beneficial effect of relamorelin, unique and important insights with regard to the nature of constipation in PD were recognized, which hopefully will lead to more effective clinical trials in the future. It is clear that what PD patients understand as constipation may be more complex than previously realized and does not appear to be characterized by decreased stool frequency alone. © 2017 Elsevier Ltd.

To identify common alleles associated with different histotypes of epithelial ovarian cancer (EOC), we pooled data from multiple genome-wide genotyping projects totaling 25,509 EOC cases and 40,941 controls. We identified nine new susceptibility loci for different EOC histotypes: six for serous EOC histotypes (3q28, 4q32.3, 8q21.11, 10q24.33, 18q11.2 and 22q12.1), two for mucinous EOC (3q22.3 and 9q31.1) and one for endometrioid EOC (5q12.3). We then performed meta-analysis on the results for high-grade serous ovarian cancer with the results from analysis of 31,448 BRCA1 and BRCA2 mutation carriers, including 3,887 mutation carriers with EOC. This identified three additional susceptibility loci at 2q13, 8q24.1 and 12q24.31. Integrated analyses of genes and regulatory biofeatures at each locus predicted candidate susceptibility genes, including OBFC1, a new candidate susceptibility gene for low-grade and borderline serous EOC.


Conflict of Interest Statement The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Funding This publication was supported by the Cooperative Agreement, Number 5 U17 CE 001994-05, funded by the Centers for Disease Control and Prevention. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention or the Department of Health and Human Services. © 2016 Phelan, Aerts, Dowler, Eckstrom and Casey.


The lack of high-throughput methods to analyze the adipose tissue protein composition limits our understanding of the protein networks responsible for age and diet related metabolic response. We have developed an approach using multiple-dimension liquid chromatography tandem mass spectrometry and extended multiplexing (24 biological samples) with TMT labeling to analyze proteomes of epididymal adipose tissues isolated from mice fed either low or high fat diet for a short or a long-term, and from mice that aged on low vs. high fat diets. The peripheral metabolic health (as measured by body weight, adiposity, plasma fasting glucose, insulin, triglycerides, total cholesterol levels, and glucose and insulin tolerance tests) deteriorated with diet and advancing age, with long-term high fat diet exposure being the worst. In response to short-term high fat diet, 43 proteins representing lipid metabolism (e.g., AACS, ACOX1, ACLY) and red-ox pathways (e.g., CPD2, CYP2E, SOD3) were significantly altered (FDR < 10%). Long-term high fat diet significantly altered 55 proteins associated with immune response (e.g., IGBP2, IFIT3, LGALS1) and rennin angiotensin system (e.g. ENPEP, CMA1, CPA3, ANPEP). Age-related changes on low fat diet significantly altered only 18 proteins representing mainly urea cycle (e.g., OTC, ARG1, CPS1), and amino acid biosynthesis (e.g., GMT, AKR1C6). Surprisingly, high fat diet driven age-related changes culminated with alterations in 155 proteins involving primarily the urea cycle (e.g., ARG1, CPS1), immune response/complement activation (e.g., C3, C4b, C8, C9, CFb, CFH, FGA), extracellular remodeling (e.g., EFEMP1, FBNI, FBN2, LTBP4, FERMT2, ECM1, EMILIN2, ITIH3) and apoptosis (e.g., YAP1, HIP1, NDRG1, PRKCD, MUL1) pathways. Using our adipose tissue tailored...
approach we have identified both age-related and high fat diet specific proteomic signatures highlighting a
pronounced involvement of arginine metabolism in response to advancing age, and branched chain amino
acid metabolism in early response to high fat feeding. Data are available via ProteomeXchange with
identifier PXD005953.

Method to Quantify in Parallel Tau and Amyloid β 1-42 in CSF for the Diagnosis of Alzheimer’s Disease. Journal of Proteome Research, 16(3), 1228-1238. doi:10.1021/acs.jproteome.6b00829

Alzheimer’s disease (AD), the most common form of dementia, afflicts about 50 million people worldwide. Currently,
AD diagnosis is primarily based on psychological evaluation and can only be confirmed post-mortem. Reliable and objective biomarkers for prognosis and diagnosis have been sought for years. Together, tau and amyloid β 1-42 (Aβ42) in cerebrospinal fluid (CSF) have been shown to provide good diagnostic sensitivity and specificity. Additionally, phosphorylated forms of tau, such as tau pS181, have also shown promising results. However, the measurement of such markers currently relies on antibody-based immunoassays that have shown variability, leading to discrepant results across laboratories. To date, mass spectrometry methods developed to evaluate CSF tau and Aβ42 are not compatible. We present in this article the development of a mass-spectrometry-based method of quantification for CSF tau and Aβ42 in parallel. The absolute concentrations of tau and Aβ42 we measured are on average 50 ng/mL (7-130 ng/mL) and 7.1 ng/mL (3-13 ng/mL), respectively. Analyses of CSF tau and Aβ42, in a cohort of patients with AD, mild cognitive impairment, and healthy controls (30 subjects), provide significant group differences evaluated with ROC curves (AUC(control-AD) and AUC(control-MCI) = 1, AUC(MCI-AD) = 0.76), with at least equivalent diagnostic utility to immunoassay measurements in the same sample set. Finally, a significant and negative correlation was found between the tau and Aβ peptides ratio and the disease severity. © 2017 American Chemical Society.


Globally, annual spending on anticancer drugs is around US$100 billion, and is predicted to rise to $150 billion by
2020. In the USA, a novel anticancer drug routinely costs more than $100,000 per year of treatment. When
adjusted for per capita spending power, however, drugs are most unaffordable in economically developing
nations, such as India and China. Not only are launch prices high and rising, but individual drug prices are
often escalated during exclusivity periods. High drug prices harm patients — often directly through
increased out-of-pocket expenses, which reduce levels of patient compliance and lead to unfavourable
outcomes — and harms society — by imposing cumulative price burdens that are unsustainable. Moreover,
high drug prices are not readily explained by rational factors, including the extent of benefit patients are
likely to derive, the novelty of the agents, or spending on research and development. Herein, we summarize
the available empirical evidence on the costs of anticancer drugs, probe the origins and implications of these
high costs, and discuss proposed solutions. © 2017 Nature Publishing Group, a division of Macmillan
Publishers Limited. All Rights Reserved.

cost of care for emergency department syncope patients: Comparison of three models. Western Journal
of Emergency Medicine, 18(2), 253-257. doi:10.5811/westjem.2016.10.31171
Introduction: We sought to compare three hospital cost-estimation models for patients undergoing evaluation for unexplained syncope using hospital cost data. Developing such a model would allow researchers to assess the value of novel clinical algorithms for syncope management. Methods: We collected complete health services data, including disposition, testing, and length of stay (LOS), on 67 adult patients (age 60 years and older) who presented to the emergency department (ED) with syncope at a single hospital. Patients were excluded if a serious medical condition was identified. We created three hospital cost-estimation models to estimate facility costs: V1, unadjusted Medicare payments for observation and/or hospital admission; V2: modified Medicare payment, prorated by LOS in calendar days; and V3: modified Medicare payment, prorated by LOS in hours. Total hospital costs included unadjusted Medicare payments for diagnostic testing and estimated facility costs. We plotted these estimates against actual cost data from the hospital finance department, and performed correlation and regression analyses. Results: Of the three models, V3 consistently outperformed the others with regard to correlation and goodness of fit. The Pearson correlation coefficient for V3 was 0.88 (95% confidence interval [CI] 0.81, 0.92) with an R-square value of 0.77 and a linear regression coefficient of 0.87 (95% CI 0.76, 0.99). Conclusion: Using basic health services data, it is possible to accurately estimate hospital costs for older adults undergoing a hospital-based evaluation for unexplained syncope. This methodology could help assess the potential economic impact of implementing novel clinical algorithms for ED syncope. © 2017 Probst et al.


Heart failure affects millions of people throughout the world and is a growing epidemic with a significant impact on the economics and systems of care delivery. The goal of therapy in advanced heart failure is to improve quality of life and prolong survival. Standard medical therapies may require tailoring as advanced therapies are considered in the context of patient and caregiver goals. The aim of this review is to summarize concepts for tailored medical therapy and monitoring in advanced heart failure and discuss the importance of tailoring systems of care and shared decision making in advanced heart failure.


Coagulation factor (F)XI has been described as a component of the early phase of the contact pathway of blood coagulation, acting downstream of factor XII. However, patients deficient in upstream members of the contact pathway, including FXII and prekallikrein, do not exhibit bleeding complications, while FXI-deficient patients sometimes experience mild bleeding, suggesting FXI plays a role in hemostasis independent of the contact pathway. Further complicating the picture, bleeding risk in FXI-deficient patients is difficult to predict because bleeding symptoms have not been found to correlate with FXI antigen levels or activity. However, recent studies have emerged to expand our understanding of FXI, demonstrating that activated FXI is able to activate coagulation factors FX, FV, and FVIII, and inhibit the anti-coagulant tissue factor pathway inhibitor (TFPI). Understanding these activities of FXI may help to better diagnose which FXI-deficient patients are at risk for bleeding. In contrast to its mild hemostatic activities, FXI is known to play a significant role in thrombosis, as it is a demonstrated independent risk factor for deep vein thrombosis, ischemic stroke, and myocardial infarction. Recent translational approaches have begun testing FXI as an antithrombotic, with one promising clinical study showing that an anti-sense oligonucleotide against FXI prevented venous thrombosis in elective knee surgery. A better understanding of the varied and complex role of FXI in both thrombosis and hemostasis will help to allow better prediction of bleeding risk in FXI-deficient patients and also informing the development of targeted agents to inhibit the thrombotic activities of FXI while preserving hemostasis.

Introduction Long-term immunosuppressants form an integral part of therapy for post-transplantation patients. Immunosuppressants may also have an anticoagulant effect, and little is known about their effects on bleeding risk after adenotonsillectomy. Our objective was to investigate whether there is an increased observed rate of post-tonsillectomy hemorrhage in a population of pediatric patients on long-term immunosuppressants after solid organ transplantation, compared to healthy controls. Methods This was a retrospective chart review of pediatric patients with a history of renal or heart transplant undergoing adenotonsillectomy at our institution between 2000 and 2014. All patients underwent tonsillectomy with monopolar electrocautery. Retrieved data included perioperative medications, occurrence of post-operative bleeding and associated treatment. For comparison, we obtained a population of age-matched controls with no history of immunosuppression who underwent the same procedure. Results A total of 34 patients meeting criteria were identified, of which 3 (8.82%) suffered a postoperative bleed. Forty-seven controls were obtained, with a total of 2 (4.26%) postoperative hemorrhages (p = 0.65). Two of the post-transplantation patients who bled postoperatively required cauterization in the operating room. None of the controls required surgical treatment. The incidences of postoperative bleeding requiring surgical treatment were 5.88% and 0%, respectively (p = 0.17). Conclusion We failed to demonstrate an increased risk of bleeding after undergoing adenotonsillectomy in our cohort of post-transplantation pediatric patients on chronic immunosuppression. Future research, likely requiring a multi-institutional effort, could stratify by immunosuppressive agent to elucidate bleeding risk with specific medications. © 2017


Exome sequencing from a patient with neurological and developmental symptoms revealed two mutations in separate genes. One was a homozygous transition mutation that results in an in-frame, premature translational stop codon in the ZNF135 gene predicted to encode a transcriptional repressor. Another mutation was heterozygous, a single nucleotide duplication in the KCNN2 gene that encodes a Ca-activated K channel, SK2, and leads to a translational frame shift and a premature stop codon. Heterologous expression studies, brain slice recordings, and coordination tests from a transgenic mouse line carrying the SK2 mutation suggest that it does not contribute to the patient’s symptoms. ZNF135 is expressed in human brain and it is likely that the homozygous mutation underlies the human phenotype. This is an open access article distributed under the Creative Commons Attribution License 4.0 (CCBY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. http://creativecommons.org/licenses/by/4.0/ © 2017 Wolters Kluwer Health | Lippincott Williams & Wilkins


Background Torso hemorrhage constitutes a leading cause of battlefield mortality. The Abdominal Aortic and Junctional Tourniquet (AAJT) uses a pneumatic bladder to compress the aorta reducing pelvic and lower extremity perfusion; however, concern exists over the risk of caval compression exacerbating hypotension after application. Methods Male swine (70–90 kg) were randomized into four groups of 10: presence or
absence of hemorrhage and AAJT placement. After a 40% hemorrhage, a 15-min period of hypovolemia was observed before the AAJT application. All animals received two 500 mL boluses of Hextend separated by 30 min. Cardiovascular, pulmonary, and oxygenation values were compared among groups. Results The AAJT was effective in reducing blood flow to the femoral arteries in both hemorrhaged and nonhemorrhaged animals (P < 0.001 for both groups). Hemorrhage resulted in significant decrease in mean arterial pressure compared with sham controls (23.5 ± 2.4 versus 61.6 ± 7.8 mm Hg, respectively, P < 0.001). AAJT application, compared with untreated controls, resulted in a significant increase in mean arterial pressure and systemic vascular resistance but not in cardiac output, oxygenation, and central venous pressure. Furthermore, no indication of overresuscitation injury was present as evidenced by pulmonary artery pressure and pulmonary histology. Conclusions AAJT application in an animal model of severe shock results in a favorable hemodynamic profile because of afterload support. The present study did not demonstrate any adverse consequences because of caval compression, bowel injury, or pulmonary dysfunction. In addition, there does not appear to be any particular intravenous fluid economy achieved by AAJT application. © 2017 Elsevier Inc.


Cleavage of the Amyloid Precursor Protein (APP) generates amyloid peptides that accumulate in Alzheimer Disease (AD), but APP is also upregulated by developing and injured neurons, suggesting that it regulates neuronal motility. APP can also function as a G protein-coupled receptor that signals via the heterotrimeric G protein Galphao, but evidence for APP-Galphao signaling in vivo has been lacking. Using Manduca as a model system, we showed that insect APP (APPL) regulates neuronal migration in a Galphao-dependent manner. Recently, we also demonstrated that Manduca Contactin (expressed by glial cells) induces APPL-Galphao retraction responses in migratory neurons, consistent with evidence that mammalian Contactins also interact with APP family members. Preliminary studies using cultured hippocampal neurons suggest that APP-Galphao signaling can similarly regulate growth cone motility. Whether Contactins (or other APP ligands) induce this response within the developing nervous system, and how this pathway is disrupted in AD, remains to be explored.


Objective: Patients with limited health literacy (LHL) and limited English proficiency (LEP) experience suboptimal communication and health outcomes. Electronic health record implementation in safety net clinics may affect communication with LHL and LEP patients. We investigated the associations between safety net clinician computer use and patient-provider communication for patients with LEP and LHL. Materials and Methods: We video-recorded encounters at 5 academically affiliated US public hospital clinics between English- and Spanish-speaking patients with chronic conditions and their primary and specialty care clinicians. We analyzed changes in communication behaviors (coded with the Roter Interaction Analysis System) with each additional point on a clinician computer use score, controlling for clinician type and visit length and stratified by English proficiency and health literacy status. Results: Greater clinician computer use was associated with more biomedical statements (+12.4, P=.03) and less positive affect (-0.6, P<.01) from LEP/LHL patients. In visits with patients with adequate English proficiency/health literacy, greater clinician computer use was associated with less positive patient affect (-0.9, P<.01), fewer clinician psychosocial statements (-3.5, P<.05), greater clinician verbal dominance (+0.09, P<.01), and lower ratings on quality of care and communication. Conclusion: Higher clinician computer use was associated with more biomedical focus with LEP/LHL patients, and clinician verbal dominance and lower ratings with patients with adequate English proficiency and health literacy. Discussion: Implementation research should explore interventions to enhance relationship-centered communication for diverse patient populations in the computer era. © The Author 2016.
A young girl, age 8.5 years, presented with profound hypercholesterolemia and early xanthomatosis, suggesting homozygous familial (or type II) hypercholesterolemia. The patient’s low density lipoprotein (LDL) receptor function and parental lipoprotein profiles were determined to be normal, prompting revision of the initial diagnosis to pseudohomozygous familial hypercholesterolemia. When she subsequently presented with giant platelets, the case was presented to colleagues on an electronic mailing list. It was recommended that plasma and sterol analysis be performed, which led to a diagnosis of sitosterolemia. The presentation of profound hypercholesterolemia in childhood that ultimately is not attributed as due to homozygous or compound heterozygous defects in the LDL receptor gene has been termed pseudohomozygous familial (or type II) hypercholesterolemia (PHT2HC). Patients diagnosed with PHT2HC subsequently confirmed to have sitosterolemia have been previously reported only rarely. The challenge of achieving accurate specific diagnosis and appropriate workup for these conditions in children is discussed in the context of this rare case and review of the historical literature concerning these conditions.

