Medicine Abstracts

Academic Medicine

K. G. Schaefer et al., **Raising the Bar for the Care of Seriously Ill Patients: Results of a National Survey to Define Essential Palliative Care Competencies for Medical Students and Residents**, *Acad Med* 89.7 (July 2014): 1024–1031 • *Purpose:* Given the shortage of palliative care specialists in the United States, to ensure quality of care for patients with serious, life-threatening illness, generalist-level palliative care competencies need to be defined and taught. The purpose of this study was to define essential competencies for medical students and internal medicine and family medicine (IM/FM) residents through a national survey of palliative care experts. *Method:* Proposed competencies were derived from existing hospice and palliative medicine fellowship competencies and revised to be developmentally appropriate for students and residents. In spring 2012, the authors administered a Web-based, national cross-sectional survey of palliative care educational experts to assess ratings and rankings of proposed competencies and competency domains. *Results:* The authors identified 18 comprehensive palliative care competencies for medical students and IM/FM residents, respectively. Over 95% of survey respondents judged the competencies as comprehensive and developmentally appropriate (survey response rate = 72%, 71/98). Using predefined cutoff criteria, experts identified 7 medical student and 13 IM/FM resident competencies as essential. Communication and pain/symptom management were rated as the most critical domains. *Conclusions:* This national survey of palliative care experts defines comprehensive and essential palliative care competencies for medical students and IM/FM residents that are specific, measurable, and can be used to report educational outcomes; provides a sequence for palliative care curricula in undergraduate and graduate medical education; and highlights the importance of educating medical trainees in communication and pain management. Next steps include seeking input and endorsement from stakeholders in the broader medical education community.

A. W. Shaheen et al., **End-of-Life and Palliative Care Curricula in Internal Medicine Clerkships: A Report on the Presence, Value, and Design of Curricula as Rated by Clerkship Directors**, *Acad Med* 89.8 (August 2014): 1168–1173 • *Purpose:* End-of-life and palliative care (EOL/PC) education is a necessary component of undergraduate medical education. The extent of EOL/PC education in internal medicine (IM) clerkships is unknown. The purpose of this national study was to investigate the presence of formal EOL/PC curricula within IM clerkships; the value placed by IM clerkship directors on this type of curricula; curricular design and implementation strategies; and related barriers and resources. *Method:* The Clerkship Directors in Internal Medicine conducted its annual survey of its institutional members in April 2012. The authors analyzed responses to survey items pertaining to formal EOL/PC curriculum and content using descriptive statistics. The authors used qualitative techniques to analyze free-text responses. *Results:* The response rate was 77.0% (94/122). Of those responding, 75.8% (69/91) believed such training should occur in the IM clerkship, and 43.6% (41/94) reported formal curricula in EOL/PC. Multiple instructional modalities were used to deliver this content, with the majority of programs dedicating four or more hours to the curriculum. Curricula covered a wide range of topics, and student assessment tools were varied. Most felt that students valued this education. The qualitative analysis revealed differences in the values clerkship directors placed on teaching EOL/PC within the IM clerkship.

Conclusions: Although many IM clerkship directors have implemented formal curricula in EOL/PC, a substantial gap remains between those who have implemented and those who believe it belongs in the clerkship. Time, faculty, cost, and competing demands are the main barriers to implementation.

Addictive Behaviors

H. Cho et al., **Development of the Internet Addiction Scale based on the Internet Gaming Disorder Criteria Suggested in DSM-5**, *Addict Behav* 39.9 (September 2014): 1361–1366 • This study was conducted to develop and validate a standardized self-diagnostic Internet addiction (IA) scale based on the diagnosis criteria for Internet Gaming Disorder (IGD) in the *Diagnostic and Statistical Manual of Mental Disorder*, 5th edition (DSM-5). Items based on the IGD diagnosis criteria were developed using items of the previous Internet addiction scales. Data were collected from a community sample. The data were divided into two sets, and confirmatory factor analysis (CFA) was performed repeatedly. The model was modified after discussion with professionals based on the first CFA results, after which the second CFA was performed. The internal consistency reliability was generally good. The items that showed significantly low correlation values based on the item-total correlation of each factor were excluded. After the first CFA was performed, some factors and items were excluded. Seven factors and 26 items were prepared for the final model. The second CFA results showed good general factor loading, squared multiple correlation (SMC) and model fit. The model fit of the final model was good, but some factors were very highly correlated. It is recommended that some of the factors be refined through further studies.

