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Henry Ford Health System Publication List – February 2020

This bibliography aims to recognize the scholarly activity and provide ease of access to journal articles, meeting abstracts, book chapters, books and other works published by Henry Ford Health System personnel. Searches were conducted in PubMed, Embase, and Google Scholar during the month, and then imported into EndNote for formatting. There are 98 unique citations listed this month; articles are listed first, followed by conference abstracts and books and book chapters. Because of various limitations, this does not represent an exhaustive list of all published works by Henry Ford Health System authors.

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Articles

Administration

Regnante JM, Richie N, Fashoyin-Aje L, Hall LL, Highsmith Q, Louis JA, Turner K, **Hoover S**, Lee SC, González E, Williams E, Adams H, Obasaju C, Sargeant I, Spinner J, Reddick C, Gandee M, Geday M, Dang J, Watson R, and Chen MS. Operational strategies in US cancer centers of excellence that support the successful accrual of racial and ethnic minorities in clinical trials. *Contemp Clin Trials Commun* 2020; 17. PMID: Not assigned. Full Text

J.M. Regnante, Center for Sustainable Health Care Quality and Equity, 1201 15th Street, NW, Suite 340, Washington, DC, United States

Background: Study populations in clinical research must reflect US changing demographics, especially with the rise of precision medicine. However, racial and ethnic minority groups (REMGs) have low rates of participation in cancer clinical trials. Methods: Criteria were developed to identify cancer centers able to accrue a higher than average proportion of REMGs into clinical trials. Comprehensive interviews were conducted with leaders of these cancer centers to identify operational strategies contributing to enhanced accrual of REMGs. Results: Eight US cancer centers reported a REMG accrual rate range in cancer research between 10 and 50% in a 12-month reporting period and met other criteria for inclusion. Fourteen leaders participated in this assessment. Key findings were that centers: had a metric collection and reporting approach; routinely captured race and ethnicity data within databases accessible to research staff; had operational standards to support access and inclusion; developed practices to facilitate sustained patient participation during clinical trials; had strategies to decrease recruitment time and optimize clinical study design; and identified low-resource strategies for REMG accrual. There was also a clear commitment to establish processes that support the patient's provider as the key influencer of patient recruitment into clinical trials. Conclusion: We have identified operational practices that facilitate increased inclusion of REMGs in cancer trials. In order to establish a sustainable cancer center inclusion research strategy, it is valuable to include an operational framework that is informed by leading US cancer centers of excellence.

Allergy and Immunology

Zoratti EM, and O'Connor GT. New Therapeutic Strategies for Asthma. *JAMA* 2020; 323(6):517-518. PMID: 32044924. Full Text

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Anesthesiology

Deer TR, Grider JS, Lamer TJ, Pope JE, Falowski S, Hunter CW, Provenzano DA, Slavin KV, Russo M, Carayannopoulos A, Shah JM, Harned ME, Hagedorn JM, Bolash RB, Arle JE, Kapural L, Amirdelfan K, Jain S, Liem L, Carlson JD, Malinowski MN, Bendel M, Yang A, **Aiyer R**, Valimahomed A, Antony A, Craig J, Fishman MA, Al-Kaisy AA, Christelis N, Rosenquist RW, Levy RM, and Mekhail N. A Systematic Literature Review of Spine Neurostimulation Therapies for the Treatment of Pain. *Pain Med* 2020; Epub ahead of print. PMID: 32034422. Full Text

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Pain Treatment Centers of America, Little Rock, Arkansas.
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OBJECTIVE: To conduct a systematic literature review of spinal cord stimulation (SCS) for pain. DESIGN: Grade the evidence for SCS. METHODS: An international, interdisciplinary work group conducted literature searches, reviewed abstracts, and selected studies for grading. Inclusion/exclusion criteria included randomized controlled trials (RCTs) of patients with intractable pain of greater than one year's duration. Full studies were graded by two independent reviewers. Excluded studies were retrospective, had small numbers of subjects, or existed only as abstracts. Studies were graded using the modified Interventional Pain Management Techniques-Quality Appraisal of Reliability and Risk of Bias Assessment, the Cochrane Collaborations Risk of Bias assessment, and the US Preventative Services Task Force level-of-evidence criteria. RESULTS: SCS has Level 1 evidence (strong) for axial back/lumbar radiculopathy or neuralgia (five high-quality RCTs) and complex regional pain syndrome (one high-quality RCT). CONCLUSIONS: High-level evidence supports SCS for treating chronic pain and complex regional pain syndrome. For patients with failed back surgery syndrome, SCS was more effective than reoperation or medical management. New stimulation waveforms and frequencies may provide a greater likelihood of pain relief compared with conventional SCS for patients with axial back pain, with or without radicular pain.

Anesthesiology

Nanchal R, Subramanian R, Karvellas CJ, Hollenberg SM, Peppard WJ, Singbartl K, Truwit J, Al-Khafaji AH, Killian AJ, Alquraini M, Alshammari K, Alshamsi F, Belley-Cote E, Cartin-Ceba R, Dionne JC, **Galusca DM**, Huang DT, Hyzy RC, Junek M, Kandiah P, Kumar G, Morgan RL, Morris PE, Olson JC, Sieracki R, Steadman R, Taylor B, and Alhazzani W. Guidelines for the Management of Adult Acute and Acute-on-Chronic Liver Failure in the ICU: Cardiovascular, Endocrine, Hematologic, Pulmonary, and Renal Considerations. *Crit Care Med* 2020; 48(3):e173-e191. PMID: 32058387. Full Text

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OBJECTIVES: To develop evidence-based recommendations for clinicians caring for adults with acute or acute on chronic liver failure in the ICU. DESIGN: The guideline panel comprised 29 members with expertise in aspects of care of the critically ill patient with liver failure and/or methodology. The Society of Critical Care Medicine standard operating procedures manual and conflict-of-interest policy were followed throughout. Teleconferences and electronic-based discussion among the panel, as well as within subgroups, served as an integral part of the guideline development. SETTING: The panel was divided into nine subgroups: cardiovascular, hematology, pulmonary, renal, endocrine and nutrition, gastrointestinal, infection, perioperative, and neurology. INTERVENTIONS: We developed and selected population, intervention, comparison, and outcomes questions according to importance to patients and practicing clinicians. For each population, intervention, comparison, and outcomes question, we conducted a systematic review aiming to identify the best available evidence, statistically summarized the evidence whenever applicable, and assessed the quality of evidence using the Grading of Recommendations Assessment, Development, and Evaluation approach. We used the evidence to decision framework to facilitate recommendations formulation as strong or conditional. We followed strict criteria to formulate best practice statements. MEASUREMENTS AND MAIN RESULTS: In this article, we report 29 recommendations (from 30 population, intervention, comparison, and outcomes questions) on the management acute or acute on chronic liver failure in the ICU, related to five groups (cardiovascular, hematology, pulmonary, renal, and endocrine). Overall, six were strong recommendations, 19 were conditional recommendations, four were best-practice statements, and in two instances, the panel did not issue a recommendation due to insufficient evidence. CONCLUSIONS: Multidisciplinary international experts were able to formulate evidence-based recommendations for the management acute or acute on chronic liver failure in the ICU, acknowledging that most recommendations were based on low-quality indirect evidence.

Anesthesiology

Nanchal R, Subramanian R, Karvellas CJ, Hollenberg SM, Peppard WJ, Singbartl K, Truwit J, Al-Khafaji AH, Killian AJ, Alquraini M, Alshammari K, Alshamsi F, Belley-Cote E, Cartin-Ceba R, Dionne JC, **Galusca DM**, Huang DT, Hyzy RC, Junek M, Kandiah P, Kumar G, Morgan RL, Morris PE, Olson JC, Sieracki R, Steadman R, Taylor B, and Alhazzani W. Guidelines for the Management of Adult Acute and Acute-on-Chronic Liver Failure in the ICU: Cardiovascular, Endocrine, Hematologic, Pulmonary and Renal Considerations: Executive Summary. *Crit Care Med* 2020; 48(3):415-419. PMID: 32058375. Full Text

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Anesthesiology
Szarpak L, Filipiak KJ, Mosteller L, Jaguszewski M, Smereka J, Ruetzler K, **Ahuja S**, and Ladny JR. Survival, neurological and safety outcomes after out of hospital cardiac arrests treated by using prehospital therapeutic hypothermia: A systematic review and meta-analysis. *Am J Emerg Med* 2020; Epub ahead of print. PMID: 32088060. Full Text

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Anesthesiology
Tanaka KA, Mondal S, **Morita Y**, Williams B, Strauss ER, and Cicardi M. Perioperative Management of Patients With Hereditary Angioedema With Special Considerations for Cardiopulmonary Bypass. *Anesth Analg* 2020; Epub ahead of print. PMID: 32102012. Full Text

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Department of Biomedical and Clinical Sciences Luigi Sacco, University of Milan, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Istituti Clinici Scientifici (ICS) Maugeri Milan, Italy.

Hereditary angioedema (HAE) is a rare autosomal dominant disorder mostly due to the deficiency of C1-esterase inhibitor (C1-INH). Reduced C1-INH activity below ~38% disrupts homeostasis of bradykinin (BK) formation by increasing kallikrein activation and causes recurrent angioedema attacks affecting the face, extremities, genitals, bowels, oropharynx, and larynx. HAE symptoms can be debilitating and potentially life-threatening. The recent clinical developments of biological and pharmacological agents have immensely improved acute and long-term care of patients with moderate-to-severe HAE. The therapies are given as on-demand and/or prophylaxis, and self-administration is highly recommended and performed with some agents via intravenous or subcutaneous route. Perioperative clinicians need to be familiar with the symptoms and diagnosis of HAE as well as available therapies because of the potential need for airway management, sedation, or anesthesia for various medical and surgical procedures and postoperative care. Cardiovascular surgery using cardiopulmonary bypass is a unique condition in which heparinized blood comes into direct contact with an artificial surface while pulmonary circulation, a major reserve of angiotensin-converting enzyme (ACE), becomes excluded. These changes result in systemic kallikrein activation and BK formation even in non-HAE patients. The objectives of this review are (1) to review pathophysiology of HAE and laboratory testing, (2) to summarize pertinent pharmacological data on the prophylactic and on-demand treatment strategies, and (3) to discuss available clinical data for perioperative management in cardiovascular surgery.

Behavioral Health Services/Psychiatry
Lynch FL, **Peterson EL**, Lu CY, **Hu Y**, Rossom RC, Waitzfelder BE, Owen-Smith AA, Hubley S, **Prabhakar D**, **Keoki Williams L**, Beck A, Simon GE, and **Ahmedani BK**. Substance use disorders and risk of suicide in a general US population: a case control study. *Addict Sci Clin Pract* 2020; 15(1):14. PMID: 32085800. Request Article

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BACKGROUND: Prior research suggests that substance use disorders (SUDs) are associated with risk of suicide mortality, but most previous work has been conducted among Veterans Health Administration patients. Few studies have examined the relationship between SUDs and suicide mortality in general populations. Our study estimates the association of SUDs with suicide mortality in a general US population of men and women who receive care across eight integrated health systems. METHODS: We conducted a case-control study using electronic health records and claims data from eight integrated health systems of the Mental Health Research Network. Participants were 2674 men and women who died by suicide between 2000-2013 and 267,400 matched controls. The main outcome was suicide mortality, assessed using data from the health systems and confirmed by state death data systems. Demographic and diagnostic data on substance use disorders and other health conditions were obtained from each health system. First, we compared descriptive statistics for cases and controls, including age, gender, income, and education. Next, we compared the rate of each substance use disorder category for cases and controls. Finally, we used conditional logistic regression models to estimate unadjusted and adjusted odds of suicide associated with each substance use disorder category. RESULTS: All categories of substance use disorders were associated with increased risk of suicide mortality. Adjusted odds ratios ranged from 2.0 (CI 1.7, 2.3) for patients with tobacco use disorder only to 11.2 (CI 8.0, 15.6) for patients with multiple alcohol, drug, and tobacco use disorders. Substance use disorders were associated with increased relative risk of suicide for both women and men across all categories, but the relative risk was more pronounced in women. CONCLUSIONS: Substance use disorders are associated with significant risk of suicide mortality, especially for women, even after controlling for other important risk factors. Experiencing multiple substance use disorders is particularly risky. These findings suggest increased suicide risk screening and prevention efforts for individuals with substance use disorders are needed.

Behavioral Health Services/Psychiatry

Owen-Smith A, Stewart C, Sesay MM, Strasser SM, Yarborough BJ, **Ahmedani B**, **Miller-Matero LR**, Waring SC, Haller IV, Waitzfelder BE, Sterling SA, Campbell CI, Hechter RC, Zeber JE, Copeland LA, Scherrer JF, Rossom R, and Simon G. Chronic pain diagnoses and opioid dispensings among insured individuals with serious mental illness. *BMC Psychiatry* 2020; 20(1):40. PMID: 32005200. Full Text

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BACKGROUND: Individuals with major depressive disorder (MDD) and bipolar disorder (BD) have particularly high rates of chronic non-cancer pain (CNCP) and are also more likely to receive prescription opioids for their pain. However, there have been no known studies published to date that have examined opioid treatment patterns among individuals with schizophrenia. METHODS: Using electronic medical record data across 13 Mental Health Research Network sites, individuals with diagnoses of MDD (N = 65,750), BD (N = 38,117) or schizophrenia or schizoaffective disorder (N = 12,916) were identified and matched on age, sex and Medicare status to controls with no documented mental illness. CNCP diagnoses and prescription opioid medication dispensings were extracted for the matched samples. Multivariate analyses were conducted to evaluate (1) the odds of receiving a pain-related diagnosis and (2) the odds of receiving opioids, by separate mental illness diagnosis category compared with matched controls, controlling for age, sex, Medicare status, race/ethnicity, income, medical comorbidities, healthcare utilization and chronic pain diagnoses. RESULTS: Multivariable models indicated that having a MDD (OR = 1.90; 95% CI = 1.85-1.95) or BD (OR = 1.71; 95% CI = 1.66-1.77) diagnosis was associated with increased odds of a CNCP diagnosis after controlling for age, sex, race, income, medical comorbidities and healthcare utilization. By contrast, having a schizophrenia diagnosis was associated with decreased odds of receiving a chronic pain diagnosis (OR = 0.86; 95% CI = 0.82-0.90). Having a MDD (OR = 2.59; 95% CI = 2.44-2.75) or BD (OR = 2.12; 95% CI = 1.97-2.28) diagnosis was associated with increased odds of receiving chronic opioid medications, even after controlling for age, sex, race, income, medical comorbidities, healthcare utilization and chronic pain diagnosis; having a schizophrenia diagnosis was not associated with receiving chronic opioid medications. CONCLUSIONS: Individuals with serious mental illness, who are most at risk for developing opioid-related problems, continue to be prescribed opioids more often than their peers without mental illness. Mental health clinicians may be particularly well-suited to lead pain assessment and management efforts for these patients. Future research is needed to evaluate the effectiveness of involving mental health clinicians in these efforts.

Cardiology/Cardiovascular Research

Al-Khadra Y, Alraies MC, Darmoch F, Pacha HM, Soud M, Kaki A, Rab T, Grines CL, Meraj P, **Alaswad K**, Kwok CS, Mamas M, and Kapadia S. Outcomes of nonemergent percutaneous coronary intervention requiring mechanical circulatory support in patients without cardiogenic shock. *Catheter Cardiovasc Interv* 2020; 95(3):503-512. PMID: 31254325. Full Text

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BACKGROUND: The utilization of mechanical circulatory support (MCS) for percutaneous coronary intervention (PCI) using percutaneous ventricular assist device (PVAD) or intra-aortic balloon pump (IABP) has been increasing. We sought to evaluate the outcome of coronary intervention using PVAD compared with IABP in noncardiogenic shock and nonacute myocardial infarction patients. METHOD: Using the National Inpatient Sampling (NIS) database from 2005 to 2014, we identified patients who underwent PCI using ICD 9 codes. Patients with cardiogenic shock, acute coronary syndrome, or acute myocardial infarction were excluded. Patient was stratified based on the MCS used, either to PVAD or IABP. Univariate and multivariate logistic regression were performed to study PCI outcome using PVAD compared with IABP. RESULTS: Out of 21,848 patients who underwent PCI requiring MCS, 17,270 (79.0%) patients received IABP and 4,578 (21%) patients received PVAD. PVAD patients were older (69 vs. 67, p < .001), were less likely to be women (23.3% vs. 33.3%, p < .001), and had higher rates of hypertension, diabetes, hyperlipidemia prior PCI, prior coronary artery bypass graft surgery, anemia, chronic lung disease, liver disease, renal failure, and peripheral vascular disease compared with IABP group (p </= .007). Using Multivariate logistic regression, PVAD patients had lower in-hospital mortality (6.1% vs. 8.8%, adjusted odds ratio [aOR] 0.62; 95% CI 0.51, 0.77, p < .001), vascular complications (4.3% vs. 7.5%, aOR 0.78; 95% CI 0.62, 0.99, p = .046), cardiac complications (5.6% vs. 14.5%, aOR 0.29; 95% CI 0.24, 0.36, p < .001), and respiratory complications (3.8% vs. 9.8%, aOR 0.37; 95% CI 0.28, 0.48, p < .001) compared with patients who received IABP. CONCLUSION: Despite

higher comorbidities, nonemergent PCI procedures using PVAD were associated with lower mortality compared with IABP.

Cardiology/Cardiovascular Research
Butler J, Khan MS, Anker SD, Fonarow GC, Kim RJ, Nodari S, O'Connor CM, Pieske B, Pieske-Kraigher E, **Sabbah HN**, Senni M, Voors AA, Udelson JE, Carr J, Gheorghiade M, and Filippatos G. Effects of Elamipretide on Left Ventricular Function in Patients with Heart Failure with Reduced Ejection Fraction: The PROGRESS-HF Phase 2 Trial. *J Card Fail* 2020; Epub ahead of print. PMID: 32068002. Full Text

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BACKGROUND: Elamipretide, a novel mitochondrial modulating agent, improves myocardial energetics, however, it is unknown whether this mechanistic benefit translates into improved cardiac structure and function in HF with reduced ejection fraction (HFrEF). The objective of this study was to evaluate the effects of multiple subcutaneous doses of elamipretide on left ventricular end systolic volume (LVESV) assessed by cardiac magnetic resonance imaging (MRI). METHODS: Seventy-one HFrEF (LVEF </= 40%) patients were randomized in a double-blind, placebo-controlled trial in a 1:1:1 ratio to receive either placebo, 4 mg or 40 mg elamipretide once daily for 28 consecutive days. RESULTS: Mean age (SD) of the study population was 65+/-10 years, 24% were females, and mean EF was 31+/-7%. The change in LVESV from baseline to week 4 was not significantly different between elamipretide 4mg (89.4 ml to 85 ml; difference, -4.4 ml) or 40 mg (77.9 ml to 76.6 ml; difference, -1.2 ml) compared with placebo (77.7 ml to 74.6 ml; difference, -3.8 ml) [4mg versus placebo: difference of means, -0.3; 95% CI, -4.6 to 4.0; P = 0.90; and 40mg versus placebo: difference of means, 2.3; 95% CI, -1.9 to 6.5; P = 0.28]. Also, no significant differences in change in left ventricular end diastolic volume and left ventricular ejection fraction were observed between placebo and either of the elamipretide group. Rates of any study drug related adverse events were similar among the three groups. CONCLUSIONS: Elamipretide was well tolerated but did not improve LVESV at 4 weeks in stable HFrEF patients compared with placebo.

Cardiology/Cardiovascular Research
DeVore AD, Granger BB, Fonarow GC, Al-Khalidi HR, Albert NM, Lewis EF, Butler J, Pina IL, Heidenreich PA, Allen LA, Yancy CW, Cooper LB, Felker GM, Kaltenbach LA, McRae AT, **Lanfear DE**, Harrison RW, Kociol RD, Disch M, Ariely D, Miller JM, Granger CB, and Hernandez AF. Care Optimization Through Patient and Hospital Engagement Clinical Trial for Heart Failure: Rationale and design of CONNECT-HF. *Am Heart J* 2020; 220:41-50. PMID: 31770656. Full Text

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Many therapies have been shown to improve outcomes for patients with heart failure (HF) in controlled settings, but there are limited data available to inform best practices for hospital and post-discharge quality improvement initiatives. The CONNECT-HF study is a prospective, cluster-randomized trial of 161 hospitals in the United States with a 2x2 factorial design. The study is designed to assess the effect of a hospital and post-discharge quality improvement intervention compared with usual care (primary objective) on HF outcomes and quality-of-care, as well as to evaluate the effect of hospitals implementing a patient-level digital intervention compared with usual care (secondary objective). The hospital and post-discharge intervention includes audit and feedback on HF clinical process measures and outcomes for patients with HF with reduced ejection fraction (HFrEF) paired with education to sites and clinicians by a trained, nationally representative group of HF and quality improvement experts. The patient-level digital intervention is an optional ancillary study and includes a mobile application and behavioral tools that are intended to facilitate improved use of guideline-directed recommendations for self-monitoring and self-management of activity and medications for HFrEF. The effects of the interventions will be measured through an opportunity-based composite score on quality and time-to-first HF readmission or death among patients with HFrEF who present to study hospitals with acute HF and who consent to participate. The CONNECT-HF study is evaluating approaches for implementing HF guideline recommendations into practice and is one of the largest HF implementation science trials performed to date.