Objective To assess parents’ perceptions and use of time-out (TO) in contrast to empirical indications and examine the relationship between reported implementation procedures and perceived effectiveness. Methods We surveyed parents of preschool and school-age children (n = 401, aged 15 months to 10 years) at well-child visits with regard to their awareness, perception, and usage of TO. Parents were specifically surveyed regarding TO components that have been empirically evaluated or pertain directly to its underlying behavioral principles. Descriptive analyses, group comparisons, and correlational analyses were used to characterize responses and evaluate the relationship between TO administration variation and perceived effectiveness. Results Most parents (76.8%) reported using TO in response to misbehavior, but a large majority of these parents (84.9%) reported implementing TO in a manner counter to empirical evidence. Parents who endorsed TO as effective varied significantly from those who did not on key implementation components (eg, use of a single warning). Further, several reported implementation practices were correlated with perceived effectiveness and challenging child behavior. For example, requiring a child to be calm before ending TO was positively correlated with perceived effectiveness. Conclusions These results cement TO as a widely disseminated practice but cast doubt on the fidelity with which it is typically implemented. Better methods of educating parents on evidence-based discipline are needed. © 2016 Academic Pediatric Association
have been published with conflicting outcomes regarding pain and quality of life compared with nonsurgical management and sham procedures. Four RCTs with discordant results were published in 2009. MATERIALS AND METHODS: The Nationwide Inpatient Sample provided longitudinal, retrospective data on United States’ inpatients between 2005 and 2011. Inclusion was determined by a principal or secondary International Classification of Diseases, Ninth Revision, Clinical Modification code of 81.65 (percutaneous vertebroplasty) or 81.66 (percutaneous vertebral augmentation; “kyphoplasty”). No diagnoses were excluded. Years were stratified as “pre” (2005-2008) and “post” (2010-2011) in relation to the 4 RCTs published in 2009. Patient, hospital, and admission characteristics were compared using Pearson chi test. RESULTS: The estimated annual inpatient procedures performed decreased from 54,833 to 39,832 in the pre and post periods, respectively. The procedural rate for fractures decreased from 20.1% to 14.7% (P<0.0001). Patient and hospital demographics did not change considerably between the time periods. In the post period, weekend admissions increased (34.2% vs. 12.4%, P<0.0001), elective admissions decreased (21.4% vs. 40.0%, P<0.0001), routine discharge decreased (33.0% vs. 52.1%, P<0.0001), and encounters with >/=3 Elixhauser comorbidities increased (54.5% vs. 39.1%, P<0.0001). CONCLUSIONS: The absolute rate of inpatient vertebroplasty and kyphoplasty procedures for fractures decreased 5% in the period (2010-2011) following the publication of 4 RCTs in 2009. The proportion of elective admissions and routine discharges decreased, possibly indicating a population with greater disease severity. Although our analysis cannot demonstrate a cause-and-effect relationship, the decreased inpatient volume and procedural rates surrounding the publication of sentinel negative RCTs is clearly observed.


Developmental differences regarding decision making are often reported in the absence of emotional stimuli and without context, failing to explain why some individuals are more likely to have a greater inclination toward risk. The current study (N = 212; 10–25y) examined the influence of emotional context on underlying functional brain connectivity over development and its impact on risk preference. Using functional imaging data in a neutral brain-state we first identify the “brain age” of a given individual then validate it with an independent measure of cortical thickness. We then show, on average, that “brain age” across the group during the teen years has the propensity to look younger in emotional contexts. Further, we show this phenotype (i.e. a younger brain age in emotional contexts) relates to a group mean difference in risk perception – a pattern exemplified greatest in young-adults (ages 18–21). The results are suggestive of a specified functional brain phenotype that relates to being at “risk to be risky.” © 2017 The Authors


Background: Ongoing research is focusing on the identification of those individuals with mild cognitive impairment (MCI) who are most likely to convert to Alzheimer’s disease (AD). We investigated whether recognition memory tasks in combination with delayed recall measure of episodic memory and CSF biomarkers can predict MCI to AD conversion at 24-month follow-up. Methods: A total of 397 amnestic-MCI subjects from Alzheimer’s disease Neuroimaging Initiative were included. Logistic regression modeling was done to assess the predictive value of all RAVLT measures, risk factors such as age, sex, education, APOE genotype, and CSF biomarkers for progression to AD. Estimating adjusted odds ratios was used to determine which variables
would produce an optimal predictive model, and whether adding tests of interaction between the RAVLT Delayed Recall and recognition measures (traditional score and d-prime) would improve prediction of the conversion from a-MCI to AD. Results: 112 (28.2%) subjects developed dementia and 285 (71.8%) subjects did not. Of the all included variables, CSF Abeta1-42 levels, RAVLT Delayed Recall, and the combination of RAVLT Delayed Recall and d-prime were predictive of progression to AD (chi2 = 38.23, df = 14, p < 0.001). Conclusions: The combination of RAVLT Delayed Recall and d-prime measures may be predictor of conversion from MCI to AD in the ADNI cohort, especially in combination with amyloid biomarkers. A predictive model to help identify individuals at-risk for dementia should include not only traditional episodic memory measures (delayed recall or recognition), but also additional variables (d-prime) that allow the homogenization of the assessment procedures in the diagnosis of MCI.


OBJECTIVES/HYPOTHESIS: Children with bilateral true vocal fold immobility (BTVFI) may present with significant airway distress necessitating tracheostomy. The objective of this study was to review our preliminary experience with the anterior-posterior cricoid split (APCS), an endoscopic intervention used as an alternative to tracheostomy in children with BTVFI. STUDY DESIGN: Multicenter review. METHODS: A review of patients undergoing endoscopic APCS for BTVFI at four institutions was performed. Patients were evaluated for the ability to ventilate without the requirement for tracheostomy or reintubation. Additional data extracted included the duration of intubation following APCS, the requirement for additional procedures, and demographics. Surgical success was defined as the ability to avoid tracheostomy and to cap or decannulate without respiratory symptoms if a tracheostomy was present prior to APCS. RESULTS: Nineteen APCS procedures were performed between October 2010 and June 2016. There were 12 male patients, the mean age at APCS was 4.7 months. BTVFI was primarily idiopathic (58%) and associated with other comorbidities (74%). All patients were candidates for tracheostomy prior to APCS. Fourteen patients (74%) were considered surgical successes. Of the unsuccessful patients, three (66%) required tracheostomy following APCS, and one was treated with a posterior cartilage graft. There was one nonsurgical mortality greater than 2 months after APCS and thought to be unrelated to the airway. CONCLUSIONS: Endoscopic APCS appears to be a safe and effective intervention for pediatric BTVFI. Under the correct circumstances, this can be performed as a single procedure, obviating tracheostomy. Further study is warranted. LEVEL OF EVIDENCE: 4 Laryngoscope, 2017.


BACKGROUND Interleukin-31 may play a role in the pathobiologic mechanism of atopic dermatitis and pruritus. We wanted to assess the efficacy and safety of nemolizumab (CIM331), a humanized antibody against interleukin-31 receptor A, in the treatment of atopic dermatitis. METHODS In this phase 2, randomized, double-blind, placebo-controlled, 12-week trial, we assigned adults with moderate-to-severe atopic dermatitis that was inadequately controlled by topical treatments to receive subcutaneous nemolizumab (at a dose of 0.1 mg, 0.5 mg, or 2.0 mg per kilogram of body weight) or placebo every 4 weeks or an exploratory dose of 2.0 mg of nemolizumab per kilogram every 8 weeks. The primary end point was the percentage improvement from baseline in the score on the pruritus visual-analogue scale (on which a negative change indicates improvement) at week 12. Secondary end points included changes in the score on the Eczema Area and Severity Index (EASI, on which a negative change indicates improvement), and body-surface area of atopic dermatitis. RESULTS Of 264 patients who underwent randomization, 216 (82%) completed the study. At week 12, among the patients who received nemolizumab every 4 weeks, changes on the pruritus visual-analogue scale were -43.7% in the 0.1-mg group, -59.8% in the 0.5-mg group, and -63.1% in the 2.0-mg group, versus -20.9% in the placebo group (P<0.01 for all comparisons). Changes on the EASI were -23.0%, -42.3%, and -40.9%, respectively, in the nemolizumab groups, versus -26.6% in the placebo group. Respective
changes in body-surface area affected by atopic dermatitis were -7.5%, -20.0%, and -19.4% with nemolizumab, versus -15.7% with placebo. Among the patients receiving nemolizumab every 4 weeks, treatment discontinuations occurred in 9 of 53 patients (17%) in the 0.1-mg group, in 9 of 54 (17%) in the 0.5-mg group, and in 7 of 52 (13%) in the 2.0-mg group, versus in 9 of 53 (17%) in the placebo group.

CONCLUSIONS In this phase 2 trial, nemolizumab at all monthly doses significantly improved pruritus in patients with moderate-to-severe atopic dermatitis, which showed the efficacy of targeting interleukin-31 receptor A. The limited size and length of the trial preclude conclusions regarding adverse events. Copyright © 2017 Massachusetts Medical Society.


PURPOSE. Prospective treatments for age-related macular degeneration and inherited retinal degenerations are commonly evaluated in the Royal College of Surgeons (RCS) rat before translation into clinical application. Historically, retinal thickness obtained through postmortem anatomic assessments has been a key outcome measure; however, utility of this measurement is limited because it precludes the ability to perform longitudinal studies. To overcome this limitation, the present study was designed to provide a baseline longitudinal quantification of retinal thickness in the RCS rat by using spectral-domain optical coherence tomography (SD-OCT).

METHODS. Horizontal and vertical linear SD-OCT scans centered on the optic nerve were captured from Long-Evans control rats at P30, P60, P90 and from RCS rats between P17 and P90. Total retina (TR), outer nuclear layer+ (ONL+), inner nuclear layer (INL), and retinal pigment epithelium (RPE) thicknesses were quantified. Histologic sections of RCS retina obtained from P21 to P60 were compared to SD-OCT images. RESULTS. In RCS rats, TR and ONL+ thickness decreased significantly as compared to Long-Evans controls. Changes in INL and RPE thickness were not significantly different between control and RCS retinas. From P30 to P90 a subretinal hyperreflective layer (HRL) was observed and quantified in RCS rats. After correlation with histology, the HRL was identified as disorganized outer segments and the location of accumulated debris.

CONCLUSIONS. Retinal layer thickness can be quantified longitudinally throughout the course of retinal degeneration in the RCS rat by using SD-OCT. Thickness measurements obtained with SD-OCT were consistent with previous anatomic thickness assessments. This study provides baseline data for future longitudinal assessment of therapeutic agents in the RCS rat. © 2017 The Authors.


Background. We investigated the reliability of combined DOG1 and mammaglobin immunohistochemistry compared with ETV6 fluorescence in situ hybridization (FISH) in the assessment of salivary tumors previously diagnosed as acinic cell carcinoma (ACC). Ultrastructural features of cases reclassified as mammary analogue secretory carcinoma (MASC) were assessed by transmission electron microscopy (TEM). Methods. Immunohistochemical (IHC) reactivity to DOG1 and mammaglobin was validated against FISH targeting the ETV6 gene in all 14 cases. Results. Three cases with papillary cystic histomorphology previously diagnosed as ACC were revised to MASC. TEM features of the ETV6 rearrangement-positive MASC cases showed large numbers of secretory granules with extrusion into the intercellular spaces, well-developed endoplasmic reticulum, lipid-laden vacuoles, well-formed microvilli, and large lining cystic spaces. Conclusions. Combined DOG1 and mammaglobin immunohistochemistry is comparable to ETV6-breakapart analysis for differentiating between papillary cystic variants of ACC and MASC. © SAGE Publications.


PURPOSE: To report a case of frosted branch angiitis in a patient with granulomatosis with polyangiitis. METHODS: Clinical case report. Imaging was obtained with pseudo-color scanning laser ophthalmoscope photographs, fluorescein angiography, spectral domain optical coherence tomography, and B-scan ultrasound. RESULTS: A 24-year-old woman with a clinical history of granulomatosis with polyangiitis who presented with acute vision loss was found to have frosted branch angiitis with concurrent posterior scleritis and orbital inflammation. These findings improved rapidly after initiation of high-dose intravenous solumedrol. CONCLUSION: This is a unique case of frosted branch angiitis associated with granulomatosis with polyangiitis. The authors are not aware of a previous report of this association. Although rare, retinal vasculitis should be recognized as a potential complication of granulomatosis with polyangiitis and can respond rapidly to prompt initiation of therapy.


Sleep-wake disturbances following traumatic brain injury (TBI) are increasingly recognized as a serious consequence following injury and as a barrier to recovery. Injury-induced sleep-wake disturbances can persist for years, often impairing quality of life. Recently, there has been a nearly exponential increase in the number of primary research articles published on the pathophysiology and mechanisms underlying sleep-wake disturbances after TBI, both in animal models and human subjects, including in the pediatric population. In this review, we summarize over two hundred articles on the topic, most of which were identified objectively using reproducible online search terms in PubMed. Although these studies differ in terms of methodology and detailed outcomes, overall, recent research describes a common phenotype of excessive daytime sleepiness, nighttime sleep fragmentation, insomnia, and EEG spectral changes after TBI. Given the heterogeneity of the human disease phenotype, rigorous translation of animal models to the human condition is critical to our understanding of the mechanisms and of the temporal course of sleep-wake disturbances after injury. Arguably, this is most effectively accomplished when animal and human studies are performed by the same or collaborating research programs. Given the number of symptoms associated with TBI that are intimately related to, or directly stem from sleep dysfunction, sleep-wake disorders represent an important area in which mechanistic-based therapies may substantially impact recovery after TBI.


With the aim to improve the efficacy of therapeutic vaccines that target self-antigens, we have developed a novel fusion protein vaccine on the basis of the C-terminal multimerizing end of the variable lymphocyte receptor B (VLRB), the Ig equivalent in jawless fishes. Recombinant vaccines were produced in Escherichia coli by fusing the VLRB sequence to 4 different cancer-associated target molecules. The anti-self-immune response
generated in mice that were vaccinated with VLRB vaccines was compared with the response in mice that received vaccines that contained bacterial thioredoxin (TRX), previously identified as an efficient carrier. The anti-self-Ab were analyzed with respect to titers, binding properties, and duration of response. VLRB-vaccinated mice displayed a 2- to 10-fold increase in anti-self-Ab titers and a substantial decrease in Abs against the foreign part of the fusion protein compared with the response in TRX-vaccinated mice (P < 0.01). VLRB-generated Ab response had duration similar to the corresponding TRX-generated Abs, but displayed a higher diversity in binding characteristics. Of importance, VLRB vaccines could sustain an immune response against several targets simultaneously. VLRB vaccines fulfill several key criteria for an efficient therapeutic vaccine that targets self-antigens as a result of its small size, its multimerizing capacity, and nonexposed foreign sequences in the fusion protein. © FASEB.


Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disease with an incidence of 1:5000. Recurrent, spontaneous epistaxis is the most common presenting symptom. Severity of epistaxis varies widely, from mild, self-limited nosebleeds to severe, life-threatening nasal hemorrhage. Treatment of HHT-related epistaxis presents a challenge to the otolaryngologist due to the recurrent, persistent nature of epistaxis often requiring multiple treatments. Treatment modalities range from conservative topical therapies to more aggressive surgical treatments.


KIT, PDGFRA, NF1 and SDH mutations are alternate initiating events, fostering hyperplasia in gastrointestinal stromal tumours (GISTs), and additional genetic alterations are required for progression to malignancy. The most frequent secondary alteration, demonstrated in approximately 70% of GISTs, is chromosome 14q deletion. Here we report hemizygous or homozygous inactivating mutations of the chromosome 14q MAX gene in 16 of 76 GISTs (21%). We find MAX mutations in 17% and 50% of sporadic and NF1-syndromic GISTs, respectively, and we find loss of MAX protein expression in 48% and 90% of sporadic and NF1-syndromic GISTs, respectively, and in three of eight micro-GISTs, which are early GISTs. MAX genomic inactivation is associated with p16 silencing in the absence of p16 coding sequence deletion and MAX induction restores p16 expression and inhibits GIST proliferation. Hence, MAX inactivation is a common event in GIST progression, fostering cell cycle activity in early GISTs.