American Heart Journal

E. C. Perin et al., **Adipose-Derived Regenerative Cells in Patients with Ischemic Cardiomyopathy: The PRECISE Trial**, *Am Heart J* 168.1 (July 2014): 88–95.e2 • *Aims:* Adipose-derived regenerative cells (ADRCs) can be isolated from liposuction aspirates and prepared as fresh cells for immediate administration in cell therapy. We performed the first randomized, placebo-controlled, double-blind trial to examine the safety and feasibility of the transendocardial injections of ADRCs in no-option patients with ischemic cardiomyopathy. *Methods and Results:* Procedural, postoperative, and follow-up safety end points were monitored up to 36 months. After baseline measurements, efficacy was assessed by echocardiography and single-photon emission computed tomography (6, 12, and 18 months), metabolic equivalents and maximal oxygen consumption (MVO2) (6 and 18 months), and cardiac magnetic resonance imaging (6 months). We enrolled 21 ADRC-treated and 6 control patients. Liposuction was well tolerated, ADRCs were successfully prepared, and transendocardial injections were feasible in all patients. No malignant arrhythmias were seen. Adverse events were similar between groups. Metabolic equivalents and MVO2 values were preserved over time in ADRC-treated patients but declined significantly in the control group. The difference in the change in MVO2 from baseline to 6 and 18 months was significantly better in ADRC-treated patients compared with controls. The ADRC-treated patients showed significant improvements in total left ventricular mass by magnetic resonance imaging and wall motion score index. Single-photon emission computed tomography results suggested a reduction in inducible ischemia in ADRC-treated patients up to 18 months. *Conclusion:* Isolation and transendocardial injection of autologous ADRCs in no-option patients were safe and feasible. Our results suggest that ADRCs may preserve ventricular function, myocardial perfusion, and exercise capacity in these patients.

American Journal of Obstetrics and Gynecology

R. Salani, C. C. Billingsley, and S. M. Crafton, **Cancer and Pregnancy: An Overview for Obstetricians and Gynecologists**, *Am J Obstet Gynecol* 211.1 (July 2014): 7–14 • A relatively rare occurrence, pregnancy-associated cancer affects approximately 1 in 1000 pregnancies. Optimizing treatment of the cancer and minimizing harm to the

fetus are often dependent on the extent of disease, treatment options required, and the impact on the pregnancy as well as the gestational age of pregnancy. When malignancy is diagnosed, the obstetrician-gynecologist plays a key role in the diagnosis, initial evaluation, and coordination of patient care. Furthermore, the obstetrician-gynecologist may be asked to assist in fertility planning for young women with a new diagnosis of cancer and may be responsible for addressing questions about family-planning needs and the safety of future pregnancy. Therefore, the purpose of this article was to provide the obstetrician-gynecologist with a relevant overview of the current literature regarding concurrent pregnancy and cancer diagnoses, management options, including maternal and neonatal outcomes, as well as the future needs of young women diagnosed with cancer who desire fertility preservation.

British Journal of Surgery

R. Desai et al., **Estimated Risk of Cancer Transmission from Organ Donor to Graft Recipient in a National Transplantation Registry**, *Br J Surg* 101.7 (June 2014): 768–774 • *Background:* Transplanted organs carry the risk of inadvertent donor cancer transmission. Some cancers in organ donors have been classified as being associated with a high or unacceptable risk, but the evidence for such recommendations is scanty. *Methods:* The risk of cancer transmission from donors characterized as high or unacceptable risk was studied by analysing transplant and cancer registry data. Donors and recipients from England (1990–2008) were identified from the UK Transplant Registry. Cancer details were obtained from cancer registries and classified using guidelines from the Council of Europe and Organ Procurement and Transplantation Network/United Network for Organ Sharing. *Results:* Of 17,639 donors, 202 (1.1 per cent) had a history of cancer, including 61 donors with cancers classed as having an unacceptable/high risk of transmission. No cancer transmission was noted in 133 recipients of organs from these 61 donors. At 10 years after transplantation, the additional survival benefit gained by transplanting organs from donors with unacceptable/high-risk cancer was 944 (95 per cent confidence interval (c.i.) 851 to 1037) life-years, with a mean survival of 7.1 (95 per cent c.i. 6.4 to 7.8) years per recipient. *Conclusion:* Strict implementation of present guidelines is likely to result in overestimation of cancer transmission risk in some donors. Organs from some donors with cancers defined as unacceptable/high risk can be used safely.