Cardiology/Cardiovascular Research

Korsholm K, Berti S, Iriart X, Saw J, **Wang DD**, Cochet H, Chow D, Clemente A, De Backer O, Moller Jensen J, and Nielsen-Kudsk JE. Expert Recommendations on Cardiac Computed Tomography for Planning Transcatheter Left Atrial Appendage Occlusion. *JACC Cardiovasc Interv* 2020; 13(3):277-292. PMID: 31678086. Full Text

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Transcatheter left atrial appendage occlusion is an increasingly used alternative to oral anticoagulation in selected patients with atrial fibrillation. Pre-procedural imaging is a prerequisite to a successful intervention, with transesophageal echocardiography as the current gold standard. However, cardiac computed tomography offers improved imaging with high-quality multiplanar and 3-dimensional reconstructed images. Nevertheless, the lack of a standardized imaging protocol has slowed the adoption of cardiac computed tomography into clinical practice. On the basis of current research and expert consensus, this paper provides a protocol for the preparation, acquisition, and interpretation of cardiac computed tomographic imaging in pre-procedural planning of left atrial appendage occlusion.

Cardiology/Cardiovascular Research

Lupercio F, Giancaterino S, **Villablanca PA**, Han F, Hoffmayer K, Ho G, Raissi F, Krummen D, Birgersdotter-Green U, Feld G, Reeves R, Mahmud E, and Hsu JC. P2Y12 inhibitors with oral anticoagulation for percutaneous coronary intervention with atrial fibrillation: a systematic review and meta-analysis. *Heart* 2020; Epub ahead of print. PMID: 32034008. Full Text

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OBJECTIVE: This study aimed to compare the safety and efficacy of third-generation P2Y12 inhibitors versus clopidogrel in combination with oral anticoagulation (OAC) with or without aspirin in patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI). METHODS: We performed a systematic review including both prospective and retrospective studies that compared dual and triple antithrombotic regimens for bleeding and major adverse cardiac events (MACE) in patients with AF undergoing PCI. We analysed rates of bleeding and MACE by P2Y12 inhibitor choice. Risk ratio (RR) 95% CIs were measured using the Mantel-Haenszel method. Where study heterogeneity was low (I(2) <25%), we used the fixed effects model, otherwise the random effects model was used. RESULTS: A total of 22 014 patients were analysed from the seven studies included. Among patients treated with both OAC and P2Y12 inhibitor with or without aspirin, 90% (n=9708) were treated with clopidogrel, 8% (n=830) with ticagrelor, and 2% (n=191) with prasugrel. When compared with clopidogrel, use of ticagrelor (RR 1.36; 95% CI 1.18 to 1.57) and prasugrel (RR 2.11; 95% CI 1.34 to 3.30) were associated with increased rates of bleeding. Compared with clopidogrel, there were no significant differences in rates of MACE with ticagrelor (RR 1.03; 95% CI 0.65 to 1.62) or prasugrel (RR 1.49; 95% CI 0.69 to 3.24). CONCLUSION: Based on this meta-analysis, the use of clopidogrel is associated with a lower rate of bleeding compared with ticagrelor or prasugrel in patients with AF on OAC undergoing PCI.

Cardiology/Cardiovascular Research

Nowak RM, Christenson RH, **Jacobsen G**, **McCord J**, Apple FS, Singer AJ, Limkakeng A, Jr., Peacock WF, and deFilippi CR. Performance of Novel High-Sensitivity Cardiac Troponin I Assays for 0/1-Hour and 0/2- to 3-Hour Evaluations for Acute Myocardial Infarction: Results From the HIGH-US Study. *Ann Emerg Med* 2020; Epub ahead of print. PMID: 32046869. Full Text

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STUDY OBJECTIVE: We determine the accuracy of high-sensitivity cardiac troponin I (hs-cTnI), European-derived, rapid, acute myocardial infarction, rule-out/rule-in algorithms applied to a US emergency department (ED) population. METHODS: Adults presenting to the ED with suspected acute myocardial infarction were included. Plasma samples collected at baseline and between 40 and 90 minutes and 2 and 3 hours later were analyzed in core laboratories using the Siemens Healthineers hs-cTnI assays. Acute myocardial infarction diagnosis was independently adjudicated. The sensitivity, specificity, and negative and positive predictive values for rapid acute myocardial infarction rule-out/rule-in using European algorithms and 30-day outcomes are reported. RESULTS: From 29 US medical centers, 2,113 subjects had complete data for the 0/1-hour algorithm analyses. With the Siemens Atellica Immunoassay hs-cTnI values, 1,065 patients (50.4%) were ruled out, with a negative predictive value of 99.7% and sensitivity of 98.7% (95% confidence interval 99.2% to 99.9% and 96.3% to 99.6%, respectively), whereas 265 patients (12.6%) were ruled in, having a positive predictive value of 69.4% and specificity of 95.7% (95% confidence interval 63.6% to 74.7% and 94.7% to 96.5%, respectively). The remaining 783 patients (37.1%) were classified as having continued evaluations, with an acute myocardial infarction incidence of 5.6% (95% confidence interval 4.2% to 7.5%). The overall 30-day risk of death or postdischarge acute myocardial infarction was very low in the ruled-out patients but was incrementally increased in the other groups (rule-out 0.2%; continued evaluations 2.1%; rule-in 4.8%). Equivalent results were observed in the 0/2- to 3-hour analyses and when both algorithms were applied to the hs-cTnI ADVIA Centaur measurements. CONCLUSION: The European rapid rule-out/rule-in acute myocardial

infarction algorithm hs-cTnI cut points can be harmonized with a demographically and risk-factor diverse US ED population.

Cardiology/Cardiovascular Research
Ram P, Shah M, Lo KBU, Agarwal M, **Patel B**, Tripathi B, Arora S, Patel N, Jorde UP, and Banerji S. Etiologies and predictors of readmission among obese and morbidly obese patients admitted with heart failure. *Heart Fail Rev* 2020; Epub ahead of print. PMID: 32002731. Full Text

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The relationship between severity of obesity and outcomes in heart failure (HF) has long been under debate. We studied index HF admissions from the 2013-14 National Readmission Database. Admissions were separated into three weight-based categories: non-obese (Non-Ob), obese (Ob), and morbidly obese (Morbid-Ob) to analyze hospital mortality and readmission at 30 days and 6 months. We investigated etiologies and predictors of 30-day readmission among these weight categories. We studied a total of 578,213 patients of whom 3.0% died during index hospitalization (Non-Ob 3.3% vs. Ob 1.9% vs. Morbid-Ob 1.9%; $p < 0.01$). Non-Ob comprised 79.5%, Ob 9.9%, and Morbid-Ob 10.6% of patients. Morbid-Ob patients were the youngest among age categories and more likely to be female. In-hospital mortality during readmission at 30 days and 6 months was significantly lower among Morbid-Ob and Ob compared with Non-Ob patients (all $p < 0.01$). Thirty-day readmission among Morbid-Ob was lower than Non-Ob and higher than Ob patients (19.6% vs. 20.5% vs. 18.6%, respectively; $p < 0.01$). Morbid-Ob patients were less likely to be readmitted for cardiovascular etiologies compared with both Ob and Non-Ob (45.0% vs. 50.3% vs. 50.6%; $p < 0.01$). Multivariable regression analysis revealed that Ob (adjusted odds ratio 0.84, 95% confidence intervals 0.82-0.86) and Morbid-Ob (aOR 0.83, 95% CI 0.81-0.85) were independently associated with lower 30-day readmission. Readmission at 6 months was highest among Morbid-Ob followed by Non-Ob and Ob (51.1% vs. 50.2% vs. 49.1%, $p < 0.01$). Morbid-Ob and Ob patients experience lower in-hospital mortality during index HF admission and during readmission with 30 days or 6 months compared with Non-Ob. Morbid-Ob patients experience greater readmission at 6 months despite the lower rate at 30 days post discharge. Morbid-Ob patients are most likely to be readmitted for non-cardiovascular causes.

Cardiology/Cardiovascular Research
Roukoz H, Bhan A, Ravichandran A, Ahmed MM, Bhat G, **Cowger J**, Abdullah M, Dhawan R, Trivedi JR, Slaughter MS, and Gopinathannair R. Continued versus Suspended Cardiac Resynchronization Therapy after Left Ventricular Assist Device Implantation. *Sci Rep* 2020; 10(1):2573. PMID: 32054868. Full Text

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Cardiac resynchronization therapy (CRT) improves outcomes in heart failure patients with wide QRS complex. However, CRT management following continuous flow Left Ventricular Assist Device (LVAD) implant vary: some centers continue CRT while others turn off the left ventricular (LV) lead at LVAD implant. We sought to study the effect of continued CRT versus turning off CRT pacing following continuous flow LVAD implantation. A comprehensive retrospective multicenter cohort of 295 patients with LVAD and pre-existing CRT was studied. CRT was programmed off after LVAD implant in 44 patients. We compared their outcomes to the rest of the cohort using univariate and multivariate models. Mean age was 60 +/- 12 years, 83% were males, 52% had ischemic cardiomyopathy and 54% were destination therapy. Mean follow-up was 2.4 +/- 2.0 years, and mean LVAD support time was 1.7 +/- 1.4 years. Patients with CRT OFF had a higher Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) mean profile (3.9 vs 3.3, $p = 0.01$), more secondary prevention indication for a defibrillator (64.9% vs 44.5%, $p = 0.023$), and more pre-LVAD ventricular arrhythmias (VA) (77% vs 60%, $p = 0.048$). There were no differences between the CRT OFF and CRT ON groups in overall mortality (Log rank $p = 0.32$,

adjusted HR = 1.14 [0.54-2.22], p = 0.71), heart transplantation, cardiac and noncardiac mortality, all cause hospitalizations, hospitalizations for ICD shocks, and number and frequency of ICD shocks or anti-tachycardia pacing therapy. There were no differences in post LVAD atrial arrhythmias (AA) (Adjusted OR = 0.45 [0.18-1.06], p = 0.31) and ventricular arrhythmias (OR = 0.65 [0.41-1.78], p = 0.41). There was no difference in change in LVEF, LV end diastolic and end systolic diameters between the 2 groups. Our study suggests that turning off CRT pacing after LVAD implantation in patients with previous CRT pacing did not affect mortality, heart transplantation, device therapies or arrhythmia burden. A prospective study is needed to confirm these findings.

Cardiology/Cardiovascular Research
So CY, **Kang G**, **Wang DD**, **Villablanca PA**, **Lee JC**, **Eng MH**, **O'Neill WW**, and **Frisoli TM**. The "Snare-and-Anchor" Technique to Rescue Frozen Mechanical Mitral Valve Leaflet After Transcatheter Aortic Valve Replacement. *JACC Cardiovasc Interv* 2020; Epub ahead of print. PMID: 32061606. Full Text

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Cardiology/Cardiovascular Research
Strobel RJ, **Harrington SD**, Hill C, Thompson MP, Cabrera L, Theurer P, Wilton P, Gandhi D, DeLucia A, 3rd, **Paone G**, Wu X, Zhang M, Krein SL, Prager RL, and Likosky DS. Evaluating The Impact of Pneumonia Prevention Recommendations Following Cardiac Surgery. *Ann Thorac Surg* 2020; Epub ahead of print. PMID: 32035918. Full Text

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BACKGROUND: While pneumonia is the most prevalent healthcare-associated infection following coronary artery bypass surgery grafting (CABG), the relative effectiveness of strategies to reduce its incidence remains unclear. We evaluated the relationship between healthcare-associated infection recommendations and risk of pneumonia following CABG. METHODS: Pneumonia prevention practice recommendations were developed based on literature review and analysis of semi-structured interviews with key healthcare personnel across low (<5.9%), medium (5.9-6.1%) and high (>6.1%) pneumonia rate centers. These practices were implemented among 2,482 patients undergoing CABG from 2016 to 2017 across 18 centers. The independent effect of each practice in reducing pneumonia was assessed using multivariable logistic regression, adjusting for baseline risk and center. A composite (bundle) score was calculated as the number of practices (0 to 4) received by each patient. RESULTS: Recommended pneumonia prevention practices included: lung protective ventilation management, early extubation, progressive ambulation and avoidance of postoperative bronchodilator therapy. Pneumonia occurred in 2.4% of patients. Lung protective ventilation (ORadj 0.45, 95%CI 0.22-0.92), ambulation (ORadj 0.08, 95%CI 0.04-0.17), and postoperative ventilation less than 6 hours (ORadj 0.47, 95%CI 0.26-0.87) were significantly associated with lower odds of pneumonia; postoperative bronchodilator therapy (ORadj 4.83, 95%CI 2.20-10.7) was significantly associated with higher odds. Risk-adjusted rates of pneumonia, operative mortality, and ICU length of stay were lower in patients with higher bundle scores (all p-trend < 0.01). CONCLUSIONS: These pneumonia prevention recommendations may serve as effective targets for avoiding postoperative healthcare-associated infections.

Cardiology/Cardiovascular Research
Ton VK, Xie R, Hernandez-Montfort JA, Meyns B, Nakatani T, Yanase M, Shaw S, Pettit S, Netuka I, Kirklin J, Goldstein DJ, and **Cowger J**. Short- and long-term adverse events in patients on temporary circulatory support before durable ventricular assist device: An IMACS registry analysis. *J Heart Lung Transplant* 2020; Epub ahead of print. PMID: 32029401. Full Text

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BACKGROUND: Patients with cardiogenic shock (CS) needing temporary circulatory support (TCS) have poor survival rates after implantation of durable ventricular assist device (dVAD). We aimed to characterize post-dVAD adverse event burden and survival rates in patients requiring pre-operative TCS. METHOD: We analyzed 13,511 adults (Interagency Registry for Mechanically Assisted Circulatory Support [INTERMACS] Profiles 1-3) with continuous-flow dVADs in International Society for Heart and Lung Transplantation Registry for Mechanically Assisted Circulatory Support (2013-2017) according to the need for pre-operative TCS (n=5,632) vs no TCS (n=7,879). Of these, 726 (5.4%) had biventricular assist devices (BiVAD). Furthermore, we compared prevalent rates (events/100 patient-months) of bleeding, device-related infection, hemorrhagic and ischemic cerebrovascular accidents (hemorrhagic cerebral vascular accident [hCVA], and ischemic cerebral vascular accident [iCVA]) in early (<3 months) and late (>/=3 months) post-operative periods. RESULTS: TCS included extracorporeal membrane oxygenation (ECMO) (n=1,138), intra-aortic balloon pump (IABP) (n=3,901), and other TCS (n=593). Within 3 post-operative months, there were more major bleeding and cerebrovascular accidents (CVAs) in patients with pre-operative ECMO (events/100 patient-months rates: bleeding=19, hCVA=1.6, iCVA=2.8) or IABP (bleeding=17.3, hCVA=1.5, iCVA=1.5) vs no TCS (bleeding=13.2, hCVA=1.1, iCVA=1.2, all $p < 0.05$). After 3 months, adverse events were lower and similar in all groups. Patients with ECMO had the worst short- and long-term survival rates. Patients with BiVAD had the worst survival rate regardless of need for pre-operative TCS. CVA and multiorgan failures were the common causes of death for patients with TCS and patients without TCS. CONCLUSIONS: Patients requiring TCS before dVAD had a sicker phenotype and higher rates of early post-operative adverse events than patients without TCS. ECMO was associated with very high early ischemic stroke, bleeding, and mortality. The extreme CS phenotype needing ECMO warrants a higher-level profile status, such as INTERMACS "0."

Center for Health Policy and Health Services Research

Cook JM, Zeber JE, Simiola V, Rossom R, Scherrer JF, Owen-Smith AA, **Ahmedani BK**, Zolfaghari K, and Copeland LA. Comparisons Between Patients Diagnosed with PTSD in Primary Care Versus Mental Health Care in Five Large Civilian Health Care Systems. *J Clin Psychol Med Settings* 2020; Epub ahead of print. PMID: 32048114. Full Text

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Posttraumatic stress disorder (PTSD) is a serious mental health disorder that may not be adequately detected or treated in primary care (PC). The purpose of this study was to compare the clinical characteristics and health care utilization of PTSD patients diagnosed in PC versus in specialty mental health care (MHC) across five large, civilian, not-for-profit healthcare systems. Electronic claims and medical record data on patients treated during 2014 were analyzed. Treatment was considered in terms of initiation and dose (i.e., psychotherapy sessions; pharmacotherapy-prescription psychotropics). Of 5256 patients aged 15-88 with a diagnosis of PTSD, 84.4% were diagnosed by a MHC provider. Patients diagnosed by MHC providers had 4 times the rate of and more enduring psychotherapy than those diagnosed by PC providers. Receipt of psychotropics varied by provider type, with generally higher prescription fill levels for patients in MHC. Strategies to better align patient needs with access and treatment modality in PC settings are needed.

Center for Health Policy and Health Services Research

Lynch FL, **Peterson EL**, Lu CY, **Hu Y**, Rossom RC, Waitzfelder BE, Owen-Smith AA, Hubley S, **Prabhakar D**, **Keoki Williams L**, Beck A, Simon GE, and **Ahmedani BK**. Substance use disorders and risk of suicide in a general US population: a case control study. *Addict Sci Clin Pract* 2020; 15(1):14. PMID: 32085800. Request Article

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BACKGROUND: Prior research suggests that substance use disorders (SUDs) are associated with risk of suicide mortality, but most previous work has been conducted among Veterans Health Administration patients. Few studies have examined the relationship between SUDs and suicide mortality in general populations. Our study estimates the association of SUDs with suicide mortality in a general US population of men and women who receive care across eight integrated health systems. METHODS: We conducted a case-control study using electronic health records and claims data from eight integrated health systems of the Mental Health Research Network. Participants were 2674 men and women who died by suicide between 2000-2013 and 267,400 matched controls. The main outcome was suicide mortality, assessed using data from the health systems and confirmed by state death data systems. Demographic and diagnostic data on substance use disorders and other health conditions were obtained from each health system. First, we compared descriptive statistics for cases and controls, including age, gender, income, and education. Next, we compared the rate of each substance use disorder category for cases and controls. Finally, we used conditional logistic regression models to estimate unadjusted and adjusted odds of suicide associated with each substance use disorder category. RESULTS: All categories of substance use disorders were associated with increased risk of suicide mortality. Adjusted odds ratios ranged from 2.0 (CI 1.7, 2.3) for patients with tobacco use disorder only to 11.2 (CI 8.0, 15.6) for patients with multiple alcohol, drug, and tobacco use disorders. Substance use disorders were associated with increased relative risk of suicide for both women and men across all categories, but the relative risk was more pronounced in women. CONCLUSIONS: Substance use disorders are associated with significant risk of suicide mortality, especially for women, even after controlling for other important risk factors. Experiencing multiple substance use disorders is particularly risky. These findings suggest increased suicide risk screening and prevention efforts for individuals with substance use disorders are needed.