PURPOSE: To distinguish between corneal ectasia and contact lens-related warpage by characteristic patterns on corneal topography and optical coherence tomography (OCT) epithelial thickness maps. SETTING: Casey Eye Institute, Portland, Oregon, USA. DESIGN: Prospective and retrospective case series. METHODS: Axial and mean power maps were obtained on corneal topography systems. Epithelial thickness maps were generated using RTVue OCT. A sector divider was applied to all maps. The locations of the minimum epithelial thickness, maximum epithelial thickness, maximum axial power, and maximum mean power were determined based on sector averages. Agreement was defined as the extremums occurring in the same or adjacent sectors. RESULTS: Twenty-one eyes with keratoconus, 6 eyes with forme fruste keratoconus (better eye of asymmetric keratoconus), and 15 eyes with contact lens-related warpage were identified. The keratoconus and forme fruste keratoconus eyes had coincident topographic steepening with epithelial thinning. The locations of minimum epithelial thickness and maximum axial power agreed in 90% of the keratoconic eyes,
while the minimum epithelial thickness and maximum mean power agreed in 95% of them. Conversely, the warpage eyes had coincident topographic steepening with epithelial thickening and normal pachymetry maps. The locations of maximum epithelial thickness and maximum axial power agreed in 93% of the warpage eyes, while the maximum epithelial thickness and maximum mean power agreed in all warpage eyes. CONCLUSION: Results show that epithelial thickness maps and corneal topographic maps are powerful synergistic tools in evaluating eyes with abnormal topography and can help differentiate between keratoconus and nonectatic conditions.


STUDY DESIGN:: Multicenter prospective pilot study. OBJECTIVE:: To evaluate if continuous physical activity monitoring by a personal electronic 3-dimensional accelerometer device is feasible and can provide objective data that correlates with patient-reported outcomes following spine surgery. SUMMARY OF BACKGROUND DATA:: Self-reported health-related quality-of-life (HRQOL) metrics are inherently limited by being very subjective, having a low frequency of data collection, and inconsistent follow-up. METHODS:: Inclusion criteria: adults (18+), thoracolumbar deformity or degenerative disease, and regular access to a computer with internet connection. Physical activity parameters included: number of daily steps, maximum hourly steps, and activity intensity. Patients completed the Oswestry Disability Index (ODI), the Short-Form Health Survey 36 (SF-36), and the Scoliosis Research Society-22r (SRS22) preoperatively and postoperatively at 6 weeks, 3 months, and 6 months. RESULTS:: Thirty-two patients were enrolled, 8 (25%) withdrew, 1 (3.1%) died, and 1 (3.1%) did not end up undergoing surgery resulting in 22 (68.8%) available patients. Mean preoperative and postoperative step ranges were 1278±767 to 17,800±6464 and 891±587 to 12,655±7038, respectively. Eleven patients improved in mean total daily steps at the final postoperative month with 2 having significant improvements (P<0.05). Five patients did not significantly change (P>0.05) and 6 patients had significantly lower mean total daily steps at 6 months (P<0.05). The entire cohort significantly improved in ODI, SF-36 Physical Component Summary, SRS Activity, SRS Appearance, SRS Mental, SRS Satisfaction, and SRS Total score at 6 months postoperative (P<0.05 for all). Both ODI and Physical Component Summary were significantly correlated with preoperative average to tal daily steps (r=−0.61, P=0.0058 and r=0.60, P=0.0114, respectively). No other HRQOL metrics were significantly correlated at baseline or at 6 months postoperative (P>0.05). CONCLUSIONS:: A prospective pilot study for continuous real-time physical activity monitoring was successfully completed. This is the first study of its kind and demonstrates a foundation to continuous physical activity monitoring following spine surgery. A larger and longer prospective study is needed to confirm long-term results and its relationship with HRQOL scores. © 2017 by Lippincott Williams & Wilkins, Inc.


OBJECTIVE The operative management of patients with adult spinal deformity (ASD) has a high complication rate and it remains unknown whether baseline patient characteristics and surgical variables can predict early complications (intraoperative and perioperative [within 6 weeks]). The development of an accurate preoperative predictive model can aid in patient counseling, shared decision making, and improved surgical planning. The purpose of this study was to develop a model based on baseline demographic, radiographic, and surgical factors that can predict if patients will sustain an intraoperative or perioperative major complication. METHODS This study was a retrospective analysis of a prospective, multicenter ASD database. The inclusion criteria were age >/= 18 years and the presence of ASD. In total, 45 variables were used in the initial training of the model including demographic data, comorbidities, modifiable surgical variables, baseline health-related quality of life, and coronal and sagittal radiographic parameters. Patients were grouped as either having at least 1 major intraoperative or perioperative complication (COMP group) or not.
An ensemble of decision trees was constructed utilizing the C5.0 algorithm with 5 different bootstrapped models. Internal validation was accomplished via a 70/30 data split for training and testing each model, respectively. Overall accuracy, the area under the receiver operating characteristic (AUROC) curve, and predictor importance were calculated. RESULTS Five hundred fifty-seven patients were included: 409 (73.4%) in the NOCOMP group, and 148 (26.6%) in the COMP group. The overall model accuracy was 87.6% correct with an AUROC curve of 0.89 indicating a very good model fit. Twenty variables were determined to be the top predictors (importance >= 0.90 as determined by the model) and included (in decreasing importance): age, leg pain, Oswestry Disability Index, number of decompression levels, number of interbody fusion levels, Physical Component Summary of the SF-36, Scoliosis Research Society (SRS)-Schwab coronal curve type, Charlson Comorbidity Index, SRS activity, T-1 pelvic angle, American Society of Anesthesiologists grade, presence of osteoporosis, pelvic tilt, sagittal vertical axis, primary versus revision surgery, SRS pain, SRS total, use of bone morphogenetic protein, use of iliac crest graft, and pelvic incidence-lumbar lordosis mismatch. CONCLUSIONS A successful model (87% accuracy, 0.89 AUROC curve) was built predicting major intraoperative or perioperative complications following ASD surgery. This model can provide the foundation toward improved education and point-of-care decision making for patients undergoing ASD surgery.


OBJECTIVE: To characterize anticipatory postural adjustments (APA) across a variety of step initiation tasks in people with Parkinson’s disease (PD) and healthy control (HC). DESIGN: Cross-sectional study. Step initiation was analyzed during a) self-initiated gait, b) perceptual cued gait, and c) compensatory forward stepping after platform perturbation. People with PD were assessed On and Off levodopa. SETTING: University research laboratory. PARTICIPANTS: PD (n=19) and healthy aged matched controls (n=12). INTERVENTIONS: Not applicable. MAIN OUTCOME MEASURES: Medio-lateral (ML) size of APA (calculated from center of pressure recordings), step kinematics and body alignment. RESULTS: With respect to self-initiated gait, the ML size of APAs were significantly larger during the cued condition and significantly smaller during the compensatory condition (p<0.001). HC 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 APA between HC and patients with PD. However, the reduction in APA size from cued to compensatory stepping was significantly less pronounced in PD Off Meds compared to HC, as indicated by a significant group by condition interaction effect (p<0.01). No significant differences were found comparing PD patients in On and Off meds. CONCLUSIONS: Specific stepping conditions had a significant effect on the preparation and execution of step initiation. Thus, APA size has to be interpreted with respect to the specific stepping condition. Across-task changes in people with PD were less pronounced compared to HC. Antiparkinsonian medication did not significantly improve step initiation in this mildly affected PD cohort.


Visceral adipose tissue (VAT) measured by computed tomography (CT) is related to insulin resistance, lipids, and serum inflammatory markers. Our objective was to compare the strength of the associations of VAT measured using dual-energy X-ray absorptiometry (DXA-VAT) and CT (CT-VAT) with insulin resistance, serum lipids, and serum markers of inflammation. For 1117 men aged 65 and older enrolled in the Osteoporotic
Fractures in Men Study, the cross-sectional associations of DXA-VAT and CT-VAT with homeostasis model assessment of insulin resistance (homa2ir), C-reactive protein, and high-density lipoprotein (HDL) cholesterol were estimated with regression models and compared using a Hausman test. Adjusted for age and body mass index, DXA-VAT was moderately associated with homa2ir (effect size 0.38, 95% confidence interval [CI]: 0.28-0.47) and modestly associated with HDL cholesterol (DXA effect size -0.29, 95% CI: -0.38 to -0.21). These associations were significantly greater than those for CT-VAT with homa2ir (0.30, 95% CI: 0.24-0.37; p value for effect size difference 0.03) and CT-VAT with HDL cholesterol (-0.22, 95% CI: -0.29 to -0.15; p value for difference 0.005). Neither DXA-VAT nor CT-VAT was associated with C-reactive protein after adjustment for age and body mass index (DXA-VAT effect size 0.14, 95% CI: 0.04 to 0.32; CT-VAT effect size 0.08, 95% CI: -0.08 to 0.25; p value for difference 0.35). DXA-VAT has similar or greater associations with insulin resistance and HDL cholesterol as does CT-VAT in older men, confirming the concurrent validity of DXA-VAT. Investigations of how well DXA measurements of VAT predict incident cardiovascular disease events are warranted. © 2017.


In this report, we describe 2 instances in which expert use of an electronic health record (EHR) system interfaced to an external clinical laboratory information system led to unintended consequences wherein 2 patients failed to have laboratory tests drawn in a timely manner. In both events, user actions combined with the lack of an acknowledgment message describing the order cancellation from the external clinical system were the root causes. In 1 case, rapid, near-simultaneous order entry was the culprit; in the second, astute order management by a clinician, unaware of the lack of proper 2-way interface messaging from the external clinical system, led to the confusion. Although testing had shown that the laboratory system would cancel duplicate laboratory orders, it was thought that duplicate alerting in the new order entry system would prevent such events.


PURPOSE: Preoperative lymphoscintigraphy is the standard for the identification of sentinel lymph nodes (SLNs) in melanoma. The impact of negative scintigraphy [nonvisualization (NV) of the SLN] on surgical outcomes is inadequately reported in the literature. The objectives of this study were to determine the incidence, predictive factors, and surgical outcomes of NV in clinically node-negative melanoma patients. PATIENTS AND METHODS: A retrospective review of a prospective, Institutional Review Board approved, melanoma sentinel node database from January 2005 to August 2015 was performed. RESULTS: Twenty-seven of the 897 (3%) patients had negative scintigraphy. Single-photon emission computed tomography/computed tomography was performed in addition to planar imaging in four patients and failed to locate the SLN in all cases. NV was associated with older age (71 vs. 59 years, P<0.001), head and neck primaries (41%), and previous operations adjacent to the primary tumor or nodal beds (37%). NV was not associated with sex, BMI, or T stage. Despite a negative scintigram, the SLN was still found at operation in 10 of the 27 (37%) patients using the hand-held gamma probe, with one (10%) patient having nodal metastasis. Two patients with NV had nodal recurrence, with a mean follow-up of 3 years. DISCUSSION: Preoperative lymphoscintigraphy in clinically node-negative melanoma patients is associated with a low NV rate. Predictors for NV include age, head and neck location, and previous operations at adjacent sites. NV should not preclude surgical exploration as the SLN can still be found at operation in over one-third of patients.

With the use of high-throughput molecular profiling technologies, precision medicine trials are ongoing for adults with cancer. Similarly, there is an interest in how these techniques can be applied to tumors in children and adolescents to expand our understanding of the biology of pediatric cancers and evaluate the clinical implications of genomic testing for these patients. This article reviews the early studies in pediatric oncology showing the feasibility of this approach, describe the future plans to evaluate the clinical implications in a multicenter clinical trial and identify the challenges of applying genomics in this patient population.


Gestational trophoblastic disease (GTD) is a spectrum of both benign and malignant gestational tumors, including hydatidiform mole (complete and partial), invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor. The latter four entities are referred to as gestational trophoblastic neoplasia (GTN). These conditions are aggressive with a propensity to widely metastasize. GTN can result in significant morbidity and mortality if left untreated. Early diagnosis of GTD is essential for prompt and successful management while preserving fertility. Initial diagnosis of GTD is based on a multifactorial approach consisting of clinical features, serial quantitative human chorionic gonadotropin (β-hCG) titers, and imaging findings. Ultrasonography (US) is the modality of choice for initial diagnosis of complete hydatidiform mole and can provide an invaluable means of local surveillance after treatment. The performance of US in diagnosing all molar pregnancies is surprisingly poor, predominantly due to the difficulty in differentiating partial hydatidiform mole from nonmolar abortion and retained products of conception. While GTN after a molar pregnancy is usually diagnosed with serial β-hCG titers, imaging plays an important role in evaluation of local extent of disease and systemic surveillance. Imaging also plays a crucial role in detection and management of complications, such as uterine and pulmonary arteriovenous fistulas. Familiarity with the pathogenesis, classification, imaging features, and treatment of these tumors can aid in radiologic diagnosis and guide appropriate management. © RSNA, 2017.


Solid tumors often contain hypoxic regions which are resistant to standard chemotherapy and radiotherapy. We have developed a liposomal delivery system for a prodrug of vinblastine (CPD100) which converts to the parent compound only in the presence of lower oxygen levels. As a part of this work we have developed and optimized two formulations of CPD100: one composed of sphingomyelin/cholesterol (55/45; mol/mol) (CPD100Li) and the other composed of sphingomyelin/cholesterol/PEG (55/40/5; mol/mol) (CPD100 PEGLi). We evaluated the antiproliferative effect of CPD100 and the two formulations against A549 non-small lung cancer cell. A549 cell line showed to be sensitive to CPD100 and the two formulations displayed a higher hypoxic: air cytotoxicity ratio compared to the pro-drug. CPD100 elimination from the circulation after injection in mouse was characterized by a very short circulation time (~0.44h), lower area under the curve (AUC) (33μg·h/mL) and high clearance (916mL/h/kg) and lower volume of distribution (17.4mL/kg). Total drug elimination from the circulation after the administration of liposomal formulation was characterized by prolonged circulation time (5.5h) along with increase in the AUC (56μg·h/mL) for CPD100 Li and (9.5h) with AUC (170μg·h/mL) for CPD100PEGLi. This was observed along with increase in volume of distribution and decrease in clearance for the liposomes. The systemic exposure of the free drug was much lower than that achieved with the liposomes. When evaluated for the efficacy in A549 xenograft model in mice, both the liposomes demonstrated excellent tumor suppression and reduction for 3months. The blood chemistry panel and the comprehensive blood analysis showed no increase or decrease in the markers and blood count. In summary, the pharmacokinetic analysis along with the efficacy data emphasis on how the delivery vehicle
modifies and enhances the accumulation of the drug and at the same time the increased systemic exposure is not related to toxicity.


BACKGROUND: Glucose homeostasis improves within days following Roux-en-Y gastric bypass (RYGB) surgery. The dynamic metabolic response to caloric intake following RYGB has been assessed using liquid mixed meal tolerance tests (MMTT). Few studies have evaluated the glycemic and hormonal response to a solid mixed meal in subjects with diabetes prior to, and within the first month following RYGB. METHODS: Seventeen women with type 2 diabetes of less than 5 years duration participated. Fasting measures of glucose homeostasis, lipids and gut hormones were obtained pre- and post-surgery. MMTT utilizing a solid 4 oz chocolate pudding performed pre-, 2 and 4 weeks post-surgery. Metabolic response to 4 and 2 oz MMTT assessed in five diabetic subjects not undergoing surgery. RESULTS: Significant reductions in fasting glucose and insulin at 3 days, and in fasting betatrophin, triglycerides and total cholesterol at 2 weeks post-surgery. Hepatic insulin clearance was greater at 3 days post-surgery. Subjects exhibited less hunger and greater feelings of fullness and satisfaction during the MMTT while consuming 52.9 +/- 6.5% and 51.0 +/- 6.5% of the meal at 2 and 4 weeks post-surgery respectively. At 2 weeks post-surgery, glucose and insulin response to MMTT were improved, with greater GLP-1 and PYY secretion. Improved response to solid MMTT not replicated by consumption of smaller pudding volume in diabetic non-surgical subjects. CONCLUSIONS: With a test meal of size and composition representative of the routine diet of post-RYGB subjects, improved glycemic and gut hormone responses occur which cannot be replicated by reducing the size of the MMTT in diabetic subjects not undergoing surgery. TRIAL REGISTRATION: Clinical Trials.gov Identifier: NCT00957957 August 11, 2009.