Fertility and Sterility

A. Pilatz et al., **Acute Epididymitis Induces Alterations in Sperm Protein Composition**, *Fertil Steril* 101.6 (June 2014): 1609–17.e1–5 • *Objective:* To use a proteomic approach to evaluate possible postinflammatory alterations in the protein composition of motile sperm in patients 3 months after acute epididymitis. *Design:* Prospective case-control study. *Setting:* University medical school research laboratory. *Patient*(*s*): Eight patients 3 months after acute unilateral epididymitis, and 10 healthy controls. *Intervention*(*s*): None. *Main Outcome Measure*(*s*): Proteome analysis of sperm samples collected by swim-up from control and acute epididymitis patients analyzed by two-dimensional gel electrophoresis and subsequent protein identification by matrix-assisted laser desorption/ionization-time-of-flight (MALDI-TOF) mass spectrometry; immunofluorescence staining for mitochondrial ATP synthase subunit β (ATP5B), α-tubulin (TUBA1A), and tubulin-β2c (TUBB4B) for validation purposes. *Result*(*s*): Proteome analysis identified 35 proteins in sperm from epididymitis patients that were down-regulated, irrespective of subcellular localization and biologic function. Furthermore, immunofluorescence microscopy confirmed ATP5B, TUBA1A, and TUBB4B were less abundantly expressed in epididymitis samples compared with controls. *Conclusion*(*s*): Despite normal semen parameters observed by conventional semen analysis in patients after epididymitis, significant changes to sperm protein composition were observed. These changes may be implicated as additional factors contributing to subfertility/infertility in men after episodes of epididymitis.

International Journal of Palliative Nursing

S. Dunkley and R. Sales, **The Challenges of Providing Palliative Care for People with Intellectual Disabilities: A Literature Review**, *Int J Palliat Nurs* 20.6 (June 2014): 279–284 • People with intellectual disabilities are often marginalised from mainstream health-care services because of the complexities of their disability. They are under-referred to specialist palliative care owing to a limited understanding of its role and little collaborative working. Furthermore, professionals caring for people with intellectual disabilities and palliative care services often lack knowledge about and confidence in their ability to meet the needs of people with an intellectual disability who require palliative care. This literature review explores the challenges of providing palliative care for people with intellectual disability. It highlights that training requirements need to be effectively identified, referrals between professional groups made, and the perspectives of patients understood to overcome the marginalisation of people with intellectual disability. There is a need for ongoing staff development focusing on staff confidence, collaborative working between professionals, and the empowerment of people with intellectual disability to be involved in decisions about their end-of-life care. Further research is needed to examine the most effective way of capturing the perspectives of those with intellectual disability and of enabling people with intellectual disability to access and engage with health surveillance, cancer screening, and palliative care services.