Center for Health Policy and Health Services Research

Owen-Smith A, Stewart C, Sesay MM, Strasser SM, Yarborough BJ, **Ahmedani B**, **Miller-Matero LR**, Waring SC, Haller IV, Waitzfelder BE, Sterling SA, Campbell CI, Hechter RC, Zeber JE, Copeland LA, Scherrer JF, Rossom R, and Simon G. Chronic pain diagnoses and opioid dispensings among insured individuals with serious mental illness. *BMC Psychiatry* 2020; 20(1):40. PMID: 32005200. Full Text

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BACKGROUND: Individuals with major depressive disorder (MDD) and bipolar disorder (BD) have particularly high rates of chronic non-cancer pain (CNCP) and are also more likely to receive prescription opioids for their pain. However, there have been no known studies published to date that have examined opioid treatment patterns among individuals with schizophrenia. METHODS: Using electronic medical record data across 13 Mental Health Research Network sites, individuals with diagnoses of MDD (N = 65,750), BD (N = 38,117) or schizophrenia or schizoaffective disorder (N = 12,916) were identified and matched on age, sex and Medicare status to controls with no documented mental illness. CNCP diagnoses and prescription opioid medication dispensings were extracted for the matched samples. Multivariate analyses were conducted to evaluate (1) the odds of receiving a pain-related diagnosis and (2) the odds of receiving opioids, by separate mental illness diagnosis category compared with matched controls, controlling for age, sex, Medicare status, race/ethnicity, income, medical comorbidities, healthcare utilization and chronic pain diagnoses. RESULTS: Multivariable models indicated that having a MDD (OR = 1.90; 95% CI = 1.85-1.95) or BD (OR = 1.71; 95% CI = 1.66-1.77) diagnosis was associated with increased odds of a CNCP diagnosis after controlling for age, sex, race, income, medical comorbidities and healthcare utilization. By contrast, having a schizophrenia diagnosis was associated with decreased odds of receiving a chronic pain diagnosis (OR = 0.86; 95% CI = 0.82-0.90). Having a MDD (OR = 2.59; 95% CI = 2.44-2.75) or BD (OR = 2.12; 95% CI = 1.97-2.28) diagnosis was associated with increased odds of receiving chronic opioid medications, even after controlling for age, sex, race, income, medical comorbidities, healthcare utilization and chronic pain diagnosis; having a schizophrenia diagnosis was not associated with receiving chronic opioid medications. CONCLUSIONS: Individuals with serious mental illness, who are most at risk for developing opioid-related problems, continue to be prescribed opioids more often than their peers without mental illness. Mental health clinicians may be particularly well-suited to lead pain assessment and management efforts for these patients. Future research is needed to evaluate the effectiveness of involving mental health clinicians in these efforts.

Dermatology

Adelman M, **Lyons AB**, **Seale L**, and **Friedman BJ**. Use of p16 immunohistochemical stain to help differentiate inflamed melanocytic nevi from metastatic melanoma in the setting of immunotherapy. *J Am Acad Dermatol* 2019; Epub ahead of print. PMID: 31765681. Full Text

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Dermatology

Gold LS, Del Rosso JQ, Kircik L, Bhatia ND, Hooper D, Nahm WK, and Stuart I. Minocycline 1.5% foam for the topical treatment of moderate to severe papulopustular rosacea: Results of 2 phase 3, randomized, clinical trials. *J Am Acad Dermatol* 2020; Epub ahead of print. PMID: 32004648. Full Text

Henry Ford Health System, Detroit, Michigan.
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BACKGROUND: Efficacious topical medications for rosacea are needed. FMX103 1.5% is a novel topical minocycline foam that may have therapeutic benefits in treating rosacea while minimizing systemic adverse effects due to its topical route of delivery. OBJECTIVE: To determine the efficacy, safety, and tolerability of 12 weeks of treatment with FMX103 1.5% topical minocycline foam for papulopustular rosacea. METHODS: Two 12-week, phase 3, randomized, multicenter, double-blind, vehicle-controlled, 2-arm studies were performed in patients with moderate to severe papulopustular rosacea. RESULTS: Participants who received FMX103 1.5%, versus control individuals treated with vehicle, exhibited a significantly greater reduction in the number of inflammatory lesions (FX2016-11: -

17.57 vs -15.65; P = .0031; FX2016-12: -18.54 vs -14.88; P < .0001) and higher rates of Investigator Global Assessment treatment success (FX2016-11: 52.1% vs 43.0%; P = .0273; FX2016-12: 49.1% vs 39.0%; P = .0077). No serious treatment-related treatment-emergent adverse events occurred. LIMITATIONS: The generalizability of these data from a controlled clinical trial should be examined in a real-world setting. CONCLUSIONS: FMX103 1.5% was efficacious for moderate to severe papulopustular rosacea and maintained a favorable safety profile.

Dermatology
Hamel R, **Mohammad TF**, Chahine A, Joselow A, Garrett V, Radosta S, Boh E, Alora-Palli M, Mistur RL, Baron ED, Cooper KD, and **Lim HW**. Comparison of racial distribution of photodermatoses in USA academic dermatology clinics: a multicenter retrospective analysis of 1080 patients over a 10-year period. *Photodermatol Photoimmunol Photomed* 2020; Epub ahead of print. PMID: 32104953. Full Text

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BACKGROUND: Previous studies at single academic institutions have identified variations in the prevalence of photodermatoses among racial groups. The purpose of the study was to compare the distribution of photodermatoses between Whites and Blacks at four academic medical centers in the USA. METHODS: A retrospective chart review was performed at four institutions' general dermatology clinics using diagnoses consistent with the International Classification of Disease (ICD), Ninth and Tenth Revisions, codes related to photodermatoses between August 2006 and August 2016. A total of 9,736 charts were manually reviewed and classified. Analyses were performed analyzing the frequency of photodermatoses between Whites and Blacks in the pooled data. RESULTS: There were 1,080 patients with photodermatoses identified. Statistically significant differences in the frequency of photodermatoses between Whites and Blacks were identified for polymorphous light eruption (more common in Blacks), photoallergic contact dermatitis, phototoxic drug eruption, phytophotodermatitis, porphyria, and solar urticaria (more common in Whites). The most commonly diagnosed photodermatoses were polymorphous light eruption (total 672), and photodermatitis not otherwise specified (total 189). CONCLUSION: Our study demonstrated significantly higher proportions of polymorphous light eruption in Blacks, and higher proportions of photoallergic contact dermatitis, phototoxic drug eruptions, phytophotodermatitis, porphyrias, and solar urticaria in Whites.

Dermatology
Iyengar S, **Yeager DG**, Cohen JL, and **Ozog DM**. Update and Review of Bleeding Considerations in Dermatologic Surgery: Anticoagulants and Antiplatelets. *Dermatol Surg* 2020; 46(2):192-201. PMID: 31743247. Full Text

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BACKGROUND: Bleeding is an unavoidable risk of dermatologic surgery. The risk may be higher in patients taking agents that affect hemostasis. OBJECTIVE: The aim of this study was to provide an updated review of current anticoagulant and antiplatelet therapy available in the market and their associated risk of bleeding complications in cutaneous surgery. MATERIALS AND METHODS: A review of PubMed and MEDLINE was performed to review the English-language medical literature. RESULTS: Many anticoagulant and antiplatelet therapies exist. Several studies recommend the continued use of antiplatelet and anticoagulant medications in the perioperative period. Combination regimens and novel oral anticoagulants may be associated with an increased risk of bleeding. CONCLUSION: An updated understanding of antiplatelet and anticoagulant agents is critical for the surgeon. Current evidence does not support the discontinuation of antiplatelet and anticoagulant agents in the perioperative period under most circumstances. However, relevant data on novel oral anticoagulant agents are still sparse, suggesting that a precautionary approach is warranted.

Dermatology
Iyengar S, **Yeager DG**, Cohen JL, and **Ozog DM**. Update and Review of Bleeding Considerations in Dermatologic Surgery: Hemostatic Techniques and Treatment Strategies for Bleeding Complications. *Dermatol Surg* 2020; 46(2):203-212. PMID: 31592926. Full Text

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BACKGROUND: There are many intraoperative and postoperative techniques to aid hemostasis in dermatologic procedures. An updated understanding is critical for the surgeon. OBJECTIVE: To provide an updated review of methods for hemostasis and therapies for postprocedural purpura and ecchymosis applicable to dermatology. MATERIALS AND METHODS: A review of Ovid MEDLINE was performed to review the English-language medical literature of hemostatic options and their use in cutaneous surgery. All available publication years were included from 1946 to present. RESULTS: A comprehensive and current list of hemostatic options used in the intraoperative and postoperative period is provided along with traditional and emerging therapies for postprocedural purpura and ecchymosis. CONCLUSION: A myriad of options exist for minimizing and treating bleeding complications. The appropriate use and updated knowledge of hemostatic options is provided.

Dermatology
Levoska MA, **Griffith JL**, **Nagai S**, **Collins K**, and **Lim HW**. A multi-disciplinary approach utilizing filters for surgical procedures in erythropoietic protoporphyria. *J Am Acad Dermatol* 2020; Epub ahead of print. PMID: 32068036. Full Text

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Dermatology
Lyons AB, Kaddurah H, Peacock A, Zubair R, Vellaichamy G, Norwick P, **Ramesh M**, **Jacobsen G**, and **Hamzavi IH**. Hidradenitis suppurativa and risk for development of Clostridium difficile colitis. *Int J Dermatol* 2020; Epub ahead of print. PMID: 32010962. Full Text

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Dermatology
Narla S, and Silverberg JI. Multimorbidity and mortality risk in hospitalized adults with chronic inflammatory skin disease in the United States. *Arch Dermatol Res* 2020; Epub ahead of print. PMID: 32047999. Full Text

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Chronic inflammatory skin diseases (CISD) represent a significant burden of skin disease in the United States, and a growing number of studies demonstrate that CISD are associated with multiple comorbidities. However, few studies examined multimorbidity in adults with CISD. We sought to determine whether hospitalized US adults with chronic inflammatory skin disorders have increased multi-morbidity and mortality risk. Data from the 2002-2012 Nationwide Inpatient Sample were analyzed, including a representative 20% sample of US hospitalizations. Charlson comorbidity index (CCI) and mean estimated 10-year survival were calculated. Multivariable linear regression models were constructed with CCI score and mean estimated 10-year survival as the dependent variables and chronic inflammatory skin diagnosis, age and sex as the independent variables. CCI scores were significantly higher in bullous pemphigoid ($P = 0.0005$) and dermatomyositis ($P < 0.0001$), lower in hidradenitis suppurativa ($P < 0.0001$), pemphigus ($P < 0.0001$), rosacea ($P < 0.0001$), and not significantly different in atopic dermatitis, alopecia areata, and lichen planus compared to psoriasis. Conversely, the mean estimated 10-year survival was higher in pemphigus ($P = 0.0451$), lichen planus ($P = 0.0352$), rosacea ($P < 0.0001$), lower in bullous pemphigoid and dermatomyositis ($P < 0.0001$), and similar in atopic dermatitis, alopecia areata, and hidradenitis suppurativa compared to psoriasis. Each CISD had a distinct profile of comorbidities when compared to psoriasis. Hospitalized adults with multiple CISD have increased multimorbidity and decreased 10-year survival. Further studies are needed to develop multidisciplinary strategies aimed at preventing and treating multimorbidity, especially modifiable cardiovascular factors in adults with CISD.

Dermatology
Powell A, Nelson KN, **Awosika O**, Rengifo-Pardo M, and Ehrlich A. Burning Mouth Syndrome and Contact Dermatitis. *Dermatitis* 2020; Epub ahead of print. PMID: 32091459. Full Text

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Burning mouth syndrome (BMS) is a condition that remains a diagnostic challenge and is frequently difficult to treat. Rather than being a singular entity, more recent research has suggested that the diagnosis of BMS encompasses a family of syndromes. Of this family, type 3 has been identified as being related to contact dermatitis. Although this subtype has been most commonly associated with dental allergens, several food, cosmetic, and pharmaceutical products have also been identified as allergens related to the onset of BMS. Failure to identify these allergens prevents timely diagnosis and initiation of treatment for patients with BMS related to contact dermatitis. This article identifies the allergens most relevant to this type 3 and describes the commercially available allergy panels needed to ensure that all relevant allergens are included during patch testing. This study also describes approaches to diagnosis of BMS and discusses approaches to treatment based on subtypes of the condition.

Dermatology
Soliman YS, **Lim HW**, and **Kerr HA**. Recalcitrant, delayed pressure urticaria treated with long-term intravenous immunoglobulin. *JAAD Case Rep* 2020; 6(3):176-177. PMID: 32099887. Full Text

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Dermatology
Thiboutot D, Anderson R, Cook-Bolden F, Draelos Z, Gallo R, Granstein R, Kang S, Macsai M, **Gold LS**, and Tan J. Standard Management Options for Rosacea: the 2019 Update by the National Rosacea Society Expert Committee. *J Am Acad Dermatol* 2020; Epub ahead of print. PMID: 32035944. Full Text

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In 2017 a National Rosacea Society expert committee developed and published an updated classification of rosacea to reflect current insights into rosacea pathogenesis, pathophysiology, and management. These developments suggest that a multivariate disease process underlies the various clinical manifestations of the disorder. The new system is consequently based on phenotypes that link to this process, providing clear parameters for research and diagnosis, as well as encouraging clinicians to assess and treat the disorder as it may occur in each individual. Meanwhile, a range of therapies has become available for rosacea, and their roles have been increasingly defined in clinical practice as the disorder has become more widely recognized. This update is intended to provide a comprehensive summary of management options, including expert evaluations, to serve as a guide for tailoring treatment and care on an individual basis to achieve optimal patient outcomes.

Emergency Medicine
Nowak RM, Christenson RH, **Jacobsen G**, **McCord J**, Apple FS, Singer AJ, Limkakeng A, Jr., Peacock WF, and deFilippi CR. Performance of Novel High-Sensitivity Cardiac Troponin I Assays for 0/1-Hour and 0/2- to 3-Hour Evaluations for Acute Myocardial Infarction: Results From the HIGH-US Study. *Ann Emerg Med* 2020; Epub ahead of print. PMID: 32046869. Full Text

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STUDY OBJECTIVE: We determine the accuracy of high-sensitivity cardiac troponin I (hs-cTnI), European-derived, rapid, acute myocardial infarction, rule-out/rule-in algorithms applied to a US emergency department (ED) population. METHODS: Adults presenting to the ED with suspected acute myocardial infarction were included. Plasma samples collected at baseline and between 40 and 90 minutes and 2 and 3 hours later were analyzed in core laboratories using the Siemens Healthineers hs-cTnI assays. Acute myocardial infarction diagnosis was independently adjudicated. The sensitivity, specificity, and negative and positive predictive values for rapid acute myocardial infarction rule-out/rule-in using European algorithms and 30-day outcomes are reported. RESULTS: From 29 US medical centers, 2,113 subjects had complete data for the 0/1-hour algorithm analyses. With the Siemens Atellica Immunoassay hs-cTnI values, 1,065 patients (50.4%) were ruled out, with a negative predictive value of 99.7% and sensitivity of 98.7% (95% confidence interval 99.2% to 99.9% and 96.3% to 99.6%, respectively), whereas 265 patients (12.6%) were ruled in, having a positive predictive value of 69.4% and specificity of 95.7% (95% confidence interval 63.6% to 74.7% and 94.7% to 96.5%, respectively). The remaining 783 patients (37.1%) were classified as having continued evaluations, with an acute myocardial infarction incidence of 5.6% (95% confidence interval 4.2% to 7.5%). The overall 30-day risk of death or postdischarge acute myocardial infarction was very low in the ruled-out patients but was incrementally increased in the other groups (rule-out 0.2%; continued evaluations 2.1%; rule-in 4.8%). Equivalent results were observed in the 0/2- to 3-hour analyses and when both algorithms were applied to the hs-cTnI ADVIA Centaur measurements. CONCLUSION: The European rapid rule-out/rule-in acute myocardial infarction algorithm hs-cTnI cut points can be harmonized with a demographically and risk-factor diverse US ED population.

Endocrinology and Metabolism

Arya AK, Singh P, Saikia UN, Sachdeva N, Dahiya D, Behera A, **Rao SD**, and Bhadada SK. Dysregulated mitogen-activated protein kinase pathway mediated cell cycle disruption in sporadic parathyroid tumors. *J Endocrinol Invest* 2020; 43(2):247-253. PMID: 31535356. Request Article

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OBJECTIVES: The study was designed to evaluate expression profiling of mitogen-activated protein kinase (MAPK) signalling pathway genes in sporadic parathyroid adenoma. METHODS: Expression of MAPK signalling pathway genes including activated transcription factors and cell cycle regulatory genes was analysed by real-time PCR- based array in parathyroid adenoma (N = 20) and normal parathyroid tissue (N = 4). RESULTS: MAPK signalling pathway as studied by PCR array revealed that a total of 22 genes were differentially expressed (>/= twofold change, p </= 0.05) in parathyroid adenoma. Up-regulated genes were ARAF, MAPK12, CREBBP, MYC, HSPB1, HRAS, CDK4, CCND1, and E2F1, and down-regulated genes were MAP4K1, DLK1, MAP3K4, MAPK10, MAPK8, ATF2, SMAD4, MEF2C, LAMTOR3, FOS, CDKN2A CDKN2B, and RB1. The present study revealed that ERK1/2 signalling pathway with up-regulation of HRAS, ARAF, and MEK1 genes and up-regulation of positive regulators of cell cycle (CCND1, CDK4, and E2F1) and down-regulation negative regulators of cell cycle (CDKN2A, CDKN2B, and RB1) made highly dysregulated MAPK signalling pathway in parathyroid adenoma. Expression of CDK4 was positively associated with plasma PTH level (r = 0.60, p = 0.04) and tumor weight (r = 0.80, p = 0.02) of the adenoma patients, respectively. Expression of CDKN2A was correlated negatively with PTH level (r = - 0.52, p = 0.04) of the adenoma patients. CONCLUSION: The current study revealed that ERK pathway and associated cell cycle regulator genes are dysregulated in sporadic parathyroid adenoma.

Gastroenterology

Ahsan BU, **Alhamar M**, **Hogan KM**, **Schultz D**, **Zuchelli T**, and **Zhang Z**. Endometrial clear cell carcinoma with metastasis to the common hepatic duct: A rare etiology of obstructive jaundice, diagnosed by biliary cytology brushing specimen. *Cytopathology* 2020; Epub ahead of print. PMID: 32049406. Full Text

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Clear cell carcinoma is an aggressive subtype of uterine carcinoma. Metastases can be local and/or distant but metastasis to the biliary tree resulting in obstructive jaundice is extremely rare. This is the first report of endometrial carcinoma of clear cell type with metastasis to the common hepatic duct, causing malignant biliary stricture and obstructive jaundice in a young woman, diagnosed on a biliary cytology brushing specimen.

Gastroenterology

Ali B, Jiang Y, Agbim U, Kedia SK, Satapathy SK, Barnes M, Maliakkal B, Nair SP, Eason JD, and **Gonzalez HC**. Effect of opioid treatment on clinical outcomes among cirrhotic patients in the United States. *Clin Transplant* 2020; Epub ahead of print. PMID: 32096883. Full Text

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BACKGROUND: Opioid medications are frequently used to address pain among patients with cirrhosis, including those on the liver transplant (LT) waitlist and after transplantation. However, opioid use has been associated with poor allograft outcomes and reduced transplant survival. We examined the impact of opioid use across the spectrum of advanced liver disease, from the initial hepatology consultation for cirrhosis through transplant referral, listing, and the post-LT process. METHODS: The study includes all patients referred for cirrhosis management in a single healthcare system in the United States. Data were extracted retrospectively through medical chart review. RESULTS: Of 414 patients included in the study, 104 (25%) were treated with opioid. Patients on opioids were more likely to be White, have body mass indices (BMI) >30, have HCV, suffer from hepatic encephalopathy, cigarette smokers, and use benzodiazepines concurrently. Higher doses of opioids were associated with multiple emergency department (ED). 89 underwent LT, including 20 opioid-treated patients. There was no difference found between the opioid and non-opioid group with regard to allograft loss, ED visits, hospital readmissions at two years post LT follow-up. CONCLUSIONS: Opioid treatment was common among patients with cirrhosis. We did not find increased negative outcomes among opioids-users across the spectrum of cirrhosis. However, the sample for LT patients was small.

Gastroenterology

Kitajima T, **Moonka D**, **Yeddula S**, **Rizzari M**, **Collins K**, **Yoshida A**, **Abouljoud MS**, and **Nagai S**. Liver transplant waitlist outcomes in alcoholic hepatitis compared with other liver diseases: An analysis of UNOS registry. *Clin Transplant* 2020; Epub ahead of print. PMID: 32073688. Full Text

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There is growing interest in performing liver transplantation (LT) in patients with alcoholic hepatitis (AH) without a mandated abstinence period. The aim of this study is to investigate waitlist outcomes in AH patients compared to those with other liver diseases. Using data from the UNOS registry, adult patients listed for LT between 2009 and 2018 were evaluated. Waitlist outcomes were compared among liver diseases. 64,646 patients were eligible, including 286 with AH, 16,871 with alcoholic cirrhosis (AC), 13,730 with hepatitis C (HCV), 10,315 with non-alcoholic steatohepatitis (NASH) and 5,841 with cholestatic liver disease (CLD). In comparison to AH patients, patients with HCV, NASH, and CLD had a significantly higher risk of waitlist mortality, and a lower likelihood of recovery on the waitlist. These trends were more prominent in the waiting-time period of 91-365 days than in shorter periods. In intention-to-treat analysis, positive prognostic effect of LT was significant in AH patients with MELD score>/=35 (HR 0.04, P<0.001). AH patients showed lower mortality risk and a higher chance of recovery while on waitlist than other liver diseases, especially when waiting-time exceeded 90 days. These results indicate the importance of continuous evaluation of disease progression in AH patients awaiting LT.