Even though it is only a little over a decade from the discovery of proprotein convertase subtilisin/kexin type 9 (PCSK9) as a plasma protein that associates with both high and low cholesterol syndromes, a rich body of knowledge has developed, and drugs inhibiting this target have been approved in many markets. While the majority of research in recent years has focused on the impact of therapeutic antagonism of this molecule, important lines of investigation have emerged characterizing its unique physiology as it relates to cholesterol metabolism and atherosclerosis. The PCSK9 story is unfolding rapidly but is far from complete. One chapter that is of particular interest is the possible direct link between PCSK9 and atherosclerosis. This review specifically examines this relationship drawing from data produced from experimental models of plaque biology and inflammation, atherosclerosis imaging studies, and observational epidemiology.


OBJECTIVE: To consolidate the evidence from the literature to evaluate the role of prazosin in the treatment of posttraumatic stress disorder (PTSD). DATA SOURCES: Major databases, including PubMed, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, Ovid PsycINFO, and Scopus, were searched through August 2015 for studies reporting the role of prazosin in the treatment of PTSD with no language constraints. Keywords included (PTSD OR posttraumatic stress OR posttraumatic stress OR nightmares) AND prazosin. STUDY SELECTION: Of 402 screened articles, 6 studies were included in the systematic review and meta-analysis. DATA EXTRACTION: Two reviewers independently extracted relevant data (study characteristics, type of intervention, outcome measures, and follow-up) from the included studies using a standardized data extraction form. Only randomized controlled trials comparing prazosin to a placebo or control group in patients with PTSD were included. RESULTS: The patients with PTSD receiving prazosin showed significant improvement in nightmares (standardized mean difference [SMD] = 1.01; 95% CI, 0.72-1.30), overall PTSD symptoms (SMD = 0.77; 95% CI, 0.48-1.06), and clinical global improvement (SMD = 0.94; 95% CI 0.6-1.29) compared to the placebo/control group. Prazosin improved sleep quality (SMD = 0.87; 95% CI, 0.55-1.19), hyperarousal symptoms (SMD = 1.04; 95% CI, 0.23-1.84), dream content (SMD = 1.33; 95% CI, 0.69-1.97), and total sleep time (60.98 minutes; 95% CI, 18.69-103.26). Prazosin was fairly well tolerated. Minor side effects were reported, which were similar between the prazosin and placebo groups. CONCLUSIONS: This study suggests that prazosin improves nightmares and overall PTSD symptoms including hyperarousal, sleep disturbances, total sleep time, and sleep quality.


Fueled by seasonal phytoplankton blooms, the Columbia River estuary is a natural bioreactor for organic matter transformations. Prior metagenome analyses indicated high abundances of diverse Bacteroidetes taxa in estuarine samples containing phytoplankton. To examine the hypothesis that Bacteroidetes taxa have important roles in phytoplankton turnover, we further analyzed metagenomes from water collected along a salinity gradient at 0, 5, 15, 25, and 33 PSU during bloom events. Size fractions were obtained by using a 3-mm prefilter and 0.2-mm collection filter. Although this approach targeted bacteria by removing comparatively large eukaryotic cells, the metagenome from the ES-5 sample (5 PSU) nevertheless contained an abundance of diatom DNA. Biogeochemical measurements and prior studies indicated that this finding resulted from the leakage of cellular material due to freshwater diatom lysis at low salinity. Relative to the other metagenomes, the bacterial fraction of ES-5 was dramatically depleted of genes annotated as Bacteroidetes and lysogenic bacteriophages, but was overrepresented in DNA of protists and Myxococcales bacterivores. We suggest the following equally plausible scenarios for the microbial response to phytoplankton lysis: (1) Bacteroidetes depletion in the free-living fraction may at least in part be caused by their attachment to fluvial diatoms as the latter are lysed upon contact with low-salinity estuarine waters; (2) diatom particle colonization is likely followed by rapid bacterial growth and lytic phage infection, resulting in depletion of lysogenic bacteriophages and host bacteria; and (3) the subsequent availability of labile organic matter attracted both grazers and predators to feed in this estuarine biogeochemical “hotspot,” which may have additionally depleted Bacteroidetes populations. These results represent the first detailed molecular analysis of the microbial response to phytoplankton lysis at the freshwater-brackish water interface in the fast-flowing Columbia River estuary.


Aims: Historic trials suggested significant toxicity with adjuvant radiotherapy (ART) after radical cystectomy for muscle-invasive bladder cancer (MIBC). However, recent trials have found improved locoregional control and the 2016 National Comprehensive Cancer Network (NCCN) guidelines recommend ART consideration for select patients at high risk of local recurrence. ART practice patterns among US radiation oncologists are unknown and we carried out a survey to explore current trends. Materials and methods: We conducted a survey of US radiation oncologists regarding the management of patients with cT2-3N0M0 transitional cell MIBC. Responses were reported using descriptive statistics. Chi-square and univariate logistic regression of clinical and demographic covariates were conducted, followed by multivariable logistic regression analysis to identify factors predicting for ART use. Results: In total, 277 radiation oncologists completed our survey. Nearly half (46%) have used ART for MIBC at least once in the past. In ART users, indications for ART include gross residual disease (93%), positive margins (92%), pathological nodal involvement (64%), pT3 or T4 disease (46%), lymphovascular invasion (16%) and high-grade disease (13%). On univariate logistic regression, ART use was associated with the number of years in practice (P = 0.04), pre-cystectomy radiation oncology consultation (P = 0.004), primarily treating MIBC patients fit for cystectomy (P = 0.01) and intensity-modulated radiotherapy use (P = 0.01). On multivariable logistic regression analysis, routine pre-cystectomy radiation oncology consultation (odds ratio 1.91, 95% confidence interval 1.04-3.51; P = 0.04) and intensity-modulated radiotherapy use (odds ratio 2.77, 95% confidence interval 1.48-5.22; P = 0.002) remained associated with ART use. Conclusions: ART use is controversial in bladder cancer, yet unexpectedly has commonly been used among US radiation oncologists treating patients with MIBC after radical cystectomy. NRG-GU001 was a randomised trial in the US randomizing patients with high-risk pathological findings for observation or ART after cystectomy. However, due to poor accrual it recently closed and thus it will be up to other international trials to clarify the role of ART and identify patients benefiting from this adjuvant therapy. © 2017 The Royal College of Radiologists.


Purpose of the Study: Adult daughters providing care to aging, ill mothers comprise the most prevalent caregiving dyad. Little is known, however, regarding relationship quality and its impact on care in these dyads, particularly in the context of cognitively intact patients at end of life in hospice. This interpretive descriptive work privileges voices of terminally ill mothers and care-partnering daughters in the home hospice context. Specific aims were to describe and interpret how mothers and daughters: (a) perceive relationship quality and (b) perceive how relationships have developed over time through health, chronic illness, and hospice. Design and Methods: Semistructured interviews were used to explore interdependent perceptions of relationship quality in 10 terminally-ill mother-adult daughter care dyads. A novel method of qualitative dyadic analysis was developed to analyze dyads in close parallel at both individual/descriptive and dyadic/interpretive levels, staying true to qualitative rigor. Results: A relationship quality spectrum emerged, from Close Friendship to Doing My Duty dyads. Women in Close Friendships revealed concordant narratives and emotionally satisfying relationships; women in neutral or troubled relationships revealed discordant relational stories. In these latter dyads, mothers reported more positive narratives; daughters spoke of relational problems. Implications: This work suggests deeper exploration of mother-daughter dyads within the hospice context and interventions at both individual and dyadic levels to serve relational needs of the
dying and their families. The qualitative dyadic approach also offers utility for relational investigations of any dyad.


**BACKGROUND:** The optimal management of tricuspid regurgitation (TR) in patients undergoing left ventricular assist device (LVAD) implantation is controversial. This study was undertaken to determine the impact of tricuspid valve repair (TVR) at the time of LVAD implantation on survival. **METHODS:** The Interagency Registry for Mechanically Assisted Circulatory Support was used to analyze the outcomes of patients undergoing LVAD implantation as destination therapy with or without concomitant TVR. **RESULTS:** Among 2,527 patients undergoing implant of a continuous flow LVAD as destination therapy during the study period, 989 (39%) had moderate or severe TR. The management of TR was not uniform among these patients. Patients with moderate and severe TR underwent TVR in 16.7% and 35.3% of cases, respectively. Moderate and severe TR at the time of LVAD implantation were associated with poorer survival over the entire follow-up period (p = 0.009). Interestingly, TVR at the time of LVAD implantation did not confer improved survival, even among patients with preimplant moderate or severe TR. A potential explanation for this finding is that patients with preimplant moderate or severe TR who underwent LVAD implant with concomitant TVR commonly experienced recurrent, late TR (21% to 27%). **CONCLUSIONS:** Tricuspid valve repair is performed commonly at the time of LVAD implant despite the fact that it does not confer a clear survival benefit. For many patients, LVAD implant alone relieves preimplant TR as effectively as LVAD implant with TVR. Further study is necessary to determine what factors lead to recurrence of late TR in LVAD patients both with and without TVR.


Background: The Harmonising Outcome Measures for Eczema (HOME) initiative has defined four core outcome domains for a core outcome set (COS) to be measured in all atopic eczema (AE) trials to ensure cross-trial comparison: clinical signs, symptoms, quality of life and long-term control. **Objectives:** The aim of this paper is to report on the consensus process that was used to select the core instrument to consistently assess symptoms in all future AE trials. **Methods:** Following the HOME roadmap, two systematic reviews were performed which identified three instruments that had sufficient evidence of validity, reliability and feasibility to be considered for the final COS. **Results:** At the fourth international HOME meeting, there was broad consensus among all stakeholders that the Patient-Oriented Eczema Measure (POEM) should be used as the core instrument (87.5% agreed, 9.4% unsure, 3.1% disagreed). **Conclusions:** All relevant stakeholders are encouraged to use POEM as the chosen instrument to measure the core domain of symptoms in all future AE clinical trials. Other instruments of interest can be used in addition to POEM. © 2017 British Association of Dermatologists.


Early reflections have been linked to improved speech intelligibility, while later-arriving reverberant sound has been shown to limit speech understanding. Here, these effects were examined by artificially removing either early reflections or late reflections. Removing late reflections improved performance more for colocated than for spatially separated maskers. Results of a multiple regression analysis suggest that pure-tone average (PTA) is...
a significant predictor of spatial release from masking (SRM) in all acoustic conditions. Controlling for the effects of PTA, age is a significant predictor of SRM only when early reflections are absent. © 2017 Acoustical Society of America.


**BACKGROUND:** Pediatric surgery fellowship applicants and programs coordinate over 20 interviews per cycle. We hypothesized that replacing e-mail and phone communication with a computerized-scheduling program (CSP) could benefit both parties. METHODS: We used a CSP to schedule 2016 interviews. Time to schedule and e-mail communication per applicant was compared to 2015, when traditional scheduling was used. Additionally, 2016 interviewees were surveyed about their experience with the CSP vs. traditional means. Analysis was performed using descriptive statistics and a Student’s T-test. RESULTS: We found a significant decrease in mean scheduling time from 14.4 to 1.7h (p<0.001) and in e-mails exchanged from 3.4 to 1.0 (p<0.0001). Survey respondents reported 92% satisfaction with the CSP, and 87% found it easier to schedule interviews. Applicants also reported quicker finalization of interview dates (96%), improved access to interview slots (71%), and easier coordination of additional services and time off (63%). Notably, the mean longest time reported to schedule interviews using traditional methods was 7days (range 1-30). Overall, 84% supported widespread adoption of CSPs. CONCLUSIONS: Using CSPs improved the scheduling process for the significant majority of interviewees, and our program. If widely adopted, this could greatly improve the efficiency of pediatric surgery interview scheduling. LEVEL OF EVIDENCE: N/A.


**Introduction and hypothesis:** Animal models are essential to further our understanding of the independent and combined function of human pelvic floor muscles (PFMs), as direct studies in women are limited. To assure suitability of the rhesus macaque (RM), we compared RM and human PFM architecture, the strongest predictor of muscle function. We hypothesized that relative to other models, RM best resembles human PFM. Methods: Major architectural parameters of cadaveric human coccygeus, iliococcygeus, and puboviscerals (puboccocygeus + puborectalis) and corresponding RM coccygeus, iliocaudalis, and puboviscerals (pubovaginalis + pubocaudalis) were compared using 1- and 2-way analysis of variance (ANOVA) with post hoc testing. Architectural difference index (ADI), a combined measure of functionally relevant structural parameters predictive of length-tension, force-generation, and excursional muscle properties was used to compare PFMs across RM, rabbit, rat, and mouse. Results: RM and human PFMs were similar with respect to architecture. However, the magnitude of similarity varied between individual muscles, with the architecture of the most distinct RM PFM, iliocaudalis, being well suited for quadrupedal locomotion. Except for the pubovaginalis, RM PFMs inserted onto caudal vertebrae, analogous to all tailed animals. Comparison of the PFM complex architecture across species revealed the lowest, thus closest to human, ADI for RM (1.9), followed by rat (2.0), mouse (2.6), and rabbit (4.7). Conclusions: Overall, RM provides the closest architectural representation of human PFM complex among species examined; however, differences between individual PFMs should be taken into consideration. As RM is closely followed by rat with respect to PFM similarity with humans, this less-sentient and substantially cheaper model is a good alternative for PFM studies. © 2017 The International Urogynecological Association

Background: The precise mechanism by which the immune system is adversely affected in cancer patients remains poorly understood, but the accumulation of immunosuppressive/protumorigenic myeloid-derived suppressor cells (MDSCs) is thought to be a prominent mechanism contributing to immunologic tolerance of malignant cells in epithelial ovarian cancer (EOC). To this end, we hypothesized genetic variation in MDSC pathway genes would be associated with survival after EOC diagnoses. Methods: We measured the hazard of death due to EOC within 10 years of diagnosis, overall and by invasive subtype, attributable to SNPs in 24 genes relevant in the MDSC pathway in 10,751 women diagnosed with invasive EOC. Versatile Gene-based Association Study and the admixture likelihood method were used to test gene and pathway associations with survival. Results: We did not identify individual SNPs that were significantly associated with survival after correction for multiple testing (P < 3.5 × 10^{-5}), nor did we identify significant associations between the MDSC pathway overall, or the 24 individual genes and EOC survival. Conclusions: In this well-powered analysis, we observed no evidence that inherited variations in MDSC-associated SNPs, individual genes, or the collective genetic pathway contributed to EOC survival outcomes. Impact: Common inherited variation in genes relevant to MDSCs was not associated with survival in women diagnosed with invasive EOC. © 2016 American Association for Cancer Research.


PURPOSE: Ewing Sarcoma (EWS) is a devastating soft tissue sarcoma affecting predominantly young individuals. Tyrosine kinases (TKs) 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-qPCR, luciferase reporter and qRT-PCR assays. RESULTS: SYK was identified as a candidate actionable target through both high-throughput screens. SYK was highly phosphorylated in the majority of EWS cells, and SYK inhibition by a variety of genetic and pharmacological approaches markedly inhibited EWS cells both in vitro and in vivo. Ectopic expression of SYK rescued the cytotoxicity triggered by SYK-depletion associated with the reactivation of both AKT and c-MYC. A long non-coding RNA, MALAT1, was identified to be dependent on SYK-mediated signaling. Moreover, c-MYC, a SYK-promoted gene, bound to the promoter of MALAT1 and transcriptionally activated MALAT1, which further promoted the proliferation of EWS cells. CONCLUSIONS: The present study identifies a novel signaling involving SYK/c-MYC/MALAT1 as a promising therapeutic target for the treatment of EWS.


Objective To compare outcomes after microvascular reconstructions of head and neck defects between overlapping and nonoverlapping operations. Study Design Retrospective cohort study. Setting Tertiary care center. Subjects and Methods Patients undergoing microvascular free tissue transfer operations between January 2010 and February 2015 at 2 tertiary care institutions were included (n = 1315). Patients were divided into 2 cohorts by whether the senior authors performed a single or consecutive microvascular reconstruction (nonoverlapping; n = 773, 59%) vs performing overlapping microvascular reconstructions (overlapping; n = 542, 41%). Variables reviewed were as follows: defect location, indication, T classification, surgical details, duration of the operation and hospitalization, and complications (major, minor, medical). Results Microvascular free tissue transfers performed included radial forearm (49%, n = 639), osteocutaneous radial forearm (14%, n = 182), anterior lateral thigh (12%, n = 153), fibula (10%, n = 135), rectus abdominis (7%, n =
92), latissimus dorsi (6%, n = 78), and scapula (<1%, n = 4). The mean duration of the overlapping operations was 21 minutes longer than nonoverlapping operations (P = .003). Mean duration of hospitalization was similar for nonoverlapping (9.5 days) and overlapping (9.1 days) cohorts (P = .39). There was no difference in complication rates when stratified by overlapping (45%, n = 241) and nonoverlapping (45%, n = 344) (P = .99). Subset analysis yielded similar results when minor, major, and medical complications between groups were assessed. The overall survival rate of free tissue transfers was 96%, and this was same for overlapping (96%) and nonoverlapping (96%) operations (P = .71). Conclusions Patients had similar complication rates and durations of hospitalization for overlapping and nonoverlapping operations.