JAMA

A. Kwan et al., **Newborn Screening for Severe Combined Immunodeficiency in 11 Screening Programs in the United States**, *JAMA* 312.7 (August 20, 2014): 729–738 • *Importance:* Newborn screening for severe combined immunodeficiency (SCID) using assays to detect T-cell receptor excision circles (TRECs) began in Wisconsin in 2008, and SCID was added to the national recommended uniform panel for newborn screened disorders in 2010. Currently 23 states, the District of Columbia, and the Navajo Nation conduct population-wide newborn screening for SCID. The incidence of SCID is estimated at 1 in 100,000 births. *Objectives:* To present data from a spectrum of SCID newborn screening programs, establish population-based incidence for SCID and other conditions with T-cell lymphopenia, and document early institution of effective treatments. *Design:* Epidemiological and retrospective observational study. *Setting:* Representatives in states conducting SCID newborn screening were invited to submit their SCID screening algorithms, test performance data, and deidentified clinical and laboratory information regarding infants screened and cases with nonnormal results. Infants born from the start of each participating program from January 2008 through the most recent evaluable date prior to July 2013 were included. Representatives from 10 states plus the Navajo Area Indian Health Service contributed data from 3,030,083 newborns screened with a TREC test. *Main Outcomes and Measures:* Infants with SCID and other diagnoses of T-cell lymphopenia were classified. Incidence and, where possible, etiologies were determined. Interventions and survival were tracked. *Results:* Screening detected 52 cases of typical SCID, leaky SCID, and Omenn syndrome, affecting 1 in 58,000 infants (95% CI, 1/46,000–1/80,000). Survival of SCID-affected infants through their diagnosis and immune reconstitution was 87% (45/52), 92% (45/49) for infants who received transplantation, enzyme replacement, and/or gene therapy. Additional interventions for SCID and non-SCID T-cell lymphopenia included immunoglobulin infusions, preventive antibiotics, and avoidance of live vaccines. Variations in definitions and follow-up practices influenced the rates of detection of non-SCID T-cell lymphopenia. *Conclusions and Relevance:* Newborn screening in 11 programs in the United States identified SCID in 1 in 58,000 infants, with high survival. The usefulness of detection of non-SCID T-cell lymphopenias by the same screening remains to be determined.

R. Saitz et al., **Screening and Brief Intervention for Drug Use in Primary Care: The**

ASPIRE Randomized Clinical Trial, *JAMA* 312.5 (August 6, 2014): 502–513 • *Importance:* The United States has invested substantially in screening and brief intervention for illicit drug use and prescription drug misuse, based in part on evidence of efficacy for unhealthy alcohol use. However, it is not a recommended universal preventive service in primary care because of lack of evidence of efficacy. *Objective:* To test the efficacy of 2 brief counseling interventions for unhealthy drug use (any illicit drug use or prescription drug misuse)—a brief negotiated interview (BNI) and an adaptation of motivational interviewing (MOTIV)—compared with no brief intervention. *Design, Setting, and Participants:* This 3-group randomized trial took place at an urban hospital-based primary care internal medicine practice; 528 adult primary care patients with drug use (Alcohol, Smoking, and Substance Involvement Screening Test [ASSIST] substance-specific scores of ≥4) were identified by screening between June 2009 and January 2012 in Boston, Massachusetts. *Interventions:* Two interventions were tested: the BNI is a 10- to 15-minute structured interview conducted by health educators; the MOTIV is a 30- to 45-minute intervention based on motivational interviewing with a 20- to 30-minute booster conducted by master's-level counselors. All study participants received a written list of substance use disorder treatment and mutual help resources. *Main Outcomes and Measures:* Primary outcome was number of days of use in the past 30 days of the self-identified main drug as determined by a validated calendar method at 6 months. Secondary outcomes included other self-reported measures of drug use, drug use according to hair testing, ASSIST scores (severity), drug use consequences, unsafe sex, mutual help meeting attendance, and health care utilization. *Results:* At baseline, 63% of participants reported their main drug was marijuana, 19% cocaine, and 17% opioids. At 6 months, 98% completed follow-up. Mean adjusted number of days using the main drug at 6 months was 12 for no brief intervention vs 11 for the BNI group (incidence rate ratio [IRR], 0.97; 95% CI, 0.77–1.22) and 12 for the MOTIV group (IRR, 1.05; 95% CI, 0.84–1.32; P = .81 for both comparisons vs no brief intervention). There were also no significant effects of BNI or MOTIV on any other outcome or in analyses stratified by main drug or drug use severity. *Conclusions and Relevance:* Brief intervention did not have efficacy for decreasing unhealthy drug use in primary care patients identified by screening. These results do not support widespread implementation of illicit drug use and prescription drug misuse screening and brief intervention.