Gastroenterology

Madill-Thomsen K, **Abouljoud M**, Bhatti C, Ciszek M, Durlik M, Feng S, Foroncewicz B, **Francis I**, Grat M, Jurczyk K, Klintmalm G, Krasnodebski M, McCaughan G, Miquel R, Montano-Loza A, **Moonka D**, Mucha K, Myslak M, Paczek L, Perkowska-Ptasinska A, Piecha G, Reichman T, Sanchez-Fueyo A, Tronina O, Wawrzynowicz-Syczewska M, Wiecek A, Zieniewicz K, and Halloran PF. The molecular diagnosis of rejection in liver transplant biopsies: First results of the INTERLIVER study. *Am J Transplant* 2020; Epub ahead of print. PMID: 32090446. Full Text

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Molecular diagnosis of rejection is emerging in kidney, heart, and lung transplant biopsies and could offer insights for liver transplant biopsies. We measured gene expression by microarrays in 235 liver transplant biopsies from 10 centers. Unsupervised archetypal analysis based on expression of previously annotated rejection-related transcripts identified four groups: normal 'R1normal ' (N=129), T cell-mediated rejection (TCMR) 'R2TCMR ' (N=37), early injury 'R3injury ' (N=61), and fibrosis 'R4late ' (N=8). Groups differed in median time post-transplant e.g. R3injury 99 days vs. R4late 3117 days. R2TCMR biopsies expressed typical TCMR-related transcripts e.g. intense IFNG-induced effects. R3injury displayed increased expression of parenchymal injury transcripts (e.g. hypoxia-inducible factor EGLN1). R4late biopsies showed immunoglobulin transcripts and injury-related transcripts. R2TCMR correlated with histologic rejection although with many discrepancies, and R4late with fibrosis. R2TCMR , R3injury , and R4late correlated with liver function abnormalities. Supervised classifiers trained on histologic rejection showed less agreement with histology than unsupervised R2TCMR scores. No confirmed cases of clinical ABMR were present in the population, and strategies that previously revealed antibody-mediated rejection (ABMR) in kidney and heart transplants failed to reveal a liver ABMR phenotype. In conclusion, molecular analysis of liver transplant biopsies detects rejection, has the potential to resolve ambiguities, and could assist with immunosuppressive management.

Gastroenterology

Meighani A, **Alimirah M**, **Ramesh M**, and **Salgia R**. Fecal Microbiota Transplantation for Clostridioides Difficile Infection in Patients with Chronic Liver Disease. *Int J Hepatol* 2020; 2020. PMID: Not assigned. Request Article

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Background. Fecal microbiota transplantation (FMT) is a well-established therapeutic option for patients with antibiotic resistant Clostridioides difficile infection (CDI). However, the efficacy of FMT in patients with chronic liver disease remains elusive. Aims. We studied the effect of FMT on chronic liver disease (CLD) patients with CDI at our tertiary medical center. Methods. A cohort of all patients who received FMT from December 2012 to May 2014 for refractory or recurrent CDI was identified. Patients were monitored for a year after FMT. Descriptive analysis was conducted to compare the effect of FMT in patients with and without CLD. Results. A total of 201 patients with CDI received FMT, 14 of which had a history of CLD. Nine of these patients exhibited cirrhosis of the liver with a mean Child-Turcotte-Pugh score of 8. CDI development in these patients was associated with recent exposure to antibiotics and was observed to be significantly different between both groups (17% of CLD patients vs. 58% in the general cohort, p=0.01). Four patients with CLD received >1 FMT, of which 2 did not respond to treatment. There was no significant difference between patients with liver disease and the rest of the cohort with regard to FMT response (12/14 (87%) vs. 164/187 (88%), p=0.68). Conclusion. FMT is a safe and effective therapy against CDI for patients with CLD and cirrhosis.

Graduate Medical Education

Harmes KM, Shih E, Plegue M, **Shultz C**, and Diez HL. Family physician perceptions of the role and value of the clinical pharmacist in the management of patients with type 2 diabetes. *J Am Coll Clin Pharm* 2020; 3(1):15-20. PMID: Not assigned. Full Text

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Purpose: Clinical pharmacists can help primary care physicians (PCPs) manage medications for patients with poorly controlled type 2 diabetes. Studies have shown that clinical pharmacist involvement in care can improve outcomes such as glycosylated hemoglobin (A1C), blood pressure and lipid control, and decrease episodes of hypoglycemia. Despite these findings, some PCPs may be slow or disinclined to refer to clinical pharmacists when available. This study addressed PCP perceptions regarding referral to clinical pharmacists and endocrinologists for patients with poorly controlled type 2 diabetes. Methods: Physicians from five family medicine sites were surveyed. Physicians were queried regarding their patterns for patient referral to endocrinologists and/or clinical pharmacists. Clinical contributions and importance of factors to consider when referring were compared between clinical pharmacists and endocrinologists using paired t tests. Results: Fifty physicians responded to the survey, resulting in a response rate of 73.5%. The majority of PCPs indicated that they have referred to endocrinologists (89.5%) and clinical pharmacists (93.5%) for specialty care. PCPs tended to refer to clinical pharmacists sooner and at lower A1C values than to endocrinologists. PCPs also considered multiple medical comorbidities, history of noncompliance with medical recommendations, low reading ability or math skills, complex psychosocial situations, fear of needles, or difficulty affording medications or supplies to be more important when referring patients to clinical pharmacists than endocrinologists. Conclusion: We hypothesized that referrals to a clinical pharmacist or endocrinologist are made with careful consideration of the patients' needs. PCPs reported increased utilization of clinical pharmacists for patients with nonmedical needs, indicating that extra time, education, and psychosocial support provided by the clinical pharmacist is highly valued.

Hematology-Oncology

Duric N, Sak M, Fan S, Pfeiffer RM, Littrup PJ, Simon MS, Gorski DH, **Ali H**, Purrington KS, Brem RF, Sherman ME, and Gierach GL. Using whole breast ultrasound tomography to improve breast cancer risk assessment: A novel risk factor based on the quantitative tissue property of sound speed. *J Clin Med* 2020; 9(2). PMID: Not assigned. Request Article

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Mammographic percent density (MPD) is an independent risk factor for developing breast cancer, but its inclusion in clinical risk models provides only modest improvements in individualized risk prediction, and MPD is not typically assessed in younger women because of ionizing radiation concerns. Previous studies have shown that tissue sound speed, derived from whole breast ultrasound tomography (UST), a non-ionizing modality, is a potential surrogate marker of breast density, but prior to this study, sound speed has not been directly linked to breast cancer risk. To that end, we explored the relation of sound speed and MPD with breast cancer risk in a case-control study, including 61 cases with recent breast cancer diagnoses and a comparison group of 165 women, frequency matched to cases on age, race, and menopausal status, and with a recent negative mammogram and no personal history of breast cancer. Multivariable odds ratios (ORs) and 95% confidence intervals (CIs) were estimated for the relation of quartiles of MPD and sound speed with breast cancer risk adjusted for matching factors. Elevated MPD was associated with increased breast cancer risk, although the trend did not reach statistical significance (OR per quartile = 1.27, 95% CI: 0.95, 1.70; ptrend = 0.10). In contrast, elevated sound speed was significantly associated with breast cancer risk in a dose–response fashion (OR per quartile = 1.83, 95% CI: 1.32, 2.54; ptrend = 0.0003). The OR trend for sound speed was statistically significantly different from that observed for MPD (p = 0.005). These findings suggest that whole breast sound speed may be more strongly associated with breast cancer risk than MPD and offer future opportunities for refining the magnitude and precision of risk associations in larger, population-based studies, including women younger than usual screening ages.

Hematology-Oncology

Johnson TA, Morris JD, Coppage DA, Cook CV, Persi LN, Ogarrio MA, Garcia TC, McIntosh NL, McCauley EP, **Media J**, **Maheshwari M**, **Valeriote FA**, Shaw J, and Crews P. Reinvestigation of Mycothiazole Reveals the Penta-2,4-dien-1-ol Residue Imparts Picomolar Potency and 8S Configuration. *ACS Med Chem Lett* 2020; 11(2):108-113. PMID: 32071675. Request Article

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Reinvestigation of mycothiazole (1) revealed picomolar potency (IC50 = 0.00016, 0.00027, 0.00035 muM) against pancreatic, (PANC-1), liver (HepG2), and colon (HCT-116) tumor cell lines. Reevaluation of 1 provided [alpha]D data indicating Vanuatu specimens of C. mycofijiensis contain the 8S enantiomer of 1 and not the 8R configuration previously reported. Semisynthesis provided 8-O-acetylmycothiazole (2), 8-oxomycothiazole (8), mycothiazole nitrosobenzene derivatives (MND1, MND2: 9a, 9b), and MND3 (10) with IC50 = 0.00129, >1.0, >1.0, >1.0, >1.0 muM, respectively, against PANC-1 cell lines. These results highlight the significance of the penta-2,4-dien-1-ol residue as a key structural feature of 1 required for its cytotoxicty against tumor cell lines.

Hematology-Oncology
Schmidt JJ, **Khatri Y**, **Brody SI**, **Zhu C**, **Pietraszkiewicz H**, **Valeriote FA**, and **Sherman DH**. A Versatile Chemoenzymatic Synthesis for the Discovery of Potent Cryptophycin Analogs. *ACS Chem Biol* 2020; 15(2):524-532. PMID: 31961651. Request Article

Department of Internal Medicine, Henry Ford Cancer Institute , Henry Ford Health System , Detroit , Michigan 48202 , United States.

The cryptophycins are a family of macrocyclic depsipeptide natural products that display exceptionally potent antiproliferative activity against drug-resistant cancers. Unique challenges facing the synthesis and derivatization of this complex group of molecules motivated us to investigate a chemoenzymatic synthesis designed to access new analogs for biological evaluation. The cryptophycin thioesterase (CrpTE) and the cryptophycin epoxidase (CrpE) are a versatile set of enzymes that catalyze macrocyclization and epoxidation of over 20 natural cryptophycin metabolites. Thus, we envisioned a drug development strategy involving their use as standalone biocatalysts for production of unnatural derivatives. Herein, we developed a scalable synthesis of 12 new unit A-B-C-D linear chain elongation intermediates containing heterocyclic aromatic groups as alternatives to the native unit A benzyl group. N-Acetyl cysteamine activated forms of each intermediate were assessed for conversion to macrocyclic products using wild type CrpTE, which demonstrated the exceptional flexibility of this enzyme. Semipreparative scale reactions were conducted for isolation and structural characterization of new cryptophycins. Each was then evaluated as a substrate for CrpE P450 and its ability to generate the epoxidized products from these substrates that possess altered electronics at the unit A styrenyl double bond position. Finally, biological evaluation of the new cryptophycins revealed a des-beta-epoxy analog with low picomolar potency, previously limited to cryptophycins bearing epoxide functionality.

Infectious Diseases
Meighani A, **Alimirah M**, **Ramesh M**, and **Salgia R**. Fecal Microbiota Transplantation for Clostridioides Difficile Infection in Patients with Chronic Liver Disease. *Int J Hepatol* 2020; 2020. PMID: Not assigned. Request Article

A. Meighani, Division of Gastroenterology and Hepatology, Henry Ford Hospital, 2799 W. Grand Blvd, Detroit, MI, United States

Background. Fecal microbiota transplantation (FMT) is a well-established therapeutic option for patients with antibiotic resistant Clostridioides difficile infection (CDI). However, the efficacy of FMT in patients with chronic liver disease remains elusive. Aims. We studied the effect of FMT on chronic liver disease (CLD) patients with CDI at our tertiary medical center. Methods. A cohort of all patients who received FMT from December 2012 to May 2014 for refractory or recurrent CDI was identified. Patients were monitored for a year after FMT. Descriptive analysis was conducted to compare the effect of FMT in patients with and without CLD. Results. A total of 201 patients with CDI received FMT, 14 of which had a history of CLD. Nine of these patients exhibited cirrhosis of the liver with a mean Child-Turcotte-Pugh score of 8. CDI development in these patients was associated with recent exposure to antibiotics and was observed to be significantly different between both groups (17% of CLD patients vs. 58% in the general cohort, p=0.01). Four patients with CLD received >1 FMT, of which 2 did not respond to treatment. There was no significant difference between patients with liver disease and the rest of the cohort with regard to FMT response (12/14 (87%) vs. 164/187 (88%), p=0.68). Conclusion. FMT is a safe and effective therapy against CDI for patients with CLD and cirrhosis.

Internal Medicine
Mahajan M, **Venkatesulu BP**, **Sallam O**, **Taneja K**, **Scott M**, and **Brar I**. Unmasking lymphoma immune reconstitution inflammatory syndrome in a patient with pyrexia of unknown origin: a case report. *J Egypt Natl Canc Inst* 2020; 32(1). PMID: Not assigned. Request Article

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Background: Immune reconstitution inflammatory syndrome (IRIS) is a constellation of inflammatory disorders that are unmasked after the initiation of anti-retroviral therapy (ART) in Human immunodeficiency virus (HIV) infected patients. Unmasking lymphoma IRIS is a relatively rare manifestation after initiation of anti-retroviral therapy. Case presentation: We report a 44-year-old male with HIV on 4 months of ART presenting with pyrexia of unknown origin with a diagnosis of unmasking Hodgkin's lymphoma IRIS stage IV with B symptoms. This case portrays the importance of recognizing the possibility of Hodgkin's lymphoma as a possible manifestation of IRIS within the first 6 months of initiation of ART. Conclusion: Patients presenting with pyrexia of unknown origin and lymphadenopathy within the first 6 months of initiation of ART, lymphoma diagnosis should be on the high threshold of suspicion as portrayed by our case.

Internal Medicine
Meighani A, **Alimirah M**, **Ramesh M**, and **Salgia R**. Fecal Microbiota Transplantation for Clostridioides Difficile Infection in Patients with Chronic Liver Disease. *Int J Hepatol* 2020; 2020. PMID: Not assigned. Request Article

A. Meighani, Division of Gastroenterology and Hepatology, Henry Ford Hospital, 2799 W. Grand Blvd, Detroit, MI, United States

Background. Fecal microbiota transplantation (FMT) is a well-established therapeutic option for patients with antibiotic resistant Clostridioides difficile infection (CDI). However, the efficacy of FMT in patients with chronic liver disease remains elusive. Aims. We studied the effect of FMT on chronic liver disease (CLD) patients with CDI at our tertiary medical center. Methods. A cohort of all patients who received FMT from December 2012 to May 2014 for refractory or recurrent CDI was identified. Patients were monitored for a year after FMT. Descriptive analysis was conducted to compare the effect of FMT in patients with and without CLD. Results. A total of 201 patients with CDI received FMT, 14 of which had a history of CLD. Nine of these patients exhibited cirrhosis of the liver with a mean Child-Turcotte-Pugh score of 8. CDI development in these patients was associated with recent exposure to antibiotics and was observed to be significantly different between both groups (17% of CLD patients vs. 58% in the general cohort, p=0.01). Four patients with CLD received >1 FMT, of which 2 did not respond to treatment. There was no significant difference between patients with liver disease and the rest of the cohort with regard to FMT response (12/14 (87%) vs. 164/187 (88%), p=0.68). Conclusion. FMT is a safe and effective therapy against CDI for patients with CLD and cirrhosis.

Nephrology
Bixby AL, Shaikh SA, Naik AS, Cotiguala L, McMurry K, **Samaniego-Picota MD**, Marshall VD, and Park JM. Safety and Efficacy of Direct-acting Oral Anticoagulants Versus Warfarin in Kidney Transplant Recipients: A Retrospective Single Center Cohort Study. *Transpl Int* 2020; Epub ahead of print. PMID: 32107804. Full Text

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Despite the increased use, comparative safety and efficacy of direct-acting oral anticoagulants (DOACs) against warfarin have not been well studied in kidney transplant recipients. In this single-center retrospective study, we evaluated 197 adult kidney transplant recipients on DOAC or warfarin between January 1, 2011 to June 30, 2018. The primary outcome was incidence of major bleeding defined as a hemoglobin decrease >/= 2 g/dl, blood transfusion >/= 2 units, or symptomatic bleeding in a critical area or organ. Patients were initiated on anticoagulation therapy at a median of 6.5 years post-transplant and followed for a median of 12.3 months. The rates of major bleeding were 7.2% per year with DOACs vs. 11.4% per year with warfarin (Mantel-Cox p=0.15). No difference was found in composite bleeding, clinically relevant nonmajor bleeding, or thromboembolic events between the groups. There was a lower incidence of major bleeding with apixaban compared to all other anticoagulants (6.7% vs. 19.0%,

p=0.027). After controlling for potential confounders, DOAC use was not associated with an increased risk of major bleeding (HR 0.73, 95% CI 0.27-1.95). Further research is warranted to definitively determine whether DOACs are effective and safe alternatives to warfarin for anticoagulation in kidney transplant recipients.

Neurology
Consortium ITP-CAoWG, and **Mikkelsen T**. Pan-cancer analysis of whole genomes. *Nature* 2020; 578(7793):82-93. PMID: 32025007. Full Text

Cancer is driven by genetic change, and the advent of massively parallel sequencing has enabled systematic documentation of this variation at the whole-genome scale(1-3). Here we report the integrative analysis of 2,658 whole-cancer genomes and their matching normal tissues across 38 tumour types from the Pan-Cancer Analysis of Whole Genomes (PCAWG) Consortium of the International Cancer Genome Consortium (ICGC) and The Cancer Genome Atlas (TCGA). We describe the generation of the PCAWG resource, facilitated by international data sharing using compute clouds. On average, cancer genomes contained 4-5 driver mutations when combining coding and non-coding genomic elements; however, in around 5% of cases no drivers were identified, suggesting that cancer driver discovery is not yet complete. Chromothripsis, in which many clustered structural variants arise in a single catastrophic event, is frequently an early event in tumour evolution; in acral melanoma, for example, these events precede most somatic point mutations and affect several cancer-associated genes simultaneously. Cancers with abnormal telomere maintenance often originate from tissues with low replicative activity and show several mechanisms of preventing telomere attrition to critical levels. Common and rare germline variants affect patterns of somatic mutation, including point mutations, structural variants and somatic retrotransposition. A collection of papers from the PCAWG Consortium describes non-coding mutations that drive cancer beyond those in the TERT promoter(4); identifies new signatures of mutational processes that cause base substitutions, small insertions and deletions and structural variation(5,6); analyses timings and patterns of tumour evolution(7); describes the diverse transcriptional consequences of somatic mutation on splicing, expression levels, fusion genes and promoter activity(8,9); and evaluates a range of more-specialized features of cancer genomes(8,10-18).

Neurology
Dharaiya D, and **Memon AB**. Palatal myoclonus secondary to neurosarcoidosis. *Clin Case Rep* 2020; Epub ahead of print. PMID: Not assigned. Request Article

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Palatal myoclonus can be primary or secondary. In primary palatal myoclonus, no obvious structural brain lesions can be found within the triangle of Guillain and Mollaret. Common causes of secondary myoclonus include stroke, demyelination, infections, trauma, and neurodegeneration.