**BACKGROUND:** A three-dimensional electrocardiographic (ECG) metric, the sum absolute QRST integral (SAI QRST), predicts ventricular arrhythmias in heart failure (HF) patients with implantable cardioverter defibrillator and mechanical response to cardiac resynchronization therapy. We hypothesized that there is an association between patient-specific changes in SAI QRST and myocardial injury as measured by high-sensitivity troponin I (hsTnI). METHODS: Sum absolute integral QRST on resting 12-lead ECG and hsTnI were measured simultaneously, every 3 hours, and during 12-hour observation period in a prospective cohort of emergency department patients (n = 398; mean age 57.8 ± 13.2 years; 54% female, 64% black), diagnosed with acute coronary syndrome (ACS, n = 28), acutely decompensated HF (acute decompensated heart failure, n = 35), cardiac non-ACS (n = 19), or noncardiac condition (n = 316). Random-effects linear regression analysis assessed the association of SAI QRST and myocardial injury, with adjustment for demographics (age, sex, race), prevalent cardiovascular disease (myocardial infarction, history of revascularization, stroke, and HF), risk factors (diabetes, smoking, hypercholesterolemia, hypertension, and cocaine use), and left bundle branch block. RESULTS: Within the entire cohort, SAI QRST decreased by 3 (95%CI -5 to -1) mV*ms every 3 hours. A 10-fold increase in hsTnI was associated with a 7.7 (0.6-14.9) mV*ms increase in SAI QRST. In the subgroup of acutely decompensated HF patients (n = 35), a 10-fold increase in hsTnI was associated with a 61.0 (5.9-116.1) mV*ms increase in SAI QRST. CONCLUSION: Patient-specific time-varying changes in the surface ECG scalar measure of global electrical heterogeneity, as measured by SAI QRST, and in myocardial injury as measured by hsTnI are independently and directly associated with each other, likely reflecting a common underlying mechanism. 2016 Wiley Periodicals, Inc.


There is, perhaps, no parallel in history where massive numbers of people have rapidly become ill without an infectious agent as perpetrator. This article is protected by copyright. All rights reserved.


This is the first comprehensive clinical reference on cancer emergencies. It is edited and written by world-renowned experts in emergency medicine and oncology and covers the diagnosis and management of the full range of emergencies caused directly by cancer or by its treatment. It shows how the entire spectrum of clinical medicine is brought to bear in the care of cancer patients in the unique setting of the emergency department (ED), from health promotion and prevention, to treatment and palliative care. Recognizing the multiple, overlapping contexts in which emergency care of cancer patients occurs, the book addresses clinically crucial interdisciplinary topics such as the ethics of ED cancer care, the interface with palliative social work, substance abuse, and more. Finally, perspective on care system and social forces that shape ED cancer care, such as cancer care disparities and care models, and on how ED cancer care is delivered outside of the United States, frame the book as a whole. Against the backdrop of rising numbers of cancer patients and survivors as the United States population ages and a forecast shortage of oncologists, this book is designed to serve as the authoritative, single-source clinical reference on cancer emergencies. The intended audience includes emergency physicians, oncologists, internists, family physicians, emergency nurses, nurse practitioners, physician assistants, policy makers as well as pre- and postgraduate trainees. © Springer International Publishing Switzerland 2016.


We have repurposed (N)-methanocarba adenosine derivatives (A3 adenosine receptor (AR) agonists) to enhance radioligand binding allosterically at the human dopamine (DA) transporter (DAT) and inhibit DA uptake. We extended the structure-activity relationship of this series with small N6-alkyl substitution, 5'-esters, deaza modifications of adenine, and ribose restored in place of methanocarba. C2-(5-Halothen-2-yl)-ethynyl 5'-methyl 9 (MRS7292) and 5'-ethyl 10 (MRS7232) esters enhanced binding at DAT (EC50 approximately 35 nM) and at the norepinephrine transporter (NET). 9 and 10 were selective for DAT compared to A3AR in the mouse but not in humans. At DAT, the binding of two structurally dissimilar radioligands was enhanced; NET binding of only one radioligand was enhanced; SERT radioligand binding was minimally affected. 10 was more potent than cocaine at inhibiting DA uptake (IC50 = 107 nM). Ribose analogues were weaker in DAT interaction than the corresponding bicyclics. Thus, we enhanced the neurotransmitter transporter activity of rigid nucleosides while reducing A3AR affinity.


Quantitative structure-activity relationships (QSARs) have long been used in the environmental sciences. More recently, molecular modeling and chemoinformatic methods have become widespread. These methods have the potential to expand and accelerate advances in environmental chemistry because they complement observational and experimental data with "in silico" results and analysis. The opportunities and challenges that arise at the intersection between statistical and theoretical in silico methods are most apparent in the context of properties that determine the environmental fate and effects of chemical contaminants (degradation rate constants, partition coefficients, toxicities, etc.). The main example of this is the calibration of QSARs using descriptor variable data calculated from molecular modeling, which can make QSARs more
useful for predicting property data that are unavailable, but also can make them more powerful tools for diagnosis of fate determining pathways and mechanisms. Emerging opportunities for “in silico environmental chemical science” are to move beyond the calculation of specific chemical properties using statistical models and toward more fully in silico models, prediction of transformation pathways and products, incorporation of environmental factors into model predictions, integration of databases and predictive models into more comprehensive and efficient tools for exposure assessment, and extending the applicability of all the above from chemicals to biologicals and materials.


Background: Reference ranges for testosterone are essential for making a diagnosis of hypogonadism in men. Objective: To establish harmonized reference ranges for total testosterone in men that can be applied across laboratories by cross-calibrating cohort-specific assays to a reference method and standard. Population: 9054 community-dwelling men in cohort studies in the United States and Europe: Framingham Heart Study; European Male Aging Study; Osteoporotic Fractures in Men Study; Male Sibling Study of Osteoporosis. Methods: Testosterone concentrations in 100 participants in each of the four cohorts were measured using a reference method at Centers for Disease Control. Generalized additive models and Bland-Altman analyses supported the use of normalizing equations for transformation between cohort-specific and CDC values. Normalizing equations, generated using Passing-Bablok regression, were employed to generate harmonized values, which were used to derive standardized, age-specific reference ranges. Results: Harmonization procedure reduced inter-cohort variation between testosterone measurements in men of similar ages. In healthy nonobese men, 19-39 years, harmonized 2.5th, 5th, 50th, 95th and 97.5th percentile values were 264, 303, 531, 852 and 916 ng/dL, respectively. Age-specific harmonized testosterone concentrations in nonobese men were similar across cohorts and greater than in all men. Conclusion: The harmonized normal range (2.5th-to-97.5th percentile) in nonobese, population of European and American men, 19-39 years, is 264-916 ng/dL. A substantial proportion of inter-cohort variation in testosterone levels is due to assay differences. These data demonstrate the feasibility of generating harmonized reference ranges for testosterone that can be applied to assays, which have been calibrated to a reference method and calibrator.


CONTEXT: -Immunohistochemical analysis of tissue biopsy specimens is a crucial tool in diagnosis of both rejection and infection in patients with solid organ transplants. In the past 15 years, the concept of antibody-mediated rejection has been refined, and diagnostic criteria have been codified in renal, heart, pancreas, and lung allografts (with studies ongoing in liver, small intestine, and composite grafts), all of which include immunoanalysis for the complement split product C4d. OBJECTIVES: -To review the general concepts of C4d biology and immunoanalysis, followed by organ-allograft-specific data, and interpretative nuances for kidney, pancreas, and heart, with discussion of early literature for lung and liver biopsies. Additionally, practical applications and limitations of immunostains for infectious organisms (Polyomavirus, Adenoviridae [adenovirus], and the herpes virus family, including Herpes simplex virus, Cytomegalovirus, Human herpes virus 8, and Epstein-Barr virus) are reviewed in the context of transplant recipients. DATA SOURCES: -Our experience and published primary and review literature. CONCLUSIONS: -Immunohistochemistry continues to have an important role in transplant pathology, most notably C4d staining in assessment of antibody-mediated rejection and assessment of viral pathogens in tissue. In all facets of transplant pathology, correlation of morphology with special studies and clinical data is critical, as is close communication with the transplant team.

Understanding how specific genes contribute to risk for addiction remains challenging. This study tests whether childhood temperament and externalizing behavior in early adolescence account for a portion of the association between specific genetic variants and substance use problems in late adolescence. The sample consisted of 487 adolescents from the Michigan Longitudinal Study, a high-risk sample (70.2% male, 81.7% European American ancestry). Polymorphisms across serotonergic (SLC6A4, 5-HTTLPR), dopaminergic (DRD4, u-VNTR), noradrenergic (SLC6A2, rs36021), and GABAergic (GABRA2, rs279858; GABRA6, rs3811995) genes were examined given prior support for associations with temperament, externalizing behavior, and substance use problems. The temperament traits behavioral control and resiliency were assessed using interviewer ratings (ages 9-11), and externalizing behavior (ages 12-14) was assessed using teacher ratings. Self-reported substance use outcomes (ages 15-17) included maximum alcoholic beverages consumed in 24 hours, and frequency of past year cigarette and marijuana use. Behavioral control, resiliency, and externalizing behavior accounted for the associations between polymorphisms in noradrenergic and GABAergic genes and substance use in late adolescence. Individual differences in emotional coping and behavioral regulation represent nonspecific neurobiological underpinnings for an externalizing pathway to addiction. (PsycINFO Database Record


At chemical synapses, voltage-activated calcium channels (VACCs) mediate Ca2+ influx to trigger action potential-evoked neurotransmitter release. However, the mechanisms by which Ca2+ regulates spontaneous transmission have not been fully determined. We have shown that VACCs are a major trigger of spontaneous release at neocortical inhibitory synapses but not at excitatory synapses suggesting fundamental differences in spontaneous neurotransmission at GABAergic and glutamatergic synapses. Recently, VACC blockers were reported to reduce spontaneous release of glutamate and it was proposed that there was conservation of underlying mechanisms of neurotransmission at excitatory and inhibitory synapses. Furthermore, it was hypothesized that the different effects on excitatory and inhibitory synapses may have resulted from off target actions of Cd2+, a non-selective VACC blocker, or other variations in experimental conditions. Here we report that in mouse neocortical neurons, selective and non-selective VACC blockers inhibit spontaneous release at inhibitory but not at excitatory terminals, and that this pattern is observed in culture and slice preparations, as well as in synapses from acute slices of the auditory brainstem. The voltage-dependence of Cd2+ block of VACCs, accounts for the apparent lower potency of Cd2+ on spontaneous release of GABA than on VACC current amplitudes. Our findings indicate fundamental differences between the regulation of spontaneous release at inhibitory and excitatory synapses by stochastic VACC activity that extend beyond the cortex to the brainstem. SIGNIFICANCE STATEMENT Presynaptic Ca2+ entry via voltage-activated Ca2+ channels (VACC) is the major trigger of action potential-evoked synaptic release. However, the role of VACCs in the regulation of spontaneous neurotransmitter release (in the absence of a synchronizing action potential) remains controversial. We show that spontaneous release is affected differently by VACCs at excitatory and inhibitory synapses. At inhibitory synapses, stochastic openings of VACCs trigger the majority of spontaneous release, whereas they do not affect spontaneous release at excitatory synapses. We find this pattern to be wide-ranging, holding for large and small synapses in the neocortex and brainstem. These findings indicate fundamental differences of the Ca2+ dependence of spontaneous release at excitatory and inhibitory synapses and heterogeneity of the mechanisms of release across the CNS.

To maintain core body temperature in mammals, the normal 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 non-hibernating/torpid species, exhibit a “Thermoregulatory Inversion”, 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 pharmacologic mechanism through which a deeply hypothermic state can be achieved in non-hibernating/torpid mammals, possibly including humans.


Like elderly men, old male rhesus macaques show attenuated circulating levels of testosterone and dehydroepiandrosterone sulfate, and many of them also show reduced levels of daytime activity. It is unclear, however, if this age-associated behavioral change is causally related to the underlying decrease in circulating androgen levels. To test this possibility, old male rhesus macaques were given daily supplements of testosterone and DHEA for 6 months, designed to mimic the mean 24-hour circulating hormone patterns of young adults. Compared with the young adults, the old controls showed attenuated daytime activity levels. However, there was no difference between the androgen-supplemented old animals and the aged-matched controls, even after 6 months of treatment. The data suggest that age-associated decreases in circulating androgen levels are unlikely to be a primary reason for altered activity-rest patterns in elderly men, and that androgen supplementation paradigms might not provide any obvious therapeutic benefit.


In the olfactory bulb, lateral inhibition mediated by local juxtaglomerular interneurons has been proposed as a gain control mechanism, important for decorrelating odorant responses. Among juxtaglomerular interneurons, short axon cells are unique as dual-transmitter neurons that release dopamine and GABA. To examine their intraglomerular function, we expressed channelrhodopsin under control of the DATcre promoter and activated olfactory afferents within individual glomeruli. Optical stimulation of labeled cells triggered endogenous dopamine release as measured by cyclic voltammetry and GABA release as measured by whole cell GABAA receptor currents. Activation of short axon cells reduced the afferent presynaptic release probability via D2 and GABAB receptor activation, resulting in reduced spiking in both mitral and external tufted cells. Our results suggest that short axon cells influence glomerular activity not only by direct inhibition of external tufted cells but also by inhibition of afferent inputs to external tufted and mitral cells. NEW & NOTEWORTHY Sensory systems, including the olfactory system, encode information across a large dynamic range, making synaptic mechanisms of gain control critical to proper function. Here we demonstrate that a dual-transmitter interneuron in the olfactory bulb controls the gain of intraglomerular afferent input via two distinct mechanisms, presynaptic inhibition as well
as inhibition of a principal neuron subtype, and thereby potently controls the synaptic gain of afferent inputs. © 2017 the American Physiological Society.


PURPOSE: To review the available evidence on the ocular safety and efficacy of anti-vascular endothelial growth factor (VEGF) agents for the treatment of retinopathy of prematurity (ROP) compared with laser photocoagulation therapy. METHODS: A literature search of the PubMed and Cochrane Library databases was conducted last on September 6, 2016, with no date restrictions and limited to articles published in English. This search yielded 311 citations, of which 37 were deemed clinically relevant for full-text review. Thirteen of these were selected for inclusion in this assessment. The panel methodologist assigned ratings to the selected articles according to the level of evidence. RESULTS: Of the 13 citations, 6 articles on 5 randomized clinical trials provided level II evidence supporting the use of anti-VEGF agents, either as monotherapy or in combination with laser therapy. The primary outcome for these articles included recurrence of ROP and the need for retreatment (3 articles), retinal structure (2 articles), and refractive outcome (1 article). Seven articles were comparative case series that provided level III evidence. The primary outcomes included the effects of anti-VEGF treatment on development of peripheral retinal vessels (1 article), refractive outcomes (1 article), or both structural and refractive or visual outcomes (5 articles). CONCLUSIONS: Current level II and III evidence indicates that intravitreal anti-VEGF therapy is as effective as laser photocoagulation for achieving regression of acute ROP. Although there are distinct ocular advantages to anti-VEGF pharmacotherapy for some cases (such as eyes with zone I disease or aggressive posterior ROP), the disadvantages are that the ROP recurrence rate is higher, and vigilant and extended follow-up is needed because retinal vascularization is usually incomplete. After intravitreal injection, bevacizumab can be detected in serum within 1 day, and serum VEGF levels are suppressed for at least 8 to 12 weeks. The effects of lowering systemic VEGF levels on the developing organ systems of premature infants are unknown, and there are limited long-term data on potential systemic and neurodevelopmental effects after anti-VEGF use for ROP treatment. Anti-VEGF agents should be used judiciously and with awareness of the known and unknown or potential side effects.