Lancet

M.R. Capeding et al. and the CYD14 Study Group, **Clinical Efficacy and Safety of a Novel Tetravalent Dengue Vaccine in Healthy Children in Asia: A Phase 3, Randomised, Observer-Masked, Placebo-Controlled Trial**, *Lancet*, e-pub July 11, 2014, doi:10.1016/s0140–6736(14)61060–6 • *Background:* An estimated 100 million people have symptomatic dengue infection every year. This is the first report of a phase 3 vaccine efficacy trial of a candidate dengue vaccine. We aimed to assess the efficacy of the CYD dengue vaccine against symptomatic, virologically confirmed dengue in children. *Methods:* We did an observer-masked, randomised controlled, multicentre, phase 3 trial in five countries in the Asia-Pacific region. Between June 3, and Dec 1, 2011, healthy children aged 2–14 years were randomly assigned (2:1), by computer-generated permuted blocks of six with an interactive voice or web response system, to receive three injections of a recombinant, live, attenuated, tetravalent dengue vaccine (CYD-TDV) or placebo, at months 0, 6, and 12. Randomisation was stratified by age and site. Participants were followed up until month 25. Trial staff responsible for the preparation and administration of injections were unmasked to group allocation, but were not included in the follow-up of the participants; allocation was concealed from the study sponsor, investigators, and parents and guardians. Our primary objective was to assess protective efficacy against symptomatic, virologically confirmed dengue, irrespective of disease severity or serotype, that took place more

than 28 days after the third injection. The primary endpoint was for the lower bound of the 95% CI of vaccine efficacy to be greater than 25%. Analysis was by intention to treat and per procotol. *Findings:* We randomly assigned 10 275 children to receive either vaccine (n=6851) or placebo (n=3424), of whom 6710 (98%) and 3350 (98%), respectively, were included in the primary analysis. 250 cases of virologically confirmed dengue took place more than 28 days after the third injection (117 [47%] in the vaccine group and 133 [53%] in the control group). The primary endpoint was achieved with 56·5% (95% CI 43·8–66·4) efficacy. We recorded 647 serious adverse events (402 [62%] in the vaccine group and 245 [38%] in the control group). 54 (1%) children in the vaccine group and 33 (1%) of those in the control group had serious adverse events that happened within 28 days of vaccination. Serious adverse events were consistent with medical disorders in this age group and were mainly infections and injuries. *Interpretation:* Our findings show that dengue vaccine is efficacious when given as three injections at months 0, 6, and 12 to children aged 2–14 years in endemic areas in Asia, and has a good safety profile. Vaccination could reduce the incidence of symptomatic infection and hospital admission and has the potential to provide an important public health benefit.

New England Journal of Medicine

R. S. Legro et al. for the NICHD Reproductive Medicine Network, **Letrozole versus Clomiphene for Infertility in the Polycystic Ovary Syndrome**, *N Engl J Med* 2014 371.2 (July 10, 2014): 119–129 • *Background:* Clomiphene is the current first-line infertility treatment in women with the polycystic ovary syndrome, but aromatase inhibitors, including letrozole, might result in better pregnancy outcomes. *Methods:* In this double-blind, multicenter trial, we randomly assigned 750 women, in a 1:1 ratio, to receive letrozole or clomiphene for up to five treatment cycles, with visits to determine ovulation and pregnancy, followed by tracking of pregnancies. The polycystic ovary syndrome was defined according to modified Rotterdam criteria (anovulation with either hyperandrogenism or polycystic ovaries). Participants were 18 to 40 years of age, had at least one patent fallopian tube and a normal uterine cavity, and had a male partner with a sperm concentration of at least 14 million per milliliter; the women and their partners agreed to have regular intercourse with the intent of conception during the study. The primary outcome was live birth during the treatment period. *Results:* Women who received letrozole had more cumulative live births than those who received clomiphene (103 of 374 [27.5%] vs. 72 of 376 [19.1%], P=0.007; rate ratio for live birth, 1.44; 95% confidence interval, 1.10 to 1.87) without significant differences in overall congenital anomalies, though there were four major congenital anomalies in the letrozole group versus one in the clomiphene group (P=0.65). The cumulative ovulation rate was higher with letrozole than with clomiphene (834 of 1352 treatment cycles [61.7%] vs. 688 of 1425 treatment cycles [48.3%], P<0.001). There were no significant between-group differences in pregnancy loss (49 of 154 pregnancies in the letrozole group [31.8%] and 30 of 103 pregnancies in the clomiphene group [29.1%]) or twin pregnancy (3.4% and 7.4%, respectively). Clomiphene was associated with a higher incidence of hot flushes, and letrozole was associated with higher incidences of fatigue and dizziness. Rates of other adverse events were similar in the two treatment groups. *Conclusions:* As compared with clomiphene, letrozole was associated with higher live-birth and ovulation rates among infertile women with the polycystic ovary syndrome.