Neurology
Hogan J, Sun H, **Nour HA**, Jing J, Tabaeizadeh M, Shoukat M, Javed F, Kassa S, Edhi MM, Bordbar E, Gallagher J, Junior VM, Ghanta M, Shao YP, Akeju O, Cole AJ, Rosenthal ES, Zafar S, and Westover MB. Burst Suppression: Causes and Effects on Mortality in Critical Illness. *Neurocrit Care* 2020; Epub ahead of print. PMID: 32096120. Full Text

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BACKGROUND: Burst suppression in mechanically ventilated intensive care unit (ICU) patients is associated with increased mortality. However, the relative contributions of propofol use and critical illness itself to burst suppression; of burst suppression, propofol, and critical illness to mortality; and whether preventing burst suppression might reduce mortality, have not been quantified. METHODS: The dataset contains 471 adults from seven ICUs, after excluding anoxic encephalopathy due to cardiac arrest or intentional burst suppression for therapeutic reasons. We used multiple prediction and causal inference methods to estimate the effects connecting burst suppression, propofol, critical illness, and in-hospital mortality in an observational retrospective study. We also estimated the effects mediated by burst suppression. Sensitivity analysis was used to assess for unmeasured confounding. RESULTS: The expected outcomes in a "counterfactual" randomized controlled trial (cRCT) that assigned patients to mild versus severe illness are expected to show a difference in burst suppression burden of 39%, 95% CI [8-66]%, and in

mortality of 35% [29-41]%. Assigning patients to maximal (100%) burst suppression burden is expected to increase mortality by 12% [7-17]% compared to 0% burden. Burst suppression mediates 10% [2-21]% of the effect of critical illness on mortality. A high cumulative propofol dose (1316 mg/kg) is expected to increase burst suppression burden by 6% [0.8-12]% compared to a low dose (284 mg/kg). Propofol exposure has no significant direct effect on mortality; its effect is entirely mediated through burst suppression. CONCLUSIONS: Our analysis clarifies how important factors contribute to mortality in ICU patients. Burst suppression appears to contribute to mortality but is primarily an effect of critical illness rather than iatrogenic use of propofol.

Neurology
Ironside N, Chen CJ, Mutasa S, Sim JL, Ding D, Marfatiah S, Roh D, Mukherjee S, Johnston KC, Southerland AM, **Mayer SA**, Lignelli A, and Connolly ES. Fully Automated Segmentation Algorithm for Perihematomal Edema Volumetry After Spontaneous Intracerebral Hemorrhage. *Stroke* 2020; 51(3):815-823. PMID: 32078476. Full Text

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Department of Neurology (K.C.J., A.M.S.), University of Virginia Health System, Charlottesville, VA.
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Background and Purpose- Perihematomal edema (PHE) is a promising surrogate marker of secondary brain injury in patients with spontaneous intracerebral hemorrhage, but it can be challenging to accurately and rapidly quantify. The aims of this study are to derive and internally validate a fully automated segmentation algorithm for volumetric analysis of PHE. Methods- Inpatient computed tomography scans of 400 consecutive adults with spontaneous, supratentorial intracerebral hemorrhage enrolled in the Intracerebral Hemorrhage Outcomes Project (2009-2018) were separated into training (n=360) and test (n=40) datasets. A fully automated segmentation algorithm was derived from manual segmentations in the training dataset using convolutional neural networks, and its performance was compared with that of manual and semiautomated segmentation methods in the test dataset. Results- The mean volumetric dice similarity coefficients for the fully automated segmentation algorithm were 0.838+/-0.294 and 0.843+/-0.293 with manual and semiautomated segmentation methods as reference standards, respectively. PHE volumes derived from the fully automated versus manual (r=0.959; P<0.0001), fully automated versus semiautomated (r=0.960; P<0.0001), and semiautomated versus manual (r=0.961; P<0.0001) segmentation methods had strong between-group correlations. The fully automated segmentation algorithm (mean 18.0+/-1.8 seconds/scan) quantified PHE volumes at a significantly faster rate than both of the manual (mean 316.4+/-168.8 seconds/scan; P<0.0001) and semiautomated (mean 480.5+/-295.3 seconds/scan; P<0.0001) segmentation methods. Conclusions- The fully automated segmentation algorithm accurately quantified PHE volumes from computed tomography scans of supratentorial intracerebral hemorrhage patients with high fidelity and greater efficiency compared with manual and semiautomated segmentation methods. External validation of fully automated segmentation for assessment of PHE is warranted.

Neurology
Michaelidou K, Tsiverdis I, Erimaki S, Papadimitriou D, Amoiridis G, Papadimitriou A, **Mitsias P**, and Zaganas I. Whole exome sequencing establishes diagnosis of Charcot-Marie-Tooth 4J, 1C, and X1 subtypes. *Mol Genet Genomic Med* 2020; Epub ahead of print. PMID: 32022442. Request Article

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BACKGROUND: Charcot-Marie-Tooth (CMT) hereditary polyneuropathies pose a diagnostic challenge. Our aim here is to describe CMT patients diagnosed by whole exome sequencing (WES) following years of fruitless testing. METHODS/RESULTS: Three patients with polyneuropathy suspected to be genetic in origin, but not harboring PMP22 gene deletion/duplication, were offered WES. The first patient, a 66-year-old man, had been suffering from progressive weakness and atrophies in the lower and upper extremities for 20 years. Due to ambiguous electrophysiological findings, immune therapies were administered to no avail. Twelve years after PMP22 deletion/duplication testing, WES revealed two pathogenic variants in the FIG4 gene (p.Ile41Thr and p.Phe598fs, respectively), as a cause of CMT 4J. The second patient, a 19-year-old man, had been suffering from hearing and gait impairment since at least his infancy, and recently presented with weakness and dystonia of the lower

extremities. In this patient, WES identified the p.Leu122Val LITAF gene variant in heterozygous state, suggesting the diagnosis of CMT 1C, several years after initial genetic analyses. The third patient, a 44-year-old man, presented with progressive weakness and atrophies of the lower and upper extremities since the age of 17 years old. In this patient, WES identified the hemizygous p.Arg164Gln pathogenic variant in the GJB1 gene, establishing the diagnosis of CMT X1, 8 years after testing for PMP22 deletion/duplication. CONCLUSION: Novel diagnostic techniques, such as WES, offer the possibility to decipher the cause of CMT subtypes, ending the diagnostic Odyssey of the patients and sparing them from unnecessary and potentially harmful treatments.

Neurology
Mistry EA, Dakay K, Petersen NH, Jayaraman M, McTaggart R, Furie K, Mistry A, Mehta T, Arora N, De Los Rios La Rosa F, Starosciak AK, Siegler JE, Barnhill N, Patel K, **Assad S**, **Tarboosh A**, Cruz AS, Wagner J, Fortuny E, Bennett A, James RF, Jagadeesan BD, Streib C, Kasner S, Weber S, Chitale RV, Volpi J, **Mayer SA**, Khatri P, and Yaghi S. Pre-endovascular therapy change in blood pressure is associated with outcomes in patients with stroke. *J Neurol Neurosurg Psychiatry* 2020; Epub ahead of print. PMID: 32029540. Full Text

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Neurology
Moffet EW, Subramaniam T, Hirsch LJ, Gilmore EJ, Lee JW, Rodriguez-Ruiz AA, Haider HA, Dhakar MB, Jadeja N, **Osman G**, Gaspard N, and Struck AF. Validation of the 2HELPS2B Seizure Risk Score in Acute Brain Injury Patients. *Neurocrit Care* 2020; Epub ahead of print. PMID: 32107733. Full Text

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BACKGROUND AND OBJECTIVE: Seizures are common after traumatic brain injury (TBI), aneurysmal subarachnoid hemorrhage (aSAH), subdural hematoma (SDH), and non-traumatic intraparenchymal hemorrhage (IPH)-collectively defined herein as acute brain injury (ABI). Most seizures in ABI are subclinical, meaning that they are only detectable with EEG. A method is required to identify patients at greatest risk of seizures and thereby in need of prolonged continuous EEG monitoring. 2HELPS2B is a simple point system developed to address this need. 2HELPS2B estimates seizure risk for hospitalized patients using five EEG findings and one clinical finding (pre-EEG seizure). The initial 2HELPS2B study did not specifically assess the ABI subpopulation. In this study, we aim to validate the 2HELPS2B score in ABI and determine its relative predictive accuracy compared to a broader set of clinical and electrographic factors. METHODS: We queried the Critical Care EEG Monitoring Research Consortium

database for ABI patients age >/= 18 with > 6 h of continuous EEG monitoring; data were collected between February 2013 and November 2018. The primary outcome was electrographic seizure. Clinical factors considered were age, coma, encephalopathy, ABI subtype, and acute suspected or confirmed pre-EEG clinical seizure. Electrographic factors included 18 EEG findings. Predictive accuracy was assessed using a machine-learning paradigm with area under the receiver operator characteristic (ROC) curve as the primary outcome metric. Three models (clinical factors alone, EEG factors alone, EEG and clinical factors combined) were generated using elastic-net logistic regression. Models were compared to each other and to the 2HELPS2B model. All models were evaluated by calculating the area under the curve (AUC) of a ROC analysis and then compared using permutation testing of AUC with bootstrapping to generate confidence intervals. RESULTS: A total of 1528 ABI patients were included. Total seizure incidence was 13.9%. Seizure incidence among ABI subtype varied: IPH 17.2%, SDH 19.1%, aSAH 7.6%, TBI 9.2%. Age >/= 65 ($p = 0.015$) and pre-cEEG acute clinical seizure ($p < 0.001$) positively affected seizure incidence. Clinical factors AUC = 0.65 [95% CI 0.60-0.71], EEG factors AUC = 0.82 [95% CI 0.77-0.87], and EEG and clinical factors combined AUC = 0.84 [95% CI 0.80-0.88]. 2HELPS2B AUC = 0.81 [95% CI 0.76-0.85]. The 2HELPS2B AUC did not differ from EEG factors ($p = 0.51$), or EEG and clinical factors combined ($p = 0.23$), but was superior to clinical factors alone ($p < 0.001$). CONCLUSIONS: Accurate seizure risk forecasting in ABI requires the assessment of EEG markers of pathologic electro-cerebral activity (e.g., sporadic epileptiform discharges and lateralized periodic discharges). The 2HELPS2B score is a reliable and simple method to quantify these EEG findings and their associated risk of seizure.

Neurology

Singh S, Singh PK, **Suhail H**, Arumugaswami V, Pellett PE, **Giri S**, and Kumar A. AMP-Activated Protein Kinase Restricts Zika Virus Replication in Endothelial Cells by Potentiating Innate Antiviral Responses and Inhibiting Glycolysis. *J Immunol* 2020; Epub ahead of print. PMID: 32086387. Full Text

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Viruses are known to perturb host cellular metabolism to enable their replication and spread. However, little is known about the interactions between Zika virus (ZIKV) infection and host metabolism. Using primary human retinal vascular endothelial cells and an established human endothelial cell line, we investigated the role of AMP-activated protein kinase (AMPK), a master regulator of energy metabolism, in response to ZIKV challenge. ZIKV infection caused a time-dependent reduction in the active phosphorylated state of AMPK and of its downstream target acetyl-CoA carboxylase. Pharmacological activation of AMPK using 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR), metformin, and a specific AMPKalpha activator (GSK621) attenuated ZIKV replication. This activity was reversed by an AMPK inhibitor (compound C). Lentivirus-mediated knockdown of AMPK and the use of AMPKalpha(-/-) mouse embryonic fibroblasts provided further evidence that AMPK has an antiviral effect on ZIKV replication. Consistent with its antiviral effect, AMPK activation potentiated the expression of genes with antiviral properties (e.g., IFNs, OAS2, ISG15, and MX1) and inhibited inflammatory mediators (e.g., TNF-alpha and CCL5). Bioenergetic analysis showed that ZIKV infection evokes a glycolytic response, as evidenced by elevated extracellular acidification rate and increased expression of key glycolytic genes (GLUT1, HK2, TPI, and MCT4); activation of AMPK by AICAR treatment reduced this response. Consistent with this, 2-deoxyglucose, an inhibitor of glycolysis, augmented AMPK activity and attenuated ZIKV replication. Thus, our study demonstrates that the anti-ZIKV effect of AMPK signaling in endothelial cells is mediated by reduction of viral-induced glycolysis and enhanced innate antiviral responses.

Neurology

Skiba V, **Novikova M**, **Suneja A**, **McLellan B**, and **Schultz L**. Use of Positive Airway Pressure in Mild Cognitive Impairment to Delay Progression to Dementia. *J Clin Sleep Med* 2020; Epub ahead of print. PMID: 32039755. Full Text

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STUDY OBJECTIVES: To assess the relationship between continuous positive airway pressure (CPAP) therapy and cognitive function in patients with mild cognitive impairment (MCI) and obstructive sleep apnea (OSA). METHODS: This was a retrospective chart review of patients with MCI and OSA. CPAP compliance was defined as average use of CPAP for at least 4 hours a night. Kaplan-Meier estimates, logrank tests and Cox proportional hazards regression were done to compare the compliance groups in terms of progression to dementia, defined as Clinical Dementia Rating (CDR) of 1 or greater. Linear mixed models were used to assess the relationships between CPAP compliance

and neurological cognitive function outcomes over time. RESULTS: Ninety-six patients were included with mean age at MCI diagnosis of 70.4 years, mean Apnea Hypopnea Index of 25.9 and mean duration of neurology follow-up of 2.8 years. Forty-two were CPAP compliant, 30 were non-compliant and 24 had no CPAP use. No overall difference among the groups was detected for progression to dementia (p = 0.928, logrank test). Patients with amnestic MCI had better CPAP use (p = 0.016) and shorter progression time to dementia (p = 0.042), but this difference was not significant after adjusting for age, education and race (p = 0.32). CONCLUSIONS: CPAP use in MCI patients with OSA was not associated with delay in progression to dementia or cognitive decline.

Neurology
Wang H, **Jiang Q**, Shen Y, **Zhang L**, Haacke EM, Ge Y, Qi S, and Hu J. The capability of detecting small vessels beyond the conventional MRI sensitivity using iron-based contrast agent enhanced susceptibility weighted imaging. *NMR Biomed* 2020; Epub ahead of print. PMID: 32045957. Full Text

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Imaging brain microvasculature is important in cerebrovascular diseases. However, there is still a lack of non-invasive, non-radiation, and whole-body imaging techniques to investigate them. The aim of this study is to develop an ultra-small superparamagnetic iron oxide (USPIO) enhanced susceptibility weighted imaging (SWI) method for imaging micro-vasculature in both animal (~10 mum in rat) and human brain. We hypothesized that the USPIO-SWI technique could improve the detection sensitivity of the diameter of small subpixel vessels 10-fold compared with conventional MRI methods. Computer simulations were first performed with a double-cylinder digital model to investigate the theoretical basis for this hypothesis. The theoretical results were verified using in vitro phantom studies and in vivo rat MRI studies (n = 6) with corresponding ex vivo histological examinations. Additionally, in vivo human studies (n = 3) were carried out to demonstrate the translational power of the USPIO-SWI method. By directly comparing the small vessel diameters of an in vivo rat using USPIO-SWI with the small vessel diameters of the corresponding histological slide using laser scanning confocal microscopy, 13.3-fold and 19.9-fold increases in SWI apparent diameter were obtained with 5.6 mg Fe/kg and 16.8 mg Fe/kg ferumoxytol, respectively. The USPIO-SWI method exhibited its excellent ability to detect small vessels down to about 10 mum diameter in rat brain. The in vivo human study unveiled hidden arterioles and venules and demonstrated its potential in clinical practice. Theoretical modeling simulations and in vitro phantom studies also confirmed a more than 10-fold increase in the USPIO-SWI apparent diameter compared with the actual small vessel diameter size. It is feasible to use SWI blooming effects induced by USPIO to detect small vessels (down to 10 mum in diameter for rat brain), well beyond the spatial resolution limit of conventional MRI methods. The USPIO-SWI method demonstrates higher potential in cerebrovascular disease investigations.

Neurology
Ye LF, Reznik E, Korn JM, Lin F, Yang G, Malesky K, Gao H, Loo A, Pagliarini R, **Mikkelsen T**, Lo DC, **DeCarvalho AC**, and Stockwell BR. Patient-derived glioblastoma cultures as a tool for small-molecule drug discovery. *Oncotarget* 2020; 11(4):443-451. PMID: Not assigned. Request Article

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There is a compelling need for new therapeutic strategies for glioblastoma multiforme (GBM). Preclinical target and therapeutic discovery for GBMs is primarily conducted using cell lines grown in serum-containing media, such as U-87 MG, which do not reflect the gene expression profiles of tumors found in GBM patients. To address this lack of representative models, we sought to develop a panel of patient-derived GBM models and characterize their genomic features, using RNA sequencing (RNA-seq) and growth characteristics, both when grown as neurospheres in culture, and grown orthotopically as xenografts in mice. When we compared these with commonly used GBM cell lines in the Cancer Cell Line Encyclopedia (CCLE), we found these patient-derived models to have greater diversity in gene expression and to better correspond to GBMs directly sequenced from patient tumor samples. We also evaluated the potential of these models for targeted therapy, by using the genomic characterization to identify small molecules that inhibit the growth of distinct subsets of GBMs, paving the way for precision medicines for GBM.

Neurosurgery
Caras A, Mugge L, Miller WK, **Mansour TR**, Schroeder J, and Medhkour A. Usefulness and Impact of Intraoperative Imaging for Glioma Resection on Patient Outcome and Extent of Resection: A Systematic Review and Meta-Analysis. *World Neurosurg* 2020; 134:98-110. PMID: 31639502. Full Text

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BACKGROUND: Diffusion tensor imaging (DTI), functional magnetic resonance imaging (fMRI), and intraoperative magnetic resonance imaging (iMRI) permit greater visualization and more accurate presurgical planning. Meta-analysis of these techniques for maximizing resection, postoperative functionality, and survival may further validate purported strengths of these techniques compared with standard neuronavigation. METHODS: A systematic search of the PubMed database was conducted in line with the PRISMA guidelines for meta-analysis with the following keywords: "Diffusion tensor imaging" OR "intraoperative MRI" OR "functional MRI" AND "glioma surgery resection outcome." Articles found to meet inclusion criteria were segregated and analyzed and resulting data were compared with standard neuronavigation (control cohort). RESULTS: A total of 435 articles were identified, with 29 distinct studies meeting inclusion criteria, including DTI (n = 3), fMRI (n = 5), and iMRI (n = 21). Nine studies directly compared results with standard navigation. Mean gross total resection (GTR) rates were not different among cases using DTI, fMRI, iMRI, or traditional neuronavigation (P = 0.136). On controlling for covariates, more patients received GTR in the advanced imaging cohort, although statistically insignificant (46.5% [95% confidence interval, 38.0%-55.0%] vs. 30.4% [95% confidence interval, 11.6%-49.1%]; P = 0.127; partial eta(2) = 0.217). Patients undergoing advanced imaging showed attenuated incidence of postsurgical permanent neurologic deficits, although also statistically insignificant (11.3% vs. 13.8%; P = 0.838). CONCLUSIONS: Current data are overall insufficient to support the notion that advanced imaging techniques are superior, either as a combined cohort or individually, in achieving GTR, improved symptom resolution, or survival compared with traditional neuronavigation.

Neurosurgery
Hocker S, Shah S, Vespa P, Provencio JJ, Calvillo E, Olson DM, Venkatasubba Rao CP, Hemphill JC, 3rd, Helbok R, Human T, Kamel H, Madden LK, Nyquist P, Bentho O, O'Phelan K, Lewin JJ, 3rd, Alexander S, Ziai W, Chou SH, Rincon F, McNett M, Ko N, Zink B, Rhoney D, Diringer MN, Stevens R, Robertson CS, Sampaio G, Shutter LA, Ling G, **Rehman M**, Mahmoud SH, Yeager S, Livesay S, and Suarez JI. The Future of Neurocritical Care Research: Proceedings and Recommendations from the Fifth Neurocritical Care Research Network Conference. *Neurocrit Care* 2020; 32(1):311-316. PMID: 31264070. Full Text

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Medical University of Innsbruck, Innsbruck, Austria.
Barnes Jewish Hospital, St. Louis, MO, USA.
Weill Cornell Medical College, New York, NY, USA.
UC Davis, Davis, CA, USA.
University of Minnesota Health, Minneapolis, MN, USA.
University of Miami, Miami, FL, USA.
University of Pittsburgh, Pittsburgh, PA, USA.
Thomas Jefferson University, Philadelphia, PA, USA.
The Metro Health System, Cleveland, OH, USA.
University of North Carolina Eshelman School of Pharmacy, Chapel Hill, NC, USA.
Washington University in Saint Louis, St. Louis, MO, USA.
Federal University of Sao Paulo, Sao Paulo, Brazil.
Uniformed Services University of the Health Sciences, Bethesda, MD, USA.
Henry Ford Health System, Detroit, MI, USA.
University of Alberta, Edmonton, Alberta, Canada.
The Ohio State University Wexner Medical Center, Columbus, OH, USA.
Rush University Medical Center, Chicago, IL, USA.

The Fifth Neurocritical Care Research Network (NCRN) Conference held in Boca Raton, Florida, in September of 2018 was devoted to challenging the current status quo and examining the role of the Neurocritical Care Society (NCS) in driving the science and research of neurocritical care. The aim of this in-person meeting was to set the agenda for the NCS's Neurocritical Care Research Central, which is the overall research arm of the society. Prior to

the meeting, all 103 participants received educational content (book and seminar) on the 'Blue Ocean Strategy((R)),' a concept from the business world which aims to identify undiscovered and uncontested market space, and to brainstorm innovative ideas and methods with which to address current challenges in neurocritical care research. Three five-member working groups met at least four times by teleconference prior to the in-person meeting to prepare answers to a set of questions using the Blue Ocean Strategy concept as a platform. At the Fifth NCRN Conference, these groups presented to a five-member jury and all attendees for open discussion. The jury then developed a set of recommendations for NCS to consider in order to move neurocritical care research forward. We have summarized the topics discussed at the conference and put forward recommendations for the future direction of the NCRN and neurocritical care research in general.

Neurosurgery
Ye LF, Reznik E, Korn JM, Lin F, Yang G, Malesky K, Gao H, Loo A, Pagliarini R, **Mikkelsen T**, Lo DC, **DeCarvalho AC**, and Stockwell BR. Patient-derived glioblastoma cultures as a tool for small-molecule drug discovery. *Oncotarget* 2020; 11(4):443-451. PMID: Not assigned. Request Article

A.C. DeCarvalho, Department of Neurosurgery, Henry Ford Hospital, Detroit, MI, United States

There is a compelling need for new therapeutic strategies for glioblastoma multiforme (GBM). Preclinical target and therapeutic discovery for GBMs is primarily conducted using cell lines grown in serum-containing media, such as U-87 MG, which do not reflect the gene expression profiles of tumors found in GBM patients. To address this lack of representative models, we sought to develop a panel of patient-derived GBM models and characterize their genomic features, using RNA sequencing (RNA-seq) and growth characteristics, both when grown as neurospheres in culture, and grown orthotopically as xenografts in mice. When we compared these with commonly used GBM cell lines in the Cancer Cell Line Encyclopedia (CCLE), we found these patient-derived models to have greater diversity in gene expression and to better correspond to GBMs directly sequenced from patient tumor samples. We also evaluated the potential of these models for targeted therapy, by using the genomic characterization to identify small molecules that inhibit the growth of distinct subsets of GBMs, paving the way for precision medicines for GBM.

Neurosurgery
Zervos TM, Mg TM, **Zakaria H**, **Hlaing K**, Aung TH, Myaing W, and **Rock J**. Surgical Treatment of Intracranial Anterior Ethmoidal Aneurysm: Case Report, Literature Review, and Surgical Video. *World Neurosurg* 2019; 136:1-5. PMID: 31901499. Full Text

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BACKGROUND: Anterior ethmoid aneurysms are rare with 5 cases of intracranial rupture and 3 cases of life-threatening epistaxis described in recent literature. We present a case of an intracranial ruptured anterior ethmoid aneurysm treated surgically with a favorable outcome. CASE DESCRIPTION: A 64-year-old male presenting with a headache was found to have a right frontal intracranial hemorrhage with an associated 1.5 cm length x 1.8 cm maximal width anterior ethmoidal artery aneurysm. No definitive etiology of the aneurysm was identified. The aneurysm was treated using a bifrontal craniotomy with interhemispheric microdissection, clip ligation, and resection of the aneurysm dome for pathologic analysis, which ruled out a mycotic etiology. He recovered uneventfully and returned to work with no identifiable neurologic deficit. CONCLUSIONS: Consistent with prior reports, an intracranial, anterior ethmoidal artery aneurysm can occur in isolation without an associated vascular malformation. On the basis of a literature review and this case, surgical ligation is considered effective and possibly superior over endovascular treatment due to the risk of injury to the orbital vascular supply with transarterial treatment.

Ophthalmology and Eye Care Services
Brill DA, Lin X, Garcia AL, **Hou AC**, and **Le KH**. Case of torpedo maculopathy with two distinct zones of the retinal pigment epithelium. *Retin Cases Brief Rep* 2020; Epub ahead of print. PMID: 32039943. Full Text

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BACKGROUND/PURPOSE: To report a case of torpedo maculopathy with two distinct zones of the retinal pigment epithelium visualized on optical coherence tomography. METHODS: Observational case report. RESULTS: A 6-year-old female presented for a routine examination. Visual acuity was 20/20 bilaterally. Dilated fundus examination was normal in the right eye. Dilated fundus examination of the left eye showed a wedge-shaped area of hypopigmentation in the temporal macula. Optical coherence tomography macula of the left eye showed outer retinal cavitation with

segmentation of the foveal retinal pigment epithelium into a superficial fluffy zone and a deeper hyperreflective zone. CONCLUSION: This case helps contribute to the growing body of the torpedo maculopathy literature that may reveal different stages of the same disease evolving over time.

Ophthalmology and Eye Care Services

Salman M, Andrews C, Heister M, **Darnley-Fisch D**, and Newman-Casey PA. Psychosocial Predictors of Glaucoma Medication Adherence among the Support, Educate, Empower (SEE) Personalized Glaucoma Coaching Pilot Study Participants. *Am J Ophthalmol* 2020; Epub ahead of print. PMID: 32087145. Full Text

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PURPOSE: To evaluate the association between baseline psychosocial milieu and subsequent glaucoma medication adherence among participants in the Support, Educate, Empower (SEE) personalized glaucoma coaching program pilot study. DESIGN: Prospective cohort study. PARTICIPANTS: University of Michigan glaucoma patients >/= age 40, taking >/= 1 glaucoma medication, who self-reported poor adherence. METHODS: Participants completed a baseline survey that assessed: 1) Demographics; 2) Social network; 3) Perceived Stress; 4) Consideration of future consequences; 5) Glaucoma-related distress and 6) Social support. Medication adherence was then monitored electronically (AdhereTech, New York, NY) for 3 months and the percentage of prescribed doses taken was calculated. The relationship between baseline factors and medication adherence was assessed using univariate and multivariate analysis. MAIN OUTCOME MEASURES: Median percent adherence over three months. RESULTS: Of the 95 study participants, 63% had graduated from college, 55% were white, 35% were African-American, and 97% had insurance. Median adherence over three months was 74% + 21% (+ standard deviation, SD). Higher income and more education were significantly associated with better adherence ($p<0.0001$, $p = 0.03$). Glaucoma related distress (mean score 5.6, SD = 3.0) was inversely associated with medication adherence on univariate ($p<0.0001$) and multivariate analysis ($p=0.0002$). Every one-point increase in glaucoma related distress score predicted a 2.4 percentage-point decrease in medication adherence. CONCLUSIONS: Lower income, lower educational attainment and a higher level of glaucoma-related distress all predicted lower adherence to glaucoma medications. Additional glaucoma self-management support resources should be directed towards patients with such risk factors for poor adherence.

Orthopedics/Bone and Joint

Frisch NB, Courtney PM, **Darrith B**, Copeland LA, and Gerlinger TL. Veterans Undergoing Total Hip and Knee Arthroplasty: 30-day Outcomes as Compared to the General Population. *J Am Acad Orthop Surg* 2020; Epub ahead of print. PMID: 32004175. Full Text

From the Ascension Providence Rochester Hospital (Dr. Frisch), Rochester, MI, the Rothman Institute and Thomas Jefferson University Hospital, (Dr. Courtney), Philadelphia, PA, the Henry Ford Hospital (Darrith), Detroit, MI, the VA Central Western Massachusetts Health System (Dr. Copeland), Leeds, MA, and the Department of Orthopaedic Surgery, Rush University Medical Center (Dr. Gerlinger), Chicago, IL.

INTRODUCTION: The Veterans Affairs (VA) health system is vital to providing joint replacement care to our retired service members but has come under recent scrutiny. The purpose of this study was to compare the short-term outcomes after total hip arthroplasty (THA) and total knee arthroplasty (TKA) between the VA cohort and the general cohort. METHODS: We retrospectively reviewed 10.460 patients with primary THA and TKA from the Veterans Affairs Corporate Data Warehouse. As a control group, we queried the American College of Surgeons-National Surgical Quality Improvement Program database and identified 58,820 patients with primary THA and TKA over the same time period. We compared length of stay, mortality rates, 30-day complication rates, and 30-day readmissions. We performed a multivariate logistic regression analysis to identify the independent effect of the VA system on adverse outcomes. RESULTS: Veterans are more likely to be men (93% versus 41%, $P < 0.001$) and have increased rates of medical comorbidities (all $P < 0.001$). The rate of short-term complications (all $P < 0.001$) were all higher in the VA cohort. When controlling for demographics and medical comorbidities, VA patients were more likely to have a readmission ($P < 0.001$), prolonged length of stay > 4 days ($P < 0.001$), and experience a complication within 30 days ($P < 0.001$). DISCUSSION: Despite controlling for higher rates of medical comorbidities, VA patients undergoing primary THA and TKA had poorer short-term outcomes than the civilian cohort. Additional research is needed to ensure our veteran cohort is appropriately optimized and address the discrepancy with the outcomes of the civilian.

Orthopedics/Bone and Joint

Khalil LS, **Darrith B**, **Franovic S**, **Davis JJ**, **Weir RM**, and **Banka TR**. Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health Short Forms Demonstrate Responsiveness in Patients Undergoing Knee Arthroplasty. *J Arthroplasty* 2020; Epub ahead of print. PMID: 32037211. Full Text

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BACKGROUND: The Patient-Reported Outcomes Measurement Information System (PROMIS) is an alternative to legacy outcome metrics. We investigated the relationship between Knee Injury and Osteoarthritis Outcomes Score for Joint Replacement (KOOS-JR) and PROMIS Global Health forms of Physical Health (PH) and Mental Health (MH) in knee arthroplasty patients. METHODS: This is a retrospective cohort study of knee arthroplasty patients from December 2017 through April 2019 who had surveys collected preoperatively and postoperatively. We excluded patients undergoing revision surgery. Outcome scores were analyzed for responsiveness, effect size index (ESI), minimal clinically important difference (MCID), and correlation with each other through 12 months postoperatively. RESULTS: A total of 875 patients were included. Floor and ceiling effects were 0% for PROMIS-PH. Postoperative PROMIS-PH and KOOS-JR scores significantly correlated with one another and increased from baseline at each postoperative time point ($P < .001$ for all). PROMIS-MH did not change between time points ($P > .05$). PROMIS-PH showed moderate responsiveness at 1 and 3 months (ESI >0.2) and excellent responsiveness at 6 and 12 months (ESI >0.8), whereas KOOS-JR was responsive at all time points (ESI >0.8). The MCID of PROMIS-PH correlated significantly with KOOS-JR, and a preoperative PROMIS-PH score of less than 32.5 predicted achieving MCID with 97% specificity. CONCLUSION: PROMIS global health forms are a valid metric which capture patient outcomes and correlate with KOOS-JR scores after knee arthroplasty. Although KOOS-JR may be more responsive in the early postoperative time period, both measures show excellent responsiveness at 6 and 12 months after knee arthroplasty.

Orthopedics/Bone and Joint

Rios-Arce ND, Schepper JD, Dagenais A, Schaefer L, **Daly-Seiler CS**, **Gardinier JD**, Britton RA, McCabe LR, and Parameswaran N. Post-antibiotic gut dysbiosis-induced trabecular bone loss is dependent on lymphocytes. *Bone* 2020; 134:115269. PMID: 32061677. Full Text

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Recent studies in mouse models have shown that gut microbiota significantly influences bone health. We demonstrated that 2-week oral treatment with broad spectrum antibiotics followed by 4 weeks of recovery of the gut microbiota results in dysbiosis (microbiota imbalance)-induced bone loss in mice. Because gut microbiota is critical for the development of the immune system and since both microbiota and the immune system can regulate bone health, in this study, we tested the role of the immune system in mediating post-antibiotic dysbiosis-induced bone loss. For this, we treated wild-type (WT) and lymphocyte deficient Rag2 knockout (KO) mice with ampicillin/neomycin cocktail in water for 2 weeks followed by 4 weeks of water without antibiotics. This led to a significant bone loss (31% decrease from control) in WT mice. Interestingly, no bone loss was observed in the KO mice suggesting that lymphocytes are required for dysbiosis-induced bone loss. Bray-Curtis diversity metrics showed similar microbiota changes in both the WT and KO post-antibiotic treated groups. However, several operational taxonomic units (OTUs) classified as Lactobacillales were significantly higher in the repopulated KO when compared to the WT mice, suggesting that these bacteria might play a protective role in preventing bone loss in the KO mice after antibiotic treatment. The effect of dysbiosis on bone was therefore examined in the WT mice in the presence or absence of oral Lactobacillus reuteri treatment for 4 weeks (post-ABX treatment). As hypothesized, mice treated with L. reuteri did not display bone loss, suggesting a bone protective role for this group of bacteria. Taken together, our studies elucidate an important role for lymphocytes in regulating post-antibiotic dysbiosis-induced bone loss.

Otolaryngology

Piker EG, Jacobson GP, Romero D, Wang Y, and **Smith K**. The Clinical Significance of the Failure to Perceive Vertigo in the Postcaloric Period Despite a Robust Caloric Response. *Am J Audiol* 2020; Epub ahead of print. PMID: 32073288. Full Text

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Purpose The purpose of this project was to explore the association between the perception of motion during caloric testing and two tasks associated with central vestibular processing: postural stability and visuospatial memory. Method This was a prospective study of 25 patients who were found to have nonvestibular etiologies of their symptoms and normal vestibular function test results and who underwent caloric testing with a mean maximum slow phase eye velocity for each irrigation of 15 degrees or greater. Following each caloric irrigation, patients were asked whether they had any sensation of movement. Patients were grouped based on the presence or absence of motion during the caloric exam (motion perception vs. absent perception). Postural stability was assessed using computerized dynamic posturography, and visuospatial memory was assessed using a memory match card game application. Results There were no significant differences between groups on any measures of peripheral vestibular function. However, the Absent Perception Group showed greater postural instability during Condition 5 of posturography and performed significantly worse on a task of visuospatial working memory. Both age and absence of motion perception predicted abnormal performance on measures of postural stability and visuospatial working memory. Conclusions There appears to be clinical implications to a lack of motion perception during the caloric exam in patients with an otherwise normal peripheral vestibular system. Based on the current findings, we are unable to determine whether differences in postural stability and visuospatial memory were due to age or a central vestibular processing deficit.

Pathology
Ahsan BU, **Alhamar M**, **Hogan KM**, **Schultz D**, **Zuchelli T**, and **Zhang Z**. Endometrial clear cell carcinoma with metastasis to the common hepatic duct: A rare etiology of obstructive jaundice, diagnosed by biliary cytology brushing specimen. *Cytopathology* 2020; Epub ahead of print. PMID: 32049406. Full Text

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Clear cell carcinoma is an aggressive subtype of uterine carcinoma. Metastases can be local and/or distant but metastasis to the biliary tree resulting in obstructive jaundice is extremely rare. This is the first report of endometrial carcinoma of clear cell type with metastasis to the common hepatic duct, causing malignant biliary stricture and obstructive jaundice in a young woman, diagnosed on a biliary cytology brushing specimen.

Pathology
Bradford CR, Ferlito A, **Devaney KO**, Mäkitie AA, and Rinaldo A. Prognostic factors in laryngeal squamous cell carcinoma. *Laryngoscope Investig Otolaryngol* 2020; Epub ahead of print. PMID: Not assigned. Full Text

C.R. Bradford, Department of Otolaryngology-Head and Neck Surgery, University of Michigan Medical School, Ann Arbor, MI, United States

Background: The current treatment results of laryngeal squamous cell carcinoma still remain modest. Various prognostic factors have been investigated and need to be included in the management decision making. Methods: We reviewed the pertinent literature regarding host, tumor, and treatment factors as prognostic indicators that influence outcome in patients diagnosed with laryngeal squamous cell carcinoma. Results: Host, tumor, and treatment factors all have an important impact upon an individual patient's prognosis with laryngeal squamous cell carcinoma, whereas staging systems only take into account tumor factors. There is much work yet to be done to establish reliable, independent biomarkers that predict survival and response to treatment. Conclusions: Optimal outcomes for an individual patient can be achieved when taking into account tumor, host, and treatment factors.

Pathology
Gadde R, and **Samuel L**. Answer to March 2020 Photo Quiz. *J Clin Microbiol* 2020; 58(3). PMID: 32094123. Request Article

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Pathology
Gadde R, and **Samuel L**. Photo Quiz: Subcutaneous Infection in an Immunocompetent Patient Handling a Wooden Wheelbarrow. *J Clin Microbiol* 2020; 58(3). PMID: 32094122. Request Article

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Pathology
Mahajan M, **Venkatesulu BP**, **Sallam O**, **Taneja K**, **Scott M**, and **Brar I**. Unmasking lymphoma immune reconstitution inflammatory syndrome in a patient with pyrexia of unknown origin: a case report. *J Egypt Natl Canc Inst* 2020; 32(1). PMID: Not assigned. Request Article

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Background: Immune reconstitution inflammatory syndrome (IRIS) is a constellation of inflammatory disorders that are unmasked after the initiation of anti-retroviral therapy (ART) in Human immunodeficiency virus (HIV) infected patients. Unmasking lymphoma IRIS is a relatively rare manifestation after initiation of anti-retroviral therapy. Case presentation: We report a 44-year-old male with HIV on 4 months of ART presenting with pyrexia of unknown origin with a diagnosis of unmasking Hodgkin's lymphoma IRIS stage IV with B symptoms. This case portrays the importance of recognizing the possibility of Hodgkin's lymphoma as a possible manifestation of IRIS within the first 6 months of initiation of ART. Conclusion: Patients presenting with pyrexia of unknown origin and lymphadenopathy within the first 6 months of initiation of ART, lymphoma diagnosis should be on the high threshold of suspicion as portrayed by our case.

Pathology
Zhang SX, Carroll KC, Lewis S, Totten M, Mead P, **Samuel L**, Steed LL, Nolte FS, Thornberg A, Reid JL, Whitfield NN, and Babady NE. Multi-center Evaluation of a PCR-based Digital Microfluidics and Electrochemical Detection System for the Rapid Identification of 15 Fungal Pathogens Directly from Positive Blood Cultures. *J Clin Microbiol* 2020; Epub ahead of print. PMID: 32075904. Request Article

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Background: Routine identification of fungal pathogens from positive blood cultures by culture-based methods can be time consuming, delaying treatment with appropriate antifungal agents. The GenMark Dx ePlex(R) Investigational Use Only Blood Culture Identification Fungal Pathogen Panel (BCID-FP) rapidly detects 15 fungal targets simultaneously in blood culture samples positive for fungi by Gram stain. We aimed to determine the performance of the BCID-FP in a multi-center clinical study.Materials and Methods: Blood culture samples collected at 10 US sites and tested with BCID-FP at 4 sites were compared to the standard-of-care microbiological and biochemical techniques, PNA-FISH and MALDI-TOF MS. Discrepant results were analyzed by bi-directional PCR/sequencing of residual blood culture samples.Results: A total of 866 clinical samples, 120 retrospectively- and 21 prospectively-collected, along with 725 contrived samples were evaluated. Sensitivity and specificity of the Candida species (C. albicans, C. auris, C. dubliniensis, C. famata, C. glabrata, C. guilliermondii, C, kefyr, C. krusei, C. lusitaniae, C. parapsilosis, C. tropicalis), ranged from 97.1-100% and 99.8-100%, respectively. For the other organism targets, sensitivity and specificity were as follows: 100% each for Cryptococcus neoformans and C. gattii, 98.6% and 100% for Fusarium spp. and 96.2% and 99.9% for Rhodotorula spp. respectively. In 4 of the 141 clinical samples, the BCID-FP Panel correctly identified an additional Candida species, undetected by standard-of-care methods.Conclusion: The BCID-FP Panel offers a faster turnaround time for identification of fungal pathogens in positive blood cultures that may allow for earlier antifungal interventions and, includes C. auris, a highly multi-drug resistant fungus.

Pharmacy

Jorgensen SCJ, Trinh TD, Zasowski EJ, Lagnf AM, Bhatia S, Melvin SM, Simon SP, Rosenberg JR, Steed ME, Estrada SJ, Morrisette T, **Davis SL**, and Rybak MJ. Evaluation of the INCREMENT-CPE, Pitt Bacteremia and qPitt Scores in Patients with Carbapenem-Resistant Enterobacteriaceae Infections Treated with Ceftazidime-Avibactam. *Infect Dis Ther* 2020; Epub ahead of print. PMID: 32088843. Request Article

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BACKGROUND: The aim of this study was to evaluate the predictive performance of the INCREMENT-CPE (ICS), Pitt bacteremia score (PBS) and qPitt for mortality among patients treated with ceftazidime-avibactam for carbapenem-resistant Enterobacteriaceae (CRE) infections. METHODS: Retrospective, multicenter, cohort study of patients with CRE infections treated with ceftazidime-avibactam between 2015 and 2019. The primary outcome was 30-day all-cause mortality. Predictive performance was determined by assessing discrimination, calibration and precision. RESULTS: In total, 109 patients were included. Thirty-day mortality occurred in 18 (16.5%) patients. There were no significant differences in discrimination of the three scores [area under the curve (AUC) ICS 0.7039, 95% CI 0.5848-0.8230, PBS 0.6893, 95% CI 0.5709-0.8076, and qPitt 0.6847, 95% CI 0.5671-0.8023; P > 0.05 all pairwise comparisons]. All scores showed adequate calibration and precision. When dichotomized at the optimal cut-points of 11, 3, and 2 for the ICS, PBS, and qPitt, respectively, all scores had NPV > 90% at the expense of low PPV. Patients in the high-risk groups had a relative risk for mortality of 3.184 (95% CI 1.35-8.930), 3.068 (95% CI 1.094-8.606), and 2.850 (95% CI 1.016-7.994) for the dichotomized ICS, PBS, and qPitt, scores respectively. Treatment-related variables (early active antibiotic therapy, combination antibiotics and renal ceftazidime-avibactam dose adjustment) were not associated with mortality after controlling for the risk scores. CONCLUSIONS: In patients treated with ceftazidime-avibactam for CRE infections, mortality risk scores demonstrated variable performance. Modifications to scoring systems to more accurately predict outcomes in the era of novel antibiotics are warranted.

Pharmacy

Thomson JM, Huynh HH, Drone HM, Jantzer JL, Tsai AK, and Jancik JT. Experience in an Urban Level 1 Trauma Center With Tranexamic Acid in Pediatric Trauma: A Retrospective Chart Review. *J Intensive Care Med* 2020; Epub ahead of print. PMID: 32090705. Full Text

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BACKGROUND: Evidence for tranexamic acid (TXA) in the pharmacologic management of trauma is largely derived from data in adults. Guidance on the use of TXA in pediatric patients comes from studies evaluating its use in cardiac and orthopedic surgery. There is minimal data describing TXA safety and efficacy in pediatric trauma. The purpose of this study is to describe the use of TXA in the management of pediatric trauma and to evaluate its efficacy and safety end points. METHODS: This retrospective, observational analysis of pediatric trauma admissions at Hennepin County Medical Center from August 2011 to March 2019 compares patients who did and did not receive TXA. The primary end point is survival to hospital discharge. Secondary end points include surgical intervention, transfusion requirements, length of stay, thrombosis, and TXA dose administered. RESULTS: There were 48 patients aged </=16 years identified for inclusion using a massive transfusion protocol order. Twenty-nine (60%) patients received TXA. Baseline characteristics and results are presented as median (interquartile range) unless otherwise specified, with statistical significance defined as P < .05. Patients receiving TXA were more likely to be older, but there was no difference in injury type or Injury Severity Score at baseline. There was no difference in survival to discharge or thrombosis. Patients who did not receive TXA had numerically more frequent surgical intervention and longer length

of stay, but these did not reach significance. CONCLUSIONS: TXA was utilized in 60% of pediatric trauma admissions at a single level 1 trauma center, more commonly in older patients. Although limited by observational design, we found patients receiving TXA had no difference in mortality or thrombosis.

Public Health Sciences
Baird DD, Patchel SA, Saldana TM, Umbach DM, **Cooper T**, **Wegienka G**, and Harmon QE. Uterine fibroid incidence and growth in an ultrasound-based, prospective study of young African-Americans. *Am J Obstet Gynecol* 2020; Epub ahead of print. PMID: 32105679. Full Text

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BACKGROUND: Uterine fibroids are common. Symptoms are debilitating for many, leading to high medical and societal costs. Indirect data suggest that compared to white women, African-Americans develop fibroids at least ten years earlier on average, and their higher health burden has been well documented. OBJECTIVE: To directly measure fibroid incidence and growth in a large, community-based cohort of young African-American women. STUDY DESIGN: This observational, community-based, prospective study enrolled 1693 African American women, ages 23-35 with no prior diagnosis of fibroids. Standardized transvaginal ultrasound examinations at enrollment and after approximately 18-months were conducted to identify and measure fibroids >/=0.5 cm in diameter. Fibroid growth (change in natural log volume per 18 months) was analyzed with mixed model regression (n = 344 fibroids from 251 women whose baseline ultrasound revealed already existing fibroids). RESULTS: Among the 1123 fibroid-free women with follow-up data (88% were followed), incidence was 9.4% (95% confidence interval, CI=7.7,11.2) and increased with age (ptrend=<0.0001), from 6% (CI=3,9) for 23-25 year-olds to 13% (CI=9,17) for 32-35 year-olds. The chance of any new fibroid development was over twice as high for women with existing fibroids compared to women who were fibroid-free at baseline (age-adjusted relative risk = 2.3, (CI=1.7,3.0). The uterine position of most incident fibroids (60%) was intramural corpus. Average fibroid growth was 89% per 18 months (CI=74%,104%), but varied by baseline fibroid size (p<0.0001). Fibroids >/=2 cm in diameter had average growth rates well under 100%. In contrast, small fibroids (<1 cm diameter) had an average growth rate of nearly 200% (188%, CI=145%,238%). However, these small fibroids also had a high estimated rate of disappearance (23%). CONCLUSIONS: This is the first study to directly measure age-specific fibroid incidence with a standardized ultrasound protocol and to measure fibroid growth in a large community-based sample. Findings indicate that very small fibroids are very dynamic in their growth, with rapid growth, but a high chance of loss. Larger fibroids grow more slowly. For example, a 2-cm fibroid is likely to take 4-5 years to double its diameter. Detailed data on fibroid incidence confirm an early onset in African American women.

Public Health Sciences
Chen Y, **Susick L**, Davis M, **Bensenhaver J**, **Nathanson SD**, **Burns J**, and Newman LA. Evaluation of Triple-Negative Breast Cancer Early Detection via Mammography Screening and Outcomes in African American and White American Patients. *JAMA Surg* 2020; Epub ahead of print. PMID: 32074266. Full Text

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Public Health Sciences
Jansen EC, **She R**, Rukstalis MM, and **Alexander GL**. Sleep Duration and Quality in Relation to Fruit and Vegetable Intake of US Young Adults: a Secondary Analysis. *Int J Behav Med* 2020; Epub ahead of print. PMID: 32016881. Request Article

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BACKGROUND: Sleep is gaining recognition as a determinant of diet, yet this relationship remains understudied among young adults. We sought to examine how sleep duration and quality were related to fruit and vegetable (FV) intake within a diverse sample of young adults. METHODS: Participants (n = 1444) ages 21-30 (69% women, 15% African American, 35% full or part time in college) consuming < 5 servings/day of FV (eligibility criteria) completed a baseline survey to enroll in a randomized online FV intervention. Sleep questions included duration, perceived sleep quality, time to fall asleep, and insomnia symptoms. Overall and gender-stratified linear regression models compared average daily FV intake and sleep characteristics, adjusting for confounders. RESULTS: One-third (32%) of the participants reported < 7 h of sleep per night, and 36% noted insomnia symptoms >/= 3 times per week. Women, a BMI > 30, African American race/ethnicity, less education, unemployment, higher depression, and stress were related to suboptimal sleep. Bivariate analyses showed that better sleep was associated with higher FV intake. After accounting for confounders, men with better sleep quality and shorter time to fall asleep had higher intakes of FV (1.12 serving/day difference in highest versus lowest quality [95% CI 0.48, 1.75] and a 0.52 serving/day higher intake difference for shortest versus longest fall asleep time [95% CI 0.90, 0.15], respectively). CONCLUSION: Sleep was highly prevalent in a diverse sample of community-based young adults and may contribute to lower FV intake among men. These associations highlight young adulthood as an important period for promoting healthy sleep habits.

Public Health Sciences

Lynch FL, **Peterson EL**, Lu CY, **Hu Y**, Rossom RC, Waitzfelder BE, Owen-Smith AA, Hubley S, **Prabhakar D**, **Keoki Williams L**, Beck A, Simon GE, and **Ahmedani BK**. Substance use disorders and risk of suicide in a general US population: a case control study. *Addict Sci Clin Pract* 2020; 15(1):14. PMID: 32085800. Request Article

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BACKGROUND: Prior research suggests that substance use disorders (SUDs) are associated with risk of suicide mortality, but most previous work has been conducted among Veterans Health Administration patients. Few studies have examined the relationship between SUDs and suicide mortality in general populations. Our study estimates the association of SUDs with suicide mortality in a general US population of men and women who receive care across eight integrated health systems. METHODS: We conducted a case-control study using electronic health records and claims data from eight integrated health systems of the Mental Health Research Network. Participants were 2674 men and women who died by suicide between 2000-2013 and 267,400 matched controls. The main outcome was suicide mortality, assessed using data from the health systems and confirmed by state death data systems. Demographic and diagnostic data on substance use disorders and other health conditions were obtained from each health system. First, we compared descriptive statistics for cases and controls, including age, gender, income, and education. Next, we compared the rate of each substance use disorder category for cases and controls. Finally, we used conditional logistic regression models to estimate unadjusted and adjusted odds of suicide associated with each substance use disorder category. RESULTS: All categories of substance use disorders were associated with increased risk of suicide mortality. Adjusted odds ratios ranged from 2.0 (CI 1.7, 2.3) for patients with tobacco use disorder only to 11.2 (CI 8.0, 15.6) for patients with multiple alcohol, drug, and tobacco use disorders. Substance use disorders were associated with increased relative risk of suicide for both women and men across all categories, but the relative risk was more pronounced in women. CONCLUSIONS: Substance use disorders are associated with significant risk of suicide mortality, especially for women, even after controlling for other important risk factors. Experiencing multiple substance use disorders is particularly risky. These findings suggest increased suicide risk screening and prevention efforts for individuals with substance use disorders are needed.

Public Health Sciences

Nowak RM, Christenson RH, **Jacobsen G**, **McCord J**, Apple FS, Singer AJ, Limkakeng A, Jr., Peacock WF, and deFilippi CR. Performance of Novel High-Sensitivity Cardiac Troponin I Assays for 0/1-Hour and 0/2- to 3-Hour Evaluations for Acute Myocardial Infarction: Results From the HIGH-US Study. *Ann Emerg Med* 2020; Epub ahead of print. PMID: 32046869. Full Text

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Department of Emergency Medicine, SUNY Stony Brook, Stony Brook, NY.
Department of Medicine, Division of Emergency, Medicine, Duke University School of Medicine, Durham, NC.
Department of Emergency Medicine, Baylor College of Medicine, Houston, TX.
Inova Heart and Vascular Institute, Falls Church, VA.

STUDY OBJECTIVE: We determine the accuracy of high-sensitivity cardiac troponin I (hs-cTnI), European-derived, rapid, acute myocardial infarction, rule-out/rule-in algorithms applied to a US emergency department (ED) population. METHODS: Adults presenting to the ED with suspected acute myocardial infarction were included. Plasma samples collected at baseline and between 40 and 90 minutes and 2 and 3 hours later were analyzed in core laboratories using the Siemens Healthineers hs-cTnI assays. Acute myocardial infarction diagnosis was independently adjudicated. The sensitivity, specificity, and negative and positive predictive values for rapid acute myocardial infarction rule-out/rule-in using European algorithms and 30-day outcomes are reported. RESULTS: From 29 US medical centers, 2,113 subjects had complete data for the 0/1-hour algorithm analyses. With the Siemens Atellica Immunoassay hs-cTnI values, 1,065 patients (50.4%) were ruled out, with a negative predictive value of 99.7% and sensitivity of 98.7% (95% confidence interval 99.2% to 99.9% and 96.3% to 99.6%, respectively), whereas 265 patients (12.6%) were ruled in, having a positive predictive value of 69.4% and specificity of 95.7% (95% confidence interval 63.6% to 74.7% and 94.7% to 96.5%, respectively). The remaining 783 patients (37.1%) were classified as having continued evaluations, with an acute myocardial infarction incidence of 5.6% (95% confidence interval 4.2% to 7.5%). The overall 30-day risk of death or postdischarge acute myocardial infarction was very low in the ruled-out patients but was incrementally increased in the other groups (rule-out 0.2%; continued evaluations 2.1%; rule-in 4.8%). Equivalent results were observed in the 0/2- to 3-hour analyses and when both algorithms were applied to the hs-cTnI ADVIA Centaur measurements. CONCLUSION: The European rapid rule-out/rule-in acute myocardial infarction algorithm hs-cTnI cut points can be harmonized with a demographically and risk-factor diverse US ED population.

Public Health Sciences

Peters RM, Solberg MA, Templin TN, and **Cassidy-Bushrow AE**. Psychometric Properties of the Brief COPE Among Pregnant African American Women. *West J Nurs Res* 2020; Epub ahead of print. PMID: 32100645. Full Text

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This paper describes the assessment of the psychometric properties of the Brief COPE in a sample of 189 pregnant African-American women. Confirmatory factor analysis (CFA) tested the original 14-factor model, and exploratory structural equation modeling (ESEM) determined whether a reduced number of factors still accounted for inter-item covariances. The CFA replicated 13 of the 14 original factors. After deleting substance use items and allowing for correlated error across the support factors, the 13-factor model achieved an acceptable fit (CMIN/df = 1.77; RMSEA = 0.06, 95% CI = 0.05-0.07). ESEM resulted in three second-order factors: disengaged, active, and social support coping. Factor items were summed to create subscales with good internal consistency reliability (alpha = .74-.89). Social support coping and active coping were strongly correlated and accounted for nearly the same variance in four different psychological/affect scales, while disengaged coping was clearly distinct.

Public Health Sciences

Skiba V, **Novikova M**, **Suneja A**, **McLellan B**, and **Schultz L**. Use of Positive Airway Pressure in Mild Cognitive Impairment to Delay Progression to Dementia. *J Clin Sleep Med* 2020; Epub ahead of print. PMID: 32039755. Full Text

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STUDY OBJECTIVES: To assess the relationship between continuous positive airway pressure (CPAP) therapy and cognitive function in patients with mild cognitive impairment (MCI) and obstructive sleep apnea (OSA). METHODS: This was a retrospective chart review of patients with MCI and OSA. CPAP compliance was defined as average use of CPAP for at least 4 hours a night. Kaplan-Meier estimates, logrank tests and Cox proportional hazards regression were done to compare the compliance groups in terms of progression to dementia, defined as Clinical Dementia Rating (CDR) of 1 or greater. Linear mixed models were used to assess the relationships between CPAP compliance and neurological cognitive function outcomes over time. RESULTS: Ninety-six patients were included with mean age at MCI diagnosis of 70.4 years, mean Apnea Hypopnea Index of 25.9 and mean duration of neurology follow-up of 2.8 years. Forty-two were CPAP compliant, 30 were non-compliant and 24 had no CPAP use. No overall difference among the groups was detected for progression to dementia (p = 0.928, logrank test). Patients with amnestic MCI had better CPAP use (p = 0.016) and shorter progression time to dementia (p = 0.042), but this difference was not significant after adjusting for age, education and race (p = 0.32). CONCLUSIONS: CPAP use in MCI patients with OSA was not associated with delay in progression to dementia or cognitive decline.

Rehabilitation Services
Wilson CM, and **Stanczak JF**. Palliative pain management using transcutaneous electrical nerve stimulation (TENS). *Rehabil Oncol* 2020; 38(1):E1-E6. PMID: Not assigned. Request Article

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Sleep Medicine
Begum J, and **Skiba V**. When Using Two Patient Identifiers is Not Enough with CPAP Therapy. *J Clin Sleep Med* 2020; Epub ahead of print. PMID: 32003731. Full Text

Sleep Disorders and Research Center, Henry Ford Health System, Detroit, MI.

Sleep Medicine
Kalmbach DA, Sen S, and **Drake CL**. Poor sleep is a health crisis for physicians and nurses. *Sleep Med* 2020; Epub ahead of print. PMID: 32046921. Full Text

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Sleep Medicine
Skiba V, **Novikova M**, **Suneja A**, **McLellan B**, and **Schultz L**. Use of Positive Airway Pressure in Mild Cognitive Impairment to Delay Progression to Dementia. *J Clin Sleep Med* 2020; Epub ahead of print. PMID: 32039755. Full Text

Division of Sleep Medicine, Henry Ford Hospital.
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STUDY OBJECTIVES: To assess the relationship between continuous positive airway pressure (CPAP) therapy and cognitive function in patients with mild cognitive impairment (MCI) and obstructive sleep apnea (OSA). METHODS: This was a retrospective chart review of patients with MCI and OSA. CPAP compliance was defined as average use of CPAP for at least 4 hours a night. Kaplan-Meier estimates, logrank tests and Cox proportional hazards regression were done to compare the compliance groups in terms of progression to dementia, defined as Clinical Dementia Rating (CDR) of 1 or greater. Linear mixed models were used to assess the relationships between CPAP compliance and neurological cognitive function outcomes over time. RESULTS: Ninety-six patients were included with mean age at MCI diagnosis of 70.4 years, mean Apnea Hypopnea Index of 25.9 and mean duration of neurology follow-up of 2.8 years. Forty-two were CPAP compliant, 30 were non-compliant and 24 had no CPAP use. No overall difference among the groups was detected for progression to dementia (p = 0.928, logrank test). Patients with amnestic MCI had better CPAP use (p = 0.016) and shorter progression time to dementia (p = 0.042), but this difference was not significant after adjusting for age, education and race (p = 0.32). CONCLUSIONS: CPAP use in MCI patients with OSA was not associated with delay in progression to dementia or cognitive decline.

Surgery
Chen Y, **Susick L**, Davis M, **Bensenhaver J**, **Nathanson SD**, **Burns J**, and Newman LA. Evaluation of Triple-Negative Breast Cancer Early Detection via Mammography Screening and Outcomes in African American and White American Patients. *JAMA Surg* 2020; Epub ahead of print. PMID: 32074266. Full Text

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Surgery
de Meireles A, **Carlin AM**, Cain-Nielsen A, Stricklen A, Ross R, Finks JF, Varban OA, and Ghaferi AA. Association Between Surgeon Practice Knowledge and Venous Thromboembolism. *Obes Surg* 2020; Epub ahead of print. PMID: 32062847. Full Text

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BACKGROUND: The most common cause of mortality following bariatric surgery is venous thromboembolism. Our study aimed to (1) determine the practice patterns of venous thromboembolism (VTE) chemoprophylaxis among bariatric surgeons participating in a large statewide quality collaborative and (2) compare the results of surgeon self-reported chemoprophylaxis practices to actual practices from abstracted chart data. METHODS: We administered a 13-question survey to 66 surgeons across a statewide collaborative aimed at revealing VTE practice patterns such as medication type, dosage, timing, duration, and level of trainee involvement (response rate 93%). We conducted on-site data audits to examine the charts of all patients that had developed VTE during the study period and 15 other randomly selected patient charts per site. We then evaluated both the ordered perioperative chemoprophylaxis and the actual administered chemoprophylaxis from nursing and electronic records. RESULTS: There was 31% overall discordance between self-reported and abstracted chart data for pre-operative VTE dosing regimens. Among patients who had a VTE, 39% of administered chemoprophylaxis did not match surgeon responses. Conversely, among patients who did not have a VTE, only 29% were discordant ($p = 0.03$). In contrast, for post-operative VTE dosing, there was no significant difference in the rate of discordance in patients with and without a VTE (47% discordance vs 38%, $p = 0.0552$, respectively). CONCLUSIONS: Greater discordance between surgeon self-reported and actual perioperative VTE chemoprophylaxis is associated with significantly increased risk of VTE. Further understanding of the system characteristics associated with these practices may yield insights into how best to improve appropriate VTE chemoprophylaxis.

Surgery
De Roo AC, Morris AM, Vu JV, Schuman AD, Abbott KL, **Kandagatla P**, Hardiman KM, and Hendren S. Characteristics of Patients Seeking Second Opinions at a Multidisciplinary Colorectal Cancer Clinic. *Dis Colon Rectum* 2020; Epub ahead of print. PMID: 32109918. Full Text

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BACKGROUND: Patients seeking second opinions are a challenge for the colorectal cancer provider due to complexity, failed therapeutic relationship with another provider, need for reassurance, and desire for exploration of treatment options. OBJECTIVE: To describe the patient and treatment characteristics of patients seeking initial and second opinions in colorectal cancer care at a multidisciplinary colorectal cancer clinic. DESIGN: Retrospective cohort study SETTINGS:: Prospectively collected clinical registry of a multidisciplinary colorectal cancer clinic. PATIENTS: Patients with colon or rectal cancer seen from 2012-2017. MAIN OUTCOME MEASURES: Data were analyzed for initial vs. second opinion and demographic and clinical characteristics. RESULTS: Of 1711 colorectal cancer patients, 1008 (58.9%) sought an initial opinion, 700 (40.9%) sought a second opinion. As compared to initial opinion patients, second opinion patients were more likely to have Stage IV disease (OR 1.94, 95% CI 1.47-2.58), recurrent disease (OR 1.67, 95% CI 1.13-2.46), and be ages 40-49 (OR 1.47, 95% CI 1.02-2.12). Initial and second opinion cohorts were similar in terms of gender, race, and proportion of colon vs. rectal cancer. Among second

opinion patients, 246 (35%) second opinion patients transitioned their care to the multidisciplinary colorectal cancer clinic. LIMITATIONS: We were unable to capture final treatment plan for those patients who did not transfer care to the multidisciplinary colorectal cancer clinic. CONCLUSIONS: Patients seeking a second opinion represent a unique subset of colorectal cancer patients. In general, they are younger, and more likely to have Stage IV or recurrent disease than patients seeking an initial opinion. Although transfer of care to a multidisciplinary colorectal cancer clinic after second opinion is lower than for initial consultations, multidisciplinary colorectal cancer clinics provide an important role for patients with complex disease characteristics and treatment needs. See Video Abstract at http://links.lww.com/DCR/B192.

Surgery
Ivanics T, **Nasser H**, **Shepard A**, and **Lee A**. Aortic and superior mesenteric artery embolectomy after paradoxical embolism. *J Vasc Surg* 2020; 71(3):1027-1028. PMID: 32089198. Full Text

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Surgery
Karamanos E, **Kandagatla P**, Wang H, Gupta AH, and **Siddiqui A**. Challenging the Surgical Axiom: Albumin Level Does Not Reliably Predict Development of Wound Complications in Patients Undergoing Body Contouring. *Perm J* 2020; 24. PMID: 32097112. Request Article

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INTRODUCTION: Hypoalbuminemia has traditionally been associated with a poor nutritional status and subsequent high incidence of postoperative wound complications in surgical patients. Recent evidence, however, suggests that traditional nutritional markers are inadequate in predicting postoperative morbidity. OBJECTIVE: To test the hypothesis that preoperative albumin levels are not associated with adverse outcomes in patients undergoing body contouring. METHODS: All patients undergoing body contouring from 2015 to 2017 were identified using the American College of Surgeons National Surgical Quality Improvement Program database. Demographics, comorbidities, and wound classification were extracted from the database. The independent predictors of developing wound complications were identified. Logistic regressions were used to identify the impact of albumin on outcomes. RESULTS: During the study period, 4496 patients were identified. Wound complications developed in 202 patients (4.5%). Increasing body mass index, history of diabetes mellitus, American Society of Anesthesiologists classification, history of prior open wound, and tobacco use were independently associated with the development of postoperative complications. Albumin levels were not associated with the development of wound complications. Similarly, albumin levels were not associated with the need for a repeated operation, with readmission, or with the total hospital length of stay. CONCLUSION: Albumin values were not associated with wound complications or need for reoperation in patients undergoing body contouring. Further research is warranted.

Surgery
Kitajima T, **Moonka D**, **Yeddula S**, **Rizzari M**, **Collins K**, **Yoshida A**, **Abouljoud MS**, and **Nagai S**. Liver transplant waitlist outcomes in alcoholic hepatitis compared with other liver diseases: An analysis of UNOS registry. *Clin Transplant* 2020; Epub ahead of print. PMID: 32073688. Full Text

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There is growing interest in performing liver transplantation (LT) in patients with alcoholic hepatitis (AH) without a mandated abstinence period. The aim of this study is to investigate waitlist outcomes in AH patients compared to those with other liver diseases. Using data from the UNOS registry, adult patients listed for LT between 2009 and 2018 were evaluated. Waitlist outcomes were compared among liver diseases. 64,646 patients were eligible, including 286 with AH, 16,871 with alcoholic cirrhosis (AC), 13,730 with hepatitis C (HCV), 10,315 with non-alcoholic steatohepatitis (NASH) and 5,841 with cholestatic liver disease (CLD). In comparison to AH patients, patients with HCV, NASH, and CLD had a significantly higher risk of waitlist mortality, and a lower likelihood of recovery on the waitlist. These trends were more prominent in the waiting-time period of 91-365 days than in shorter periods. In intention-to-treat analysis, positive prognostic effect of LT was significant in AH patients with MELD score>/=35 (HR 0.04, P<0.001). AH patients showed lower mortality risk and a higher chance of recovery while on waitlist than other liver diseases, especially when waiting-time exceeded 90 days. These results indicate the importance of continuous evaluation of disease progression in AH patients awaiting LT.

Surgery
Levoska MA, **Griffith JL**, **Nagai S**, **Collins K**, and **Lim HW**. A multi-disciplinary approach utilizing filters for surgical procedures in erythropoietic protoporphyria. *J Am Acad Dermatol* 2020; Epub ahead of print. PMID: 32068036. Full Text

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Surgery
Madill-Thomsen K, **Abouljoud M**, Bhatti C, Ciszek M, Durlik M, Feng S, Foroncewicz B, **Francis I**, Grat M, Jurczyk K, Klintmalm G, Krasnodebski M, McCaughan G, Miquel R, Montano-Loza A, **Moonka D**, Mucha K, Myslak M, Paczek L, Perkowska-Ptasinska A, Piecha G, Reichman T, Sanchez-Fueyo A, Tronina O, Wawrzynowicz-Syczewska M, Wiecek A, Zieniewicz K, and Halloran PF. The molecular diagnosis of rejection in liver transplant biopsies: First results of the INTERLIVER study. *Am J Transplant* 2020; Epub ahead of print. PMID: 32090446. Full Text

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Molecular diagnosis of rejection is emerging in kidney, heart, and lung transplant biopsies and could offer insights for liver transplant biopsies. We measured gene expression by microarrays in 235 liver transplant biopsies from 10 centers. Unsupervised archetypal analysis based on expression of previously annotated rejection-related transcripts identified four groups: normal 'R1normal ' (N=129), T cell-mediated rejection (TCMR) 'R2TCMR ' (N=37), early injury 'R3injury ' (N=61), and fibrosis 'R4late ' (N=8). Groups differed in median time post-transplant e.g. R3injury 99 days vs. R4late 3117 days. R2TCMR biopsies expressed typical TCMR-related transcripts e.g. intense IFNG-induced effects. R3injury displayed increased expression of parenchymal injury transcripts (e.g. hypoxia-inducible factor EGLN1). R4late biopsies showed immunoglobulin transcripts and injury-related transcripts. R2TCMR correlated with histologic rejection although with many discrepancies, and R4late with fibrosis. R2TCMR , R3injury , and R4late correlated with liver function abnormalities. Supervised classifiers trained on histologic rejection showed less agreement with histology than unsupervised R2TCMR scores. No confirmed cases of clinical ABMR were present in the population, and strategies that previously revealed antibody-mediated rejection (ABMR) in kidney and heart transplants failed to reveal a liver ABMR phenotype. In conclusion, molecular analysis of liver transplant biopsies detects rejection, has the potential to resolve ambiguities, and could assist with immunosuppressive management.

Surgery
Oakes RS, Bushnell GG, Orbach SM, **Kandagatla P**, Zhang Y, Morris AH, Hall MS, LaFaire P, Decker JT, Hartfield RM, Brooks MD, Wicha MS, Jeruss JS, and Shea LD. Metastatic Conditioning of Myeloid Cells at a Subcutaneous Synthetic Niche Reflects Disease Progression and Predicts Therapeutic Outcomes. *Cancer Res* 2020; 80(3):602-612. PMID: 31662327. Full Text

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Monitoring metastatic events in distal tissues is challenged by their sporadic occurrence in obscure and inaccessible locations within these vital organs. A synthetic biomaterial scaffold can function as a synthetic metastatic niche to reveal the nature of these distal sites. These implanted scaffolds promote tissue ingrowth, which upon cancer initiation is transformed into a metastatic niche that captures aggressive circulating tumor cells. We hypothesized that immune cell phenotypes at synthetic niches reflect the immunosuppressive conditioning within a host that contributes to metastatic cell recruitment and can identify disease progression and response to therapy. We analyzed the expression of 632 immune-centric genes in tissue biopsied from implants at weekly intervals following inoculation. Specific immune populations within implants were then analyzed by single-cell RNA-seq. Dynamic gene expression profiles in innate cells, such as myeloid-derived suppressor cells, macrophages, and dendritic cells, suggest the development of an immunosuppressive microenvironment. These dynamics in immune phenotypes at implants was analogous to that in the diseased lung and had distinct dynamics compared with blood leukocytes. Following a therapeutic excision of the primary tumor, longitudinal tracking of immune phenotypes at the implant in individual mice showed an initial response to therapy, which over time differentiated recurrence versus survival. Collectively, the microenvironment at the synthetic niche acts as a sentinel by reflecting both progression and regression of disease. SIGNIFICANCE: Immune dynamics at biomaterial implants, functioning as a synthetic metastatic niche, provides unique information that correlates with disease progression. GRAPHICAL ABSTRACT: http://cancerres.aacrjournals.org/content/canres/80/3/602/F1.large.jpg.See related commentary by Wolf and Elisseeff, p. 377.

Urology
Sood A, **Keeley J**, **Palma-Zamora I**, **Dalela D**, **Arora S**, **Peabody JO**, **Rogers CG**, Montorsi F, **Menon M**, Briganti A, and **Abdollah F**. Extended pelvic lymph-node dissection is independently associated with improved overall survival in prostate cancer patients at high-risk for lymph-node invasion. *BJU Int* 2020; Epub ahead of print. PMID: 32045096. Full Text

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It is generally agreed upon that extended pelvic lymph-node dissection (ePLND) provides valuable staging information and helps guide adjuvant therapy, and should be undertaken in prostate cancer (CaP) patients with aggressive preoperative disease features at the time of radical prostatectomy [1, 2]. However, whether it has a 'direct' therapeutic benefit in the aforesaid patients has remained difficult to demonstrate [3]. The only patients that seem to derive a survival advantage from ePLND are patients with pN1 disease [4] - this cited study suggested a direct therapeutic effect of ePLND, with a 7% incremental benefit in 10-year cancer-specific survival per every additional lymph-node removed (p=0.02). However, it did not identify these patients preoperatively.

Conference Abstracts

Allergy and Immunology
Jackson D, Flynn K, Rosasco M, Gill M, Liu A, Gruchalla R, O G, Pongracic J, Kercsmar C, Hershey GK, **Zoratti E**, Teach S, Kattan M, Bacharier L, Gergen P, Wheatley L, Presnell S, Togias A, Busse W, and Altman M. The Influence of MUC5AC SNPs on expression of MUC5AC and mucus hypersecretion genes during asthma exacerbations. *J Allergy Clin Immunol* 2020; 145(2):AB176. PMID: Not assigned. Conference Abstract.

Rationale: Few genetic studies have specifically defined the functional consequences of genetic variations during respiratory illnesses and asthma exacerbations; we identified genetic variants that impact molecular pathways during asthma exacerbations in children with exacerbation-prone disease. Methods: Serial longitudinal nasal lavage samples were collected from 106 children with exacerbation-prone asthma during three phases: asthma under control, upper respiratory infections, and asthma exacerbations. These samples were used to generate high throughput RNA-sequencing data for both gene expression and single nucleotide polymorphism (SNP) genotype determination. Expression quantitative trait loci (eQTL) analyses were performed by linear mixed-effects modeling and allele specific expression analyses by using a beta-binomial model. Results: 13 local SNPs in the MUC5AC region of chromosome 11 demonstrated significant association with both MUC5ACexpression (fold-changes=1.25-2.0, FDR<0.05) and aggregate expression of a gene module containing MUC5ACand 68 other genes related to

mucus hypersecretion and eosinophil activation. These relationships were significant specifically during respiratory illnesses and most pronounced during asthma exacerbations, but were not significant during disease control. TheMUC5ACcoding SNP rs1132440 [synonymous variant R (CGG) àR (CGC)] showed allele specific expression of MUC5ACtranscript levels with the alternate allele (C) showing significantly higher expression than the reference allele in heterozygotic individuals (allelic-fold-change=1.53, FDR<0.05). Conclusions: MUC5AC has pathogenic roles in asthma related to airway hyper-responsiveness and mucus plugging during exacerbations. Our findings demonstrate that genetic polymorphisms in the MUC5AC gene region affect expression of this gene along with a broader molecular module of type 2 inflammation during respiratory illnesses and asthma exacerbations in children.

Allergy and Immunology
Zoratti E, Panzer A, **Sitarik A**, **Jones K**, **Wegienka G**, **Havstad S**, Lukacs N, Boushey H, **Johnson CC**, Ownby D, and Lynch S. Prenatal Indoor Dog Exposure and Early Life Gut Microbiota in the Microbes, Asthma, Allergy and Pets Birth Cohort. *J Allergy Clin Immunol* journal 2020; 145(2):AB185. PMID: Not assigned. Conference Abstract.

Rationale: Early-life indoor dog exposure associates with lower atopy and asthma in childhood and may be related to altered gut microbial profiles among dog-exposed infants. Methods: Pregnant women living with either an indoor dog(s) or living in pet-free homes were recruited in southeast Michigan. Stool samples (n=490) were collected from 131 children at five intervals beginning at 1 week until approximately 18 months of age. 16S ribosomal RNA sequencing was used for stool bacterial characterization; community characteristics were compared between infants born into dog-keeping versus pet-free homes. Mixed effect models were fit for alpha diversity longitudinal trajectory analyses. Compositional differences over time were assessed using the first component from a principle coordinates analysis, again subjected to mixed effect modeling. Results were adjusted for potentially confounding covariates. Results: Richness and Faith's diversity were higher among children from dog-keeping homes (β±SE=12.9±5.9, p=0.029; β±SE=0.83±0.34, p=0.016; respectively). Following adjustment for household income or breastfeeding duration, associations were diminished and often no longer statistically significant. Longitudinal compositional differences were observed using unweighted UniFrac and Canberra metrics (β±SE=0.039±0.017, p=0.021; β±SE=0.026±0.12, p=0.027; respectively) in unadjusted analyses. However, effects were similarly diminished following covariate adjustment. Conclusions: Infants living with dogs have more rich and diverse early-life gut microbial profiles and distinct overall compositions. However, our data indicate this relationship may be at least partially associative rather than causative. Additional work is needed to determine if specific taxa differ by dog exposure after accounting for confounders, which may not be captured by overall diversity metrics.

Cardiology/Cardiovascular Research
Rteil A, **Lin J**, **Weaver M**, **Ahsan S**, **Lee A**, and **Kabbani L**. Socioeconomic Status and Clinical Stage of Patients Presenting for Treatment of Varicose Veins. *J Vasc Surg-Venous L* 2020; 8(2):328. PMID: Not assigned. Conference Abstract.

Objective: The association between socioeconomic status (SES) and chronic venous insufficiency has not been rigorously studied. This study aimed to determine the influence of SES on the clinical stage of patients presenting for chronic venous disease therapy. Methods: By use of the local Vascular Quality Initiative Varicose Vein Registry at our tertiary referral center, all patients undergoing therapy for varicose veins between January 2015 and June 2019 were queried. SES was quantified using the Neighborhood Deprivation Index (NDI). This is a standardized and reproducible index used in research that summarizes eight domains of socioeconomic deprivation. It is based on census tract data derived from the patients' addresses at the time of the operation. The higher the number, the worse the patients' SES is. The association between SES and severity of the vein disease at presentation was studied with bivariate analysis of variance and linear regression analysis. Results: A total of 449 patients had complete SES and Clinical, Etiology, Anatomy, and Pathophysiology (CEAP) class data and were included in the study. The mean age was 58 years; 67% were female, and 60% were white. CEAP class included the following: C2, 22%; C3, 50%; C4, 15%; C5, 5%; and C6, 8%. The average NDI was 0.03 (minimum, −1.45; maximum, 2.89). There was a linear correlation between the CEAP class at presentation and the NDI (P <.05; Fig). SES was not associated with history of deep venous thrombosis, prior vein treatment, use of compression therapy, or Venous Clinical Severity Score. Conclusions: CEAP class at presentation for treatment of chronic venous disease is associated with SES. This may reflect that patients with a lower SES wait longer before seeking medical therapy for venous disease. [Formula presented]

Cardiology/Cardiovascular Research
Sitammagari K, Desai R, Kondamareddy D, Ninan J, Dontaraju V, R. DB, and **Villablanca P**. Impact of Peripheral Vascular Disease After Transcatheter Mitral Valve Repair: Insights From the National Inpatient Sample. *JACC: Cardiovasc Interv* 2020; 13(4):S59. PMID: Not assigned. Conference Abstract.

Background: Peripheral vascular disease (PVD) is an independent predictor of poor outcomes after cardiovascular interventions and surgeries. Association of PVD with in-hospital outcomes after transcatheter mitral valve repair

(TMVr) has not been studied. Methods: Adults who underwent TMVr procedures from January 2011 to September 2015 were identified using the National Inpatient Sample. ICD-9 codes were used to differentiate PVD versus non-PVD patients. Multivariate linear and logistic regressions were used to calculate odds ratios for primary and secondary outcomes while adjusting for confounders. Results: A total of 5,093 patients underwent TMVr procedure, of which 618 (12.1%) had documented PVD. Patients with PVD were more likely older, male and smokers with comorbidities including hypertension, diabetes, dyslipidemia, previous myocardial infarction, previous coronary bypass surgery, chronic pulmonary disease, liver disease, renal failure, hemodialysis status and coagulopathy ($p<0.05$ for all). Patients with PVD had lower odds of all-cause in-hospital mortality (aOR 0.35, $p=0.031$) and postoperative infection (aOR 0.31, $p=0.009$) compared to non-PVD patients. Higher odds of pacemaker requirement (aOR 2.52, $p<0.001$), pericardial complications (aOR 3.23, $p<0.001$), perioperative stroke (aOR 22.36, $p<0.001$), mechanical ventilation (aOR 1.51, $p=0.011$) and venous thromboembolism (VTE) (aOR 4.28, $p<0.001$) were noted in PVD patients. PVD patients demonstrated comparable length of hospital stay but higher hospital charges. Conclusion: Presence of PVD marginally lowered the odds of mortality, iatrogenic cardiac complications, and infection after TMVr. However, these patients are at increased risk of pacemaker requirement, stroke, pericardial complications, mechanical ventilation and VTE. [Formula presented]

Cardiology/Cardiovascular Research

Sitammagari K, Dhanireddy BR, Kondamareddy D, Gangani K, Dontaraju V, Ninan J, and **Villablanca P**. Impact of Chronic Obstructive Pulmonary Disease on Outcomes After Transcatheter Mitral Valve Repair. *JACC: Cardiovasc Interv* 2020; 13(4):S57-S58. PMID: Not assigned. Conference Abstract.

Background: Chronic obstructive pulmonary disease (COPD) is associated with increased mortality and morbidity after cardiac valve surgeries and coronary angioplasty. However, the association of COPD with in-hospital outcomes after transcatheter mitral valve repair (TMVr) has not been established. Methods: Elective TMVr procedures among adults were identified using the National Readmissions Database (NRD) from January 2012 to August 2015. ICD-9 codes were used to identify patients with and without COPD. Multivariate linear and logistic regressions were used to calculate odds ratios for primary and secondary outcomes after adjusting for confounders. Primary outcomes were all-cause in-hospital mortality and associated in-hospital complications after TMVr in COPD vs non-COPD patients. Results: Of the 1,741 patients who underwent TMVr procedures during the study period, 256 (14.7%) had documented COPD. Patients with COPD were more likely to have a high burden of comorbidities (CCI 2 vs 1, $p<0.001$), including congestive heart failure, long-term oxygen dependence, dyslipidemia, obesity, smoking, and prior coronary