OBJECTIVE: To report our experience with permanent urethral ligation for severe incontinence among men with end-stage urethra. METHODS: From our institutional Artificial Urethral Sphincter (AUS) database of 512 patients from 2010-2016, 10 men underwent permanent urethral ligation with concurrent suprapubic tube (SPT) diversion following recurrent AUS cuff erosion. Clinical characteristics and outcomes were evaluated. Quality of life (QOL) was assessed using the Michigan Incontinence Symptom Index (M-ISI) and the Patient Global Index of Improvement (PGI-I). RESULTS: Urethral ligation resulted in resolution of incontinence in 8 men (80%), including 7 (70%) after one surgery and in 1 other (10%) after a single revision. The average American Society of Anesthesiologists (ASA) physical status rating was 2.7 (range 2-3). Seven patients (70%) experienced post-operative complications [4 Clavien-Dindo Grade II complications (1 Clostridium difficile infection, 3 with refractory bladder spasms) and 5 Grade III complications (2 abscesses, 2 urethrococutaneous fistula, and 1 bladder stone formation)]. Overall, satisfactory M-ISI urinary scores were reported in 8 (80%) men. On PGI-I, 6 (60%) reported improvement in overall condition following surgery. All men (10/10) stated that they would recommend this procedure to others. CONCLUSIONS: For debilitated men with end-stage urethra and severe refractory stress urinary incontinence (SUI), permanent urethral ligation with chronic SPT drainage can restore continence and improve QOL without the need for more invasive formal urinary diversion, though with a high risk of complication.

We determined disseminated nontuberculous mycobacteria incidence in the HIV-infected population of Oregon, USA, during 2007-2012 by using statewide laboratory surveillance. We identified 37 disseminated nontuberculous mycobacteria cases among 7,349 patients with median annual incidence of 110/100,000 HIV person-years and the highest incidence in those with CD4 counts <50 cells/mm3 (5,300/100,000 person-years). © 2017, Centers for Disease Control and Prevention (CDC). All rights reserved.


Cerebrotendinous xanthomatosis (CTX) is a treatable neurodegenerative metabolic disorder of bile acid synthesis where symptoms can be prevented if treatment with chenodeoxycholic acid supplementation is initiated early in life, making CTX an excellent candidate for newborn screening. We developed a new dried blood spot screening assay for this disorder based on different ratios between the accumulating cholestanetetrol glucuronide (tetrol) and specific bile acids/bile acid intermediates, without the need for derivatization. A quarter-inch dried blood spot punch was extracted with methanol, internal standards were added and after concentration the extract was injected into the tandem mass spectrometer using a 2 minute flow injection analysis where specific transitions were measured for cholestanetetrol glucuronide, tauro-chenodeoxycholic acid (t-CDCA) and tauro-trihydroxycholestanolic acid (t-THCA). A proof of principle experiment was performed using 216 Guthrie cards from healthy term/preterm newborns, CTX patients and Zellweger patients. Using two calculated biomarkers, tetrol/t-CDCA and t-THCA/tetrol, this straightforward method achieved an excellent separation between dried blood spots of CTX patients and those of controls, Zellweger patients and newborns with cholestasis. The results of this small pilot study indicate that the tetrol/t-CDCA ratio is an excellent derived biomarker for CTX that has the potential to be used in neonatal screening programs.


In order to integrate the biological, psychological, social, and existential dimensions of care into my day-to-day clinical encounters with patients, I have worked to cultivate several intentions of practice. These intentions of practice—habits of mind that nurture my resolve to attend to patients as complex human beings—help me navigate my interactions with patients and families in ways that are simultaneously efficacious and therapeutic. When routinely recalled and adeptly implemented, they are what distinguish me as a competent and capable practitioner of person-centered care, when I am at my best, from when I am not. I present them here in hopes that others may find them useful as they progress down their ongoing paths as healing physicians. © 2017, Annals of Family Medicine, Inc. All rights reserved.


Fanconi anemia (FA) is an autosomal recessive, multisystem DNA repair disorder with prominent defects in the hematopoietic stem cell maintenance that result in the progressive attrition and failure in the early school age. Allogeneic stem cell transplantation has proved curative for patients with suitable donors. This, along with the characteristic survival advantage of phenotypically normal over non-corrected FA stem cells underscores the compelling rationale for stem cell gene therapy in the FA. While integrating lentiviral vectors (LV) have become the preferred platform for genetic correction in several hematologic and
immunodeficiency disorders, the residual oncogenic potential by these vectors raises concerns in the FA stem cells about insertional mutagenic genetic lesions. On this backdrop, investigators are developing a new generation of non-integrating viral vectors capable of nuclear persistence through serial mitotic cycles and stable under selection to offset the comparatively lower transduction rates. Here, we review the competing approaches to develop such non-integrating lentiviral (NILV) episome vectors that faithfully replicate in the stem cells. © 2016 Bentham Science Publishers.


Purpose To describe the impact of fractionation scheme and tumor location on toxicities in stereotactic body radiation therapy (SBRT) for ≥5-cm non-small cell lung cancer (NSCLC), as part of a multi-institutional analysis. Methods Patients with primary ≥5-cm N0 M0 NSCLC who underwent ≤5-fraction SBRT were examined across multiple high-volume SBRT centers. Collected data included clinical/treatment parameters; toxicities were prospectively assessed at each institution according to the Common Terminology Criteria for Adverse Events. Patients treated daily were compared with those treated every other day (QOD)/other nondaily regimens. Stratification between central and peripheral tumors was also performed. Results Ninety-two patients from 12 institutions were evaluated (2004-2016), with median follow-up of 12 months. In total there were 23 (25%) and 6 (7%) grade ≥2 and grade ≥3 toxicities, respectively. Grades 2 and 3 pulmonary toxicities occurred in 9% and 4%, respectively; 1 patient treated daily experienced grade 5 radiation pneumonitis. Of the entire cohort, 46 patients underwent daily SBRT, and 46 received QOD (n=40)/other nondaily (n=6) regimens. Clinical/treatment parameters were similar between groups; the QOD/other group was more likely to receive 3-/4-fraction schemas. Patients treated QOD/other experienced significantly fewer grade ≥2 toxicities as compared with daily treatment (7% vs 43%, P<.001). Patients treated daily also had higher rates of grade ≥2 pulmonary toxicities (P=.014). Patients with peripheral tumors (n=66) were more likely to receive 3-/4-fraction regimens than those with central tumors (n=26). No significant differences in grade ≥2 toxicities were identified according to tumor location (P>.05). Conclusions From this multi-institutional study, toxicity of SBRT for ≥5-cm lesions is acceptable, and daily treatment was associated with a higher rate of toxicities. © 2016 Elsevier Inc.


CONTEXT: Posttraumatic stress disorder (PTSD) is a serious health concern. Current evidence-based treatments for PTSD are efficacious; however, they are not appropriate or tolerated by everyone who needs them. Alternative treatment approaches are needed. Shamanic healing is one such therapy that may potentially be beneficial but no systematic research has been conducted on it for PTSD. OBJECTIVE: The objectives of the case series are to (1) develop a structured replicable shamanic treatment plan for veterans with posttraumatic stress disorder (PTSD); (2) collect preliminary data on PTSD-related outcomes, and (3) explore the feasibility and potential for adverse events of the plan. DESIGN: Case series. SETTING: Clinical. PATIENTS OR OTHER PARTICIPANTS: Veterans with PTSD. INTERVENTION: Shamanic healing. MAIN OUTCOME MEASURE(S): PTSD symptoms, quality of life, and spiritual wellness. RESULTS: A semi-structured shamanic healing protocol was created with the following components: rapport building, power animal retrieval, extraction, compassionate spirit release, curse unraveling, soul retrieval, forgiveness/cord-cutting, aspect maturing/soul rematriing, and divination. Six veterans enrolled in the study (mean age = 49.3 +/- 13.1). Qualitative descriptions of the participants, their histories, and effects from the intervention are reported. Preliminary data was collected on PTSD-related outcomes. The protocol was found feasible and acceptable and recommendations for its future use are suggested. Future research is warranted and needed to evaluate the efficacy of shamanic healing as a potential therapy for veterans with PTSD.
Application of optical coherence tomography (OCT) for in vivo imaging of tissue and skeleton structure of intact living corals enabled the non-invasive visualization of coral tissue layers (endoderm versus ectoderm), skeletal cavities and special structures such as mesenterial filaments and mucus release from intact living corals. Coral host chromatophores containing green fluorescent protein-like pigment granules appeared hyper-reflective to near-infrared radiation allowing for excellent optical contrast in OCT and a rapid characterization of chromatophore size, distribution and abundance. In vivo tissue plasticity could be quantified by the linear contraction velocity of coral tissues upon illumination resulting in dynamic changes in the live coral tissue surface area, which varied by a factor of 2 between the contracted and expanded state of a coral. Our study provides a novel view on the in vivo organization of coral tissue and skeleton and highlights the importance of microstructural dynamics for coral ecophysiology. © 2017 The Author(s) Published by the Royal Society. All rights reserved.

Tools for regulated gene expression in E. faecalis are extremely limited. In this study we describe the construction of an expression vector for E. faecalis, designated pCIE, utilizing the PQ pheromone-responsive promoter of plasmid pCF10. We demonstrate that this promoter is tightly repressed, responds to nanogram quantities of the peptide pheromone, and has a large dynamic range. To demonstrate its utility, the promoter was used to control expression of the toxic peptides of two par family toxin-antitoxin loci present in E. faecalis, parpAD1 of the pAD1 plasmid and parEF0409 located on the E. faecalis chromosome. Results demonstrated differences in the modes of regulation of toxin expression and in the effects of toxins of these two related systems. We anticipate that this vector will be useful for further investigation of par TA system function as well as the regulated expression of other genes in E. faecalis. Importance E. faecalis is an important nosocomial pathogen and a model organism for examination of the genetics and physiology of Gram-positive cocci. While numerous genetic tools have been generated for the manipulation of this organism, vectors for the regulated expression of cloned genes remain limited by high background expression and the use of inducers with undesirable effects on the cell. Here we demonstrate that the PQ pheromone-responsive promoter is repressed tightly enough to allow cloning of TA system toxins and evaluate their effects at very low induction levels. This tool will allow us to more fully examine TA system function in E. faecalis and to further elucidate its potential roles in cell physiology.

Background: Melanoma incidence has increased in recent decades in the U.S.A. Uncertainty remains regarding how much of this increase is attributable to greater melanoma screening activities, potential detection bias and overdiagnosis. Objectives: To use a cross-sectional ecological analysis to evaluate the relationship between skin biopsy and melanoma incidence rates over a more recent time period than prior reports. Methods: Examination of the association of biopsy rates and melanoma incidence (invasive and in situ) in SEER-Medicare data (including 10 states) for 2002-2009. Results: The skin biopsy rate increased by approximately 50% (6% per year) throughout this 8-year period, from 7012 biopsies per 100 000 persons in 2002 to 10 528 biopsies per 100 000 persons in 2009. The overall melanoma incidence rate increased approximately 4% (< 1% per year) over the same time period. The incidence of melanoma in situ increased approximately 10% (1% per year), while the incidence of invasive melanoma increased from 2002 to 2005 then decreased from
2006 to 2009. Regression models estimated that, on average, for every 1000 skin biopsies performed, an additional 5.2 (95% confidence interval 4.1-6.3) cases of melanoma in situ were diagnosed and 8.1 (95% confidence interval 6.7-9.5) cases of invasive melanoma were diagnosed. When considering individual states, some demonstrated a positive association between biopsy rate and invasive melanoma incidence, others an inverse association, and still others a more complex pattern. Conclusions: Increased skin biopsies over time are associated with increased diagnosis of in situ melanoma, but the association with invasive melanoma is more complex. © 2017 British Association of Dermatologists.


Clinical quality measures (CQMs) are important tools for the assessment and improvement of health care quality. Federal requirements initially set forth in the American Recovery and Reinvestment Act, and advanced in subsequent stages of the requirements, codified electronic health record (EHR)-based CQM reporting, and have made automated CQM implementation a priority amongst the clinical and informatics communities. Nevertheless, the processes surrounding CQM implementation and validation remain complex, time-consuming, and largely undefined. We collected issue-tracking data during the course of an agile and rigorous collaborative project to build an analytics platform for the Knight Cardiovascular Institute at OHSU, with nine heart failure CQMs defined by the American College of Cardiology (ACC) as an exemplar. Using a mixed methods approach we provide an overview of our CQM implementation and validation process, identify major roadblocks and bottlenecks, and make recommendations for other professionals working in the area of health care quality assessment and improvement.


Ozone causes vagally-mediated airway hyperreactivity and recruits inflammatory cells, including eosinophils, to lungs where they mediate ozone-induced hyperreactivity one day after exposure, but are paradoxically protective three days later. To test the role of newly divided eosinophils in ozone-induced airway hyperreactivity in sensitized and non-sensitized guinea pigs. Non-sensitized 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 hours. One or three days later, vagally-induced bronchoconstriction was measured and inflammatory cells harvested from bone marrow, blood, and bronchoalveolar lavage. Ozone induced eosinophil hematopoiesis. One day post ozone, mature eosinophils dominate the inflammatory response and potentiate vagally-induced bronchoconstriction. However, by three days, newly divided eosinophils have reached the lungs where they inhibit ozone-induced airway hyperreactivity, since depleting them with AbIL-5 or a TNFalpha antagonist, worsened vagally-induced bronchoconstriction. In sensitized guinea pigs, both ozone-induced eosinophil hematopoiesis and subsequent recruitment of newly divided eosinophils to lungs three 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 three days later, newly divided eosinophils attenuate vagally-mediated hyperreactivity. Ozone-induced hematopoiesis of beneficial eosinophils is blocked by a TNFalpha antagonist, or by prior sensitization. In these animals, mature eosinophils are associated with hyperreactivity. Thus, interventions targeting eosinophils, while beneficial in atopic individuals, may delay resolution of airway hyperreactivity in non-atopic individuals.

BRCA1 plays an important role in preventing breast cancer and is often silenced or repressed in sporadic cancer. The BRCA1 promoter is bidirectional: it drives transcription of the long non-coding (lnc) NBR2 transcript in the opposite orientation relative to the BRCA1 transcript. Hypoxic conditions repress BRCA1 transcription, but their effect on expression of the NBR2 transcript has not been reported. We used quantitative RT-PCR to measure BRCA1 and NBR2 transcript levels in 0% and 1% oxygen in MCF-7 breast cancer cells and found that NBR2 transcript levels increased as a function of time under hypoxic conditions, whereas BRCA1 mRNA levels were repressed. Hypoxic conditions were ineffective in reducing BRCA1 mRNA in the UACC-3199 breast cancer cell line, which is reported to have an epigenetically silenced BRCA1 promoter, even though appreciable levels of BRCA1 and NBR2 mRNA were detected. Significant recovery back to baseline RNA levels occurred within 48 h after the MCF-7 cells were restored to normoxic conditions. We used a construct with the 218 bp minimal BRCA1 promoter linked to marker genes to show that this minimal promoter repressed expression bidirectionally under hypoxic conditions, which suggests that the elements necessary for induction of NBR2 are located elsewhere. © 2017


Etiological investigations of attention-deficit hyperactivity disorder (ADHD) and disruptive behavior problems support multiple causal pathways, including involvement of pre- and perinatal risk factors. Because these risks occur early in life, well before observable ADHD and externalizing symptoms emerge, the relation between risk and symptoms may be mediated by neurodevelopmental effects that manifest later in neuropsychological functioning. However, potential dissociable effects of pre/perinatal risk elements on ADHD and familial confounds must also be considered to test alternative hypotheses. 498 youth aged 6-17 years (55.0 % male) completed a multi-stage, multi-informant assessment including parent and teacher symptom reports of symptoms and parent ratings of pre/perinatal health risk indicators. Youth completed a neuropsychological testing battery. Multiple mediation models examined direct effects of pre- and perinatal health risk on ADHD and other disruptive behavior disorders and indirect effects via neuropsychological functioning. Parental ADHD symptoms and externalizing status was covaried to control for potential familial effects. Effects of prenatal substance exposure on inattention were mediated by memory span and temporal processing deficits. Further, effects of perinatal health risk on inattention, hyperactivity-impulsivity, and ODD were mediated by deficits in response variability and temporal processing. Further, maternal health risks during pregnancy appeared to exert direct rather than indirect effects on outcomes. Results suggest that after controlling for familial relatedness of ADHD between parent and child, early developmental health risks may influence ADHD via effects on neuropsychological processes underpinning the disorder.


Importance: There is limited literature reporting circumstances surrounding end-of-life care in vascular surgery patients. Objective: To identify factors driving end-of-life decisions in vascular surgery patients. Design, Setting, and Participants: In this cohort study, medical records were reviewed for all vascular surgery patients at a tertiary care university hospital who died during their hospitalization from 2005 to 2014. Main Outcomes and Measures: Patient, family, and hospitalization variables potentially important to influencing end-of-life decisions. Results: Of 111 patients included (67 [60%] male; median age, 75 [range, 24-94] years), 81 (73%) were emergent vs 30 (27%) elective admissions. Only 15 (14%) had an advance directive. Of the 81 (73%) patients placed on comfort care, 31 (38%) had care withheld or withdrawn despite available medical options, 15 (19%) had an advance directive, and 28 (25%) had a palliative care consultation. The median time from palliative care consultation to death was 10 hours (interquartile range, 3.36-66 hours). Comparing the 31 patients placed on comfort care despite available medical options with an admission diagnosis-matched
cohort, we found that more than 5 days admitted to the intensive care unit (odds ratio [OR], 4.11; 95% CI, 1.59-10.68; P < .001), more than 5 days requiring ventilator support (OR, 9.45; 95% CI, 3.41-26.18; P < .001), new renal failure necessitating dialysis (OR, 14.48; 95% CI, 3.69-56.86; P < .001), and new respiratory failure necessitating tracheostomy (OR, 23.92; 95% CI, 2.80-204; P < .001) correlated with transition to comfort care. Conclusions and Relevance: Palliative care consultations may be underused at the end of life. A large percentage of patients were transitioned to comfort measures despite available treatment, yet few presented with advance directives. In high-risk patients, discussions regarding extended stays in the intensive care unit, prolonged ventilator management, and possible dialysis and tracheostomy should be communicated with patients and families at time of hospitalization and advance directives solicited. Copyright © 2017 American Medical Association. All rights reserved.


Background and Purpose: Despite strong evidence for endovascular therapy in adults with acute arterial ischemic stroke, limited data exist in children. We aimed to describe endovascular therapy utilization and explore outcomes in a national sample of pediatric arterial ischemic stroke. Methods: We queried the 2012 Kids’ Inpatient Database for children aged greater than 28 days to 20 years with the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for arterial ischemic stroke and evaluated groups based on the procedure code for endovascular therapy. Poor outcome was defined as need for tracheostomy or gastrostomy, discharge to rehabilitation facility, or death. Logistic regression evaluated the association between endovascular therapy and poor outcome, adjusted for age, disease severity (hemiplegia, critical care interventions, neurosurgical interventions), and comorbidities. Results: We identified 3184 pediatric discharges with a diagnosis code for arterial ischemic stroke. Thirty-eight (1%) had an endovascular therapy procedure code. Endovascular therapy patients were older (10.2 versus 4.5 years, P < 0.001) and more likely to have hemiplegia/paresis (relative risk [RR] 3.8, 95% confidence interval [CI] 2.0-7.4), aphasia (RR 5.3, 95% CI 2.8-10.1), and facial droop (RR 4.0, 95% CI 1.9-8.7). Endovascular therapy was not associated with critical care and neurosurgical interventions or intracranial hemorrhage. Length of hospitalization, mortality, and discharge disposition were similar between groups. In a multivariable model, endovascular therapy was not associated with poor outcome (adjusted odds ratio 1.7, 95% CI 0.7-4.1). Conclusions: In a national sample of children with a diagnosis of arterial ischemic stroke, endovascular therapy was infrequently utilized. Patients with a procedure code for endovascular therapy had significant stroke-related deficits, but outcomes were similar to those in children who did not receive endovascular therapy. Our data in conjunction with evidence of benefit in adults support consideration of endovascular therapy for select children with acute stroke. © 2017 Elsevier Inc.


IMPORTANCE CHARGE syndrome refers to a syndrome involving coloboma, heart defects, atresia choanae, retardation of growth and development, genitourinary disorders, and ear anomalies. However, Verloes revised the characteristics of CHARGE syndrome in 2005 to define this syndrome more broadly. Deficiency of the semicircular canals is now a major criterion for CHARGE syndrome. OBJECTIVE To characterize patients with CHARGE syndrome at our center using Verloes criteria and to reevaluate the nomenclature for this condition. DESIGN, SETTING, AND PARTICIPANTS We performed a medical chart review of patients with CHARGE syndrome and reviewed their temporal bone imaging studies at a tertiary care children’s hospital affiliated with Washington University in St Louis. Two authors independently reviewed each imaging study (A.W. and K.H.). Radiologic studies, physical findings, genetic tests, and other diagnostic tests were included. Patients with no temporal bone imaging studies were excluded. RESULTS Eighteen children were included in this study; 13 children (72%) were male, and the mean (median; range) age of patients at the time of inner ear imaging studies was 2 years (4.5 years; 8 months to 8 years). Coloboma was present in 13 patients (72%)
and choanal atresia in 5 (28%); semicircular canal anomalies were present in all patients. Additionally, 13 patients (72%) were diagnosed as having hindbrain anomalies, 17 (94%) as having endocrine disorders, 17 (94%) as having mediastinal organ malformations, and all as having middle or external ear abnormalities and development delay. Cleft lip and cleft palate were found in 6 of 14 patients (43%) who did not have choanal atresia. We tested 16 patients for mutations in the CHD7 gene; 10 were positive (63%) for mutations, 4 (25%) were negative, and 2 (13%) were inconclusive. CONCLUSIONS AND RELEVANCE Semicircular canal anomalies were the most consistent finding in our patients with CHARGE syndrome. Given the high prevalence of semicircular canal hypoplasia and importance of imaging for diagnosing CHARGE syndrome, we propose changing the term CHARGE syndrome to 3C syndrome to emphasize the importance of the semicircular canals and to recall the 3 major criteria for diagnosis: coloboma, choanal atresia, and semicircular canal anomaly. The nomenclature would also reference the 3 semicircular canals in each ear. This new name for CHARGE syndrome would provide a mnemonic and focus the disease on the most important clinical criteria for diagnosis. © 2017 American Medical Association.


Objective The aim of this study was to identify clinical and demographic characteristics that moderate response to treatment with fesoterodine among women with a diagnosis of urgency-predominant urinary incontinence. Methods A multicenter, double-blinded, 12-week randomized controlled trial of pharmacologic therapy for urgency-predominant urinary incontinence in community-dwelling women diagnosed by the 3-item Incontinence Questionnaire (3IQ) was previously performed. Participants (N = 645) were randomized to fesoterodine therapy (4-8 mg daily; n = 322) or placebo (n = 323). Urinary incontinence was assessed by 3-day voiding diaries. In this secondary analysis, a "responder" was defined as reduction of 50% or greater in overall incontinence episode frequency compared with baseline. Clinical and demographic characteristics that may moderate treatment response were assessed by testing for interaction between characteristic and intervention in logit models of responders, adjusting for clinical site. Results Participants’ ages were a mean of 56 (SD, 14) years, 68% were white race, and they had a mean of 3.9 (SD, 3.0) urgency incontinence episodes per day. There were no baseline differences in demographic, clinical, or incontinence characteristics between treatment and placebo groups or between responders and nonresponders. There was an increase in the proportion of responders to fesoterodine with increasing age (P = 0.04) and parity (0.04) and among married women (P = 0.03), but no effect modification was observed by race/ethnicity, body mass index, education, employment status, or alcohol or tobacco use. Conclusions In ambulatory women with urgency-predominant urinary incontinence, older age, being married, and higher parity significantly moderated and potentiated the effects of pharmacologic therapy on incontinence frequency. This study identifies certain populations who may have increased responsiveness to treatment with antimuscarinic therapy and may be used to inform and guide future therapy. © 2016 Wolters Kluwer Health, Inc. All rights reserved.


Fear and emotional learning are modulated by endogenous opioids but the cellular basis for this is unknown. The intercalated cells (ITCs) gate amygdala output and thus regulate the fear response. Here we find endogenous opioids are released by synaptic stimulation to act via two distinct mechanisms within the main ITC cluster. Endogenously released opioids inhibit glutamate release through the delta-opioid receptor (DOR), an effect potentiated by a DOR-positive allosteric modulator. Postsynaptically, the opioids activate a potassium conductance through the mu-opioid receptor (MOR), suggesting for the first time that endogenously released opioids directly regulate neuronal excitability. Ultrastructural localization of endogenous ligands support these functional findings. This study demonstrates a new role for endogenously released opioids as
neuromodulators engaged by synaptic activity to regulate moment-to-moment neuronal communication and excitability. These distinct actions through MOR and DOR may underlie the opposing effect of these receptor systems on anxiety and fear.


OBJECTIVES: To compare the prevalence of and association between falls and frailty of prostate cancer survivors (PCs) who were current, past or never users of androgen deprivation therapy (ADT). DESIGN: Cross-sectional. SETTING: Mail and electronic survey. PARTICIPANTS: PCS (N = 280; mean age 72 +/- 8). MEASUREMENTS: Cancer history, falls, and frailty status (robust, prefrail, frail) using traditionally defined and obese phenotypes. RESULTS: Current (37%) or past (34%) ADT users were more than twice as likely to have fallen in the previous year as never users (15%) (P = .002). ADT users had twice as many recurrent falls (P < .001) and more fall-related injuries than unexposed men (P = .01). Current (43%) or past (40%) ADT users were more likely to be classified as prefrail or frail than never users (15%) (P < .001), and the prevalence of combined obese frailty + prefrailty was even greater in current (59%) or past (62%) ADT users than never users (25%) (P < .001). Traditional and obese frailty significantly increased the likelihood of reporting falls in the previous year (odds ratio (OR) = 2.15, 95% CI = 1.18-3.94 and OR = 2.97, 95% CI = 1.62-5.58, respectively) and was also associated with greater risk of recurrent falls (OR = 3.10, 95% CI = 1.48-6.5 and OR = 3.99, 95% CI = 1.79-8.89, respectively). CONCLUSIONS: Current and past exposure to ADT is linked to higher risk of falls and frailty than no treatment. PCs should be appropriately counseled on fall prevention strategies, and approaches to reduce frailty should be considered.


Tofacitinib is the first Janus kinase (JAK) inhibitor commercially approved for the treatment of rheumatoid arthritis. This compound and a number of other JAK inhibitors are currently being tested in phase II and III trials for the treatment of a variety of autoimmune inflammatory diseases. Whereas a characteristic safety profile is emerging for some JAK inhibitors, differences between individual agents might emerge on the basis of distinct potency against their molecular targets. Similarly to biological therapy, JAK inhibition can lead to serious and opportunistic infections, and viral infections seem to be particularly frequent. Although no malignancy signals have been identified to date, long-term follow-up and further research are needed to understand the risk of malignancy associated with these compounds. As is the case for biologic agents, vaccination is important to mitigate the risks of these emerging therapies. © 2017 Nature Publishing Group, a division of Macmillan Publishers Limited. All Rights Reserved.


Nontuberculous mycobacteria (NTM) are environmental pathogens that are an increasingly common cause of pulmonary and extrapulmonary disease. Electronic laboratory-based reporting is a straightforward mechanism for identifying NTM infections and for monitoring trends in disease. Oregon was the first state to make NTM reportable, although at this time the reporting requirement is limited to extrapulmonary infection. This has assisted authorities in detecting outbreaks and healthcare-related infections. However, further consideration should be given to the reportability of pulmonary NTM disease. Pulmonary NTM disease is more common than tuberculosis in the United States and is of emerging public health concern. Although the direct public health action that would be triggered by a pulmonary NTM disease report is not clear, without surveillance, public health is missing an opportunity to better understand pulmonary NTM.
disease trends and reasons for its increasing recognition within our population. We believe state health authorities should conduct surveillance for pulmonary NTM, either by mandating reporting of laboratory isolates or by other mechanisms as we have done in Oregon. Copyright © 2017 by the American Thoracic Society.


OBJECTIVE: Recent evidence suggests in utero exposure to maternal antibodies and cytokines as important risk factors for autism spectrum disorders (ASD). We aimed to systematically review the risk of ASD in children born to mothers with rheumatoid arthritis (RA) compared to children born to mothers without RA.

METHODS: We conducted a systematic review of original articles using electronic databases: PubMed, EMBase, and Web of Science. RESULTS: Our literature search identified a total of 70 articles. Of the potentially relevant studies retrieved, 67 were excluded for lack of relevance and/or because they did not report original data. Three studies were included in the final analysis. A case-control study was unable to detect a difference in the prevalence of RA in ASD mothers versus control mothers. Another case-control study showed a statistically significant 8-fold increase in autoimmune disorders, including RA, in mothers of ASD offspring compared to controls. Forty-six percent of ASD offspring had a first-degree relative with RA compared to 26% of controls. Moreover, in a population-based cohort study, investigators observed an increased risk of ASD in children with a maternal history of RA compared to children born to unaffected mothers. These studies had methodological limitations: none controlled for medication exposures, only 1 controlled for obstetrical complications and considered the timing of RA diagnosis in relation to pregnancy, and all but 1 used a case-control study design. CONCLUSION: Observational studies suggest a potentially increased risk of ASD in children born to mothers with RA compared to children born to unaffected mothers, although data are limited. This article is protected by copyright. All rights reserved.


ZBTB transcription factors orchestrate gene transcription during tissue development. However, their roles in glioblastoma (GBM) remain unexplored. Here, through a functional screening of ZBTB genes, we identify that BCL6 is required for GBM cell viability and that BCL6 overexpression is associated with worse prognosis. In a somatic transgenic mouse model, depletion of Bcl6 inhibits the progression of KrasG12V-driven high-grade glioma. Transcriptome analysis demonstrates the involvement of BCL6 in tumor protein p53 (TP53), erythroblastic leukemia viral oncogene homolog (Erbb), and MAPK signaling pathways. Indeed, BCL6 represses the expression of wild-type p53 and its target genes in GBM cells. Knockdown of BCL6 augments the activation of TP53 pathway in response to radiation. Importantly, we discover that receptor tyrosine kinase AXL is a transcriptional target of BCL6 in GBM and mediates partially the regulatory effects of BCL6 on both MEK-ERK (mitogen-activated protein/extracellular signal-regulated kinase kinase-extracellular signal-regulated kinase) and S6K-RPS6 (ribosomal protein S6 kinase-ribosomal protein S6) axes. Similar to BCL6
silencing, depletion of AXL profoundly attenuates GBM proliferation both in vitro and in vivo. Moreover, targeted inhibition of BCL6/nuclear receptor corepressor 1 (NCoR) complex by peptidomimetic inhibitor not only significantly decreases AXL expression and the activity of MEK-ERK and S6K-RPS6 cascades but also displays a potent antiproliferative effect against GBM cells. Together, these findings uncover a glioma-promoting role of BCL6 and provide the rationale of targeting BCL6 as a potential therapeutic approach.


Traumatic brain injury (TBI) results in severe neurological impairments without effective treatments. Inflammation appears to be an important contributor to key pathogenic events such as secondary brain injury following TBI and therefore serves as a promising target for novel therapies. We have recently demonstrated the ability of a molecular construct comprised of the human leukocyte antigen (HLA)-DRalpha1 domain linked covalently to mouse (m)MOG-35-55 peptide (DRalpha1-MOG-35-55 construct) to reduce CNS inflammation and tissue injury in animal models of multiple sclerosis and ischemic stroke. The aim of the current study was to determine if DRalpha1-MOG-35-55 treatment of a fluid percussion injury (FPI) mouse model of TBI could reduce the lesion size and improve disease outcome measures. Neurodeficits, lesion size, and immune responses were determined to evaluate the therapeutic potential and mechanisms of neuroprotection induced by DRalpha1-MOG-35-55 treatment. The results demonstrated that daily injections of DRalpha1-MOG-35-55 given after FPI significantly reduced numbers of infiltrating CD74+ and CD86+ macrophages and increased numbers of CD206+ microglia in the brain concomitant with smaller lesion sizes and improvement in neurodeficits. Conversely, DRalpha1-MOG-35-55 treatment of TBI increased numbers of circulating CD11b+ monocytes and their expression of CD74 but had no detectable effect on cell numbers or marker expression in the spleen. These results demonstrate that DRalpha1-MOG-35-55 therapy can reduce CNS inflammation and significantly improve histological and clinical outcomes after TBI. Future studies will further examine the potential of DRalpha1-MOG-35-55 for treatment of TBI.


AIM: The alpha-synuclein (alpha-syn) level in human cerebrospinal fluid (CSF), as measured by immunoassays, is promising as a Parkinson’s disease (PD) biomarker. However, the levels of total alpha-syn are inconsistent among studies with large cohorts and different measurement platforms. Total alpha-syn level also does not correlate with disease severity or progression. Here, we developed a highly sensitive Multiple Reaction Monitoring (MRM) method to measure absolute CSF alpha-syn peptide concentrations without prior enrichment or fractionation, aiming to discover new candidate biomarkers. RESULTS: Six peptides covering 73% of protein sequence were reliably identified, and two were consistently quantified in cross-sectional and longitudinal cohorts. Absolute concentration of alpha-syn in human CSF was determined to be 2.1 ng/mL. A unique alpha-syn peptide, TVEGAGSIAAATGFVK (81–96), displayed excellent correlation with previous immunoassay results in two independent PD cohorts (p < 0.001), correlated with disease severity, and its changes significantly tracked the disease progression longitudinally. CONCLUSIONS: An MRM assay to quantify human CSF alpha-syn was developed and optimized. Sixty clinical samples from cross-sectional and longitudinal PD cohorts were analyzed with this approach. Although further larger-scale validation is needed, the results suggest that alpha-syn peptide could serve as a promising biomarker in PD diagnosis and progression. This article is protected by copyright. All rights reserved.

Subcutaneous (SC) injection of pasireotide, a somatostatin analog, is approved for the treatment of adults with Cushing’s disease (CD) for whom pituitary surgery was unsuccessful or is not an option. We highlight the symptomatic and biochemical improvement of six patients with recurrent CD treated with pasireotide SC at a single center for at least 1 year. Patients were treated either through commercial use (n = 5) or through the Phase 3 trial (n = 1; http://ClinicalTrials.gov identifier, NCT00434148; study number, B2305). Most patients (n = 5) were female, and the mean age at diagnosis was 35.8 years. All patients demonstrated biochemical control at 1 year of treatment. Three of the five real-world patients followed for more than 1 year remain on pasireotide SC and are controlled. Two patients discontinued pasireotide SC; one patient because of persistently elevated urinary-free cortisol levels and gallstones, and the other because of treatment for an unrelated brain tumor. Symptomatic improvement varied, but all patients demonstrated weight loss. Nausea and mild, transient injection-site reactions were the most frequently reported adverse events. Although glycated hemoglobin (HbA1c) increased after treatment initiation, four of five patients maintained HbA1c levels ≤7.0% while receiving pasireotide SC and concomitant individualized diabetes medication, if necessary. In patients who discontinued pasireotide SC, HbA1c levels decreased within 6 weeks. This report documents real-world use of pasireotide SC and indicates its effectiveness as a long-term treatment option for patients with CD. Although hyperglycemia was observed in most patients, it was managed with appropriate monitoring and treatment and was reversible upon discontinuation of pasireotide SC. © 2017 Yedinak, Hopkins, Williams, Ibrahim, Cetas and Fleseriu.


Background-Timely diagnosis of ST-segment elevation myocardial infarction (STEMI) in the emergency department (ED) is made solely by ECG. Obtaining this test within 10 minutes of ED arrival is critical to achieving the best outcomes. We investigated variability in the timely identification of STEMI across institutions and whether performance variation was associated with the ED characteristics, the comprehensiveness of screening criteria, and the STEMI screening processes. Methods and Results-We examined STEMI screening performance in 7 EDs, with the missed case rate (MCR) as our primary end point. The MCR is the proportion of primarily screened ED patients diagnosed with STEMI who did not receive an ECG within 15 minutes of ED arrival. STEMI was defined by hospital discharge diagnosis. Relationships between the MCR and ED characteristics, screening criteria, and STEMI screening processes were assessed, along with differences in door-to-ECG times for captured versus missed patients. The overall MCR for all 7 EDs was 12.8%. The lowest and highest MCRs were 3.4% and 32.6%, respectively. The mean difference in door-to-ECG times for captured and missed patients was 31 minutes, with a range of 14 to 80 minutes of additional myocardial ischemia time for missed cases. The prevalence of primarily screened ED STEMIs was 0.09%. EDs with the greatest informedness (sensitivity+specificity-1) demonstrated superior performance across all other screening measures. Conclusions-The 29.2% difference in MCRs between the highest and lowest performing EDs demonstrates room for improving timely STEMI identification among primarily screened ED patients. The MCR and informedness can be used to compare screening across EDs and to understand variable performance. © 2017 The Authors.


BACKGROUND/AIM: Although it has been shown that the neutrophil-to-lymphocyte ratio (NLR) may predict the progression of nonmuscle invasive bladder cancer (NMIBC), its association with the recurrence of NMIBC has been poorly studied. The aim of this study is to evaluate the association between NLR and disease recurrence in patients with NMIBC. MATERIALS AND METHODS: The medical records of 428 consecutive
initially diagnosed NMIBC patients who underwent transurethral resection between January 2010 and July 2014 were retrospectively reviewed. Patients without a preoperative NLR (n = 6), without a minimum of 6 months of follow-up (n = 56), who were lost to follow-up (n = 38), or who had progressive disease during follow-up (n = 42) were excluded. The demographics, tumor characteristics, and NLRs of patients with and without tumor recurrence were compared. RESULTS: Of 286 patients who met the inclusion criteria, 68 (17.43%) had recurrent disease. Tumor size (P = 0.198), tumor type (P = 0.929), and the presence of carcinoma in situ (P = 0.373) were also similar between groups. Patients with recurrent disease had a higher mean NLR (2.62 +/- 0.99 vs. 2.2 +/- 0.96, P = 0.002). CONCLUSION: Our results show that NLR may be used as a predictor of recurrence in patients with NMIBC; however, prospective studies are required to validate these findings.


In patients with colorectal cancer (CRC) that metastasizes to the liver, there are several key goals for improving outcomes including early detection, effective prognostic indicators of treatment response, and accurate identification of patients at high risk for recurrence. Although new therapeutic regimens developed over the past decade have increased survival, there is substantial room for improvement in selecting targeted treatment regimens for the patients who will derive the most benefit. Recently, there have been exciting developments in identifying high-risk patient cohorts, refinements in the understanding of systemic vs localized drug delivery to metastatic niches, liquid biomarker development, and dramatic advances in tumor immune therapy, all of which promise new and innovative approaches to tackling the problem of detecting and treating the metastatic spread of CRC to the liver. Our multidisciplinary group held a state-of-the-science symposium this past year to review advances in this rapidly evolving field. Herein, we present a discussion around the issues facing treatment of patients with CRC liver metastases, including the relationship of discrete gene signatures with prognosis. We also discuss the latest advances to maximize regional and systemic therapies aimed at decreasing intrahepatic recurrence, review recent insights into the tumor microenvironment, and summarize advances in noninvasive multimodal biomarkers for early detection of primary and recurrent disease. As we continue to advance clinically and technologically in the field of colorectal tumor biology, our goal should be continued refinement of predictive and prognostic studies to decrease recurrence after curative resection and minimize treatment toxicity to patients through a tailored multidisciplinary approach to cancer care.


Context: Daily injections are required for growth hormone replacement therapy, which may cause low compliance as a result of inconvenience and distress in patients. Objective: CTP-modified human growth hormone (MOD-4023) is developed for once-a-week dosing regimen in GH-deficient (GHD) adults and children. The present trial was a safety and dose-finding study for weekly MOD-4023 in GHD children. Design: a multi-center, open-label, randomized, controlled Phase 2 study in children with GHD, evaluating the safety, tolerability, PK/PD and efficacy of 3 different weekly MOD-4023 doses, compared to daily r-hGH. Setting: The trial was conducted in 14 endocrinology centers in Europe. Patients: 53 pre-pubertal children with GHD completed 12 months of treatment with either MOD-4023 (N=42) or r-hGH (N=11). Interventions: CTP-modified hGH (MOD-4023) was administered weekly at a dose of either 0.25, 0.48, or 0.66 mg/kg/week, and compared to daily hGH at a dose of 0.24 mg/kg/week. Results: MOD-4023 showed an estimated half-life approximately 5- to 10-fold longer when compared to daily r-hGH. IGF-I and IGFBP-3 showed dose-dependent increase during MOD-4023 treatment. IGF-I SDS for MOD-4023 did not exceed +2. All MOD-4023 cohorts demonstrated adequate catch-up growth. The 0.66 mg/kg/week dose demonstrated efficacy closest to daily r-hGH. No serious adverse events were observed during MOD-4023 treatment, and its tolerability was
consistent with known properties of r-hGH. Conclusions: this study confirms the long-acting properties of MOD-4023 and shows a promising safety and tolerability profile. This provides support for initiation of a Phase 3 study in GHD children using a single weekly injection of MOD-4023.


Fanconi anemia (FA) is an inherited bone marrow failure disorder associated with a high incidence of leukemia and solid tumors. Bone marrow transplantation is currently the only curative therapy for the hematopoietic complications of this disorder. However, long-term morbidity and mortality remain very high, and new therapeutics are badly needed. Here we show that the widely used diabetes drug metformin improves hematopoiesis and delays tumor formation in Fancd2/-/- mice. Metformin is the first compound reported to improve both of these FA phenotypes. Importantly, the beneficial effects are specific to FA mice and are not seen in the wild-type controls. In this preclinical model of FA, metformin outperformed the current standard of care, oxymetholone, by improving peripheral blood counts in Fancd2/-/- mice significantly faster. Metformin increased the size of the hematopoietic stem cell compartment and enhanced quiescence in hematopoietic stem and progenitor cells. In tumor-prone Fancd2/-/- Trp53+/- mice, metformin delayed the onset of tumors and significantly extended the tumor-free survival time. In addition, we found that metformin and the structurally related compound aminoguanidine reduced DNA damage and ameliorated spontaneous chromosome breakage and radials in human FA patient-derived cells. Our results also indicate that aldehyde detoxification might be one of the mechanisms by which metformin reduces DNA damage in FA cells. © 2016 by The American Society of Hematology.


OBJECTIVES: Despite the fact that HPV-driven oropharyngeal cancer (HPV-OPC) has relatively low recurrence rates, intensive post-therapy monitoring remains the standard of care. Post-treatment biomarkers are needed to risk stratify HPV-OPC patients for more individualized surveillance intensity and which remain at higher recurrence risk. MATERIALS AND METHODS: 115 HPV-OPC patients (ascertained by p16 immunohistochemistry and/or in-situ hybridization) from a multicenter prospective case study (HOTSPOT) had blood collected at diagnosis, and 64 of these also had blood collected at post-treatment follow-up visits for up to two years. Samples were centrally tested for antibodies to the L1, E1, E2, E4, E6, and E7 proteins of HPV16. RESULTS: At diagnosis, most HPV-OPC cases were seropositive to HPV16 E6 (85%). In posttherapeutic samples, HPV16 antibody level decreased slowly over time, but only 3 (of 51 cases seropositive at enrollment) dropped low enough to be classified as seronegative. At 3years after diagnosis, cumulative risk of recurrence was 10.2% and 0% in HPV16 E6 seropositive and E6 seronegative HPV-OPC cases, respectively (p=0.18). Risk of recurrence was increased, although not statistically significant, in those with higher HPV16 E6 antibody levels at diagnosis (per log antibody level, hazard ratio [HR]=1.81, 95%CI=0.47-6.92). CONCLUSION: This study confirms the high seroprevalence of HPV oncogenic antibodies at diagnosis of HPV-OPC. HPV16 E6 antibody levels decrease after treatment, but most cases remain seropositive for up to two years. HPV16 E6 antibody levels at diagnosis did not appear to be a strong predictor of recurrence.


The reported prevalence of autism spectrum disorder (ASD) has been increasing rapidly in many parts of the world. However, data on its prevalence in China are largely missing. Here, we assessed the suitability of the
modified Chinese version of a newly-developed ASD screening tool, the Modified Chinese Autism Spectrum Rating Scales (MC-ASRS) in screening for ASD in Chinese children aged 6-12 years, through comparison with the Social Responsiveness Scale (SRS) that has been widely used for ASD screening. We recruited the parents/caregivers of 1588 typically-developing children and 190 children with ASD aged 6-12 years to complete the MC-ASRS and SRS, and evaluated the validity of both scales in discriminating children with ASD from those developing typically. The results showed that MC-ASRS performed as well as SRS in sensitivity, specificity, and area-under-the-curve (both >0.95) in receiver operating characteristic analysis, with a fair false-negative rate. These results suggest that MC-ASRS is a promising tool for screening for children with ASD in the general Chinese population.


The purpose of this study was to explore the psychometric properties of the Chinese version of the autism spectrum rating scale (ASRS). We recruited 1,625 community-based children and 211 autism spectrum disorder (ASD) cases from 4 sites, and the parents of all participants completed the Chinese version of the ASRS. A robust weighted least squares means and variance adjusted estimator was used for exploratory factor analysis. The 3-factor structure included 59 items suitable for the current sample. The item reliability for the modified Chinese version of the ASRS (MC-ASRS) was excellent. Moreover, with 60 as the cut-off point, receiver operating characteristic analysis showed that the MC-ASRS had excellent discriminate validity, comparable to that of the unmodified Chinese version (UC-ASRS), with area under the curve values of 0.952 (95% CI: 0.936–0.967) and 0.948 (95% CI: 0.930–0.965), respectively. Meanwhile, the confirm factor analysis revealed that MC-ASRS had a better construct validity than UC-ASRS based on the above factor solution in another children sample. In conclusion, the MC-ASRS shows better efficacy in epidemiological screening for ASD in Chinese children. © 2017 The Author(s)


This study aimed to establish norms for the modified Chinese version of the Autism Spectrum Rating Scale (ASRS). Participants were recruited from Shanghai, Harbin, Guangzhou, and Changsha, China, and their parents and teachers were invited to complete the Chinese Parent version and the Teacher version of the ASRS. In both versions, boys had significantly higher sub-scale scores and total score (T-score) by 1–3 and 4–5 points respectively, than girls (both P < 0.001). Age had weak correlations with some sub-scores and the T-score (r ranged from −0.1859 to 0.0738), and some reached significance (P < 0.03). The correlations appeared stronger and were more common in females. The T-score based on Chinese norms ideally correlated with the score based on the United States norms in boys and girls for both versions. Norms for the Chinese version of the ASRS for children aged 6–12 years are proposed and may be helpful for screening individuals with autism spectrum disorders from the general population of children. © 2017 The Author(s)


The integration of biomaterials and understanding of vascular biology has led to the development of perfusable endothelialized flow models, which have been used as valuable tools to study the platelet-endothelium interface under shear. In these models, the parameters of geometry, compliance, biorheology, and cellular complexity are varied to recapitulate the physical biology of platelet recruitment and activation under physiologically relevant conditions of blood flow. In this review, we summarize the mechanistic insights
learned from perfusable microvessel models and discuss the potential utility as well as challenges of endothelialized microfluidic devices to study platelet function in the bloodstream in vitro.


Objective.: Fibromyalgia is a chronic pain condition with few effective treatments. Many fibromyalgia patients seek acupuncture for analgesia; however, its efficacy is limited and not fully understood. This may be due to heterogeneous pathologies among participants in acupuncture clinical trials. We hypothesized that pressure pain tenderness would differentially classify treatment response to verum and sham acupuncture in fibromyalgia patients. Design.: Baseline pressure pain sensitivity at the thumbnail at baseline was used in linear mixed models as a modifier of differential treatment response to sham versus verum acupuncture. Similarly, needle-induced sensation was also analyzed to determine its differential effect of treatment on clinical pain. Methods and Patients.: A cohort of 114 fibromyalgia patients received baseline pressure pain testing and were randomized to either verum (N = 59) or sham (N = 55) acupuncture. Participants received treatments from once a week to three times a week, increasing in three-week blocks for a total of 18 treatments. Clinical pain was measured on a 101-point visual analog scale, and needle sensation was measured by questionnaire throughout the trial. Results.: Participants who had higher pain pressure thresholds had greater reduction in clinical pain following verum acupuncture while participants who had lower pain pressure thresholds showed better analgesic response to sham acupuncture. Moreover, patients with lower pressure pain thresholds had exacerbated clinical pain following verum acupuncture. Similar relationships were observed for sensitivity to acupuncture needling. Conclusions.: These findings suggest that acupuncture efficacy in fibromyalgia may be underestimated and a more personalized treatment for fibromyalgia may also be possible.