Obstetrics and Gynecology

L. M. Masinter et al., **Likelihood of Continued Childbearing after Cesarean Delivery in the United States**, *Obstet Gynecol* 124.1 (July 2014): 111–119 • *Objective:* To estimate the likelihood of continued childbearing as a function of mode of delivery and number of cesarean deliveries and to explore whether it varies by sociodemographic characteristics. *Methods:* Cross-sectional data from the 2006–2010 National Survey of Family Growth were used to conduct an analysis of U.S. childbearing women.

The birth trajectory for respondents who identified a live, singleton, first birth was assessed through four births. Population-weighted analyses were performed to test the association between route of delivery and sociodemographic characteristics with the likelihood of subsequent birth. *Results:* Among 6,526 respondents, cesarean delivery, regardless of birth order, was associated with a lower likelihood of future birth, which decreased in a dose-response fashion as the number of cesarean deliveries increased. Among women with three births, those with two or three cesarean deliveries were 37% and 59% less likely (P<.05), respectively, to have a fourth birth when compared with women with three vaginal deliveries, adjusting for confounders. When interaction terms were added to the model, lower income women were significantly more likely to have a fourth birth after undergoing two or three cesarean deliveries than women with higher incomes (adjusted incidence rate ratio 2.50, 95% confidence interval [CI] 1.23–5.05 and adjusted incidence rate ratio 2.39, 95% CI 1.01–5.65, respectively). *Conclusions:* U.S. women who have cesarean deliveries are less likely to continue childbearing, especially as they undergo higher numbers of cesarean deliveries; however, this relationship is attenuated among low-income women. Given the risks associated with multiple cesarean deliveries, these findings underscore the need to further examine this relationship and what factors may be driving the income-based difference in childbearing after cesarean deliveries.

Stroke

R. G. Holloway et al. for the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, and Council on Clinical Cardiology, **Palliative and End-of-Life Care in Stroke: A Statement for Healthcare Professionals from the American Heart Association/American Stroke Association**, *Stroke* 45.6 (June 2014): 1887–1916 • *Background and Purpose:* The purpose of this statement is to delineate basic expectations regarding primary palliative care competencies and skills to be considered, learned, and practiced by providers and healthcare services across hospitals and community settings when caring for patients and families with stroke. *Methods:* Members of the writing group were appointed by the American Heart Association Stroke Council's Scientific Statement Oversight Committee and the American Heart Association's Manuscript Oversight Committee. Members were chosen to reflect the diversity and expertise of professional roles in delivering optimal palliative care. Writing group members were assigned topics relevant to their areas of expertise, reviewed the appropriate literature, and drafted manuscript content and recommendations in accordance with the American Heart Association's framework for defining classes and level of evidence and recommendations. *Results:* The palliative care needs of patients with serious or life-threatening stroke and their families are enormous: complex decision making, aligning treatment with goals, and symptom control. Primary palliative care should be available to all patients with serious or life-threatening stroke and their families throughout the entire course of illness. To optimally deliver primary palliative care, stroke systems of care and provider teams should (1) promote and practice patient- and family-centered care; (2) effectively estimate prognosis; (3) develop appropriate goals of care; (4) be familiar with the evidence for common stroke decisions with end-of-life implications; (5) assess and effectively manage emerging stroke symptoms; (6) possess experience with palliative treatments at the end of life; (7) assist with care coordination, including referral to a palliative care specialist or hospice if necessary; (8) provide the patient and family the opportunity for personal growth and make bereavement resources available if death is anticipated; and (9) actively participate in continuous quality improvement and research. *Conclusions:* Addressing the palliative care needs of patients and families throughout the course of illness can complement existing practices and improve the quality of life of stroke patients, their families, and their care providers. There is an urgent need for further research in this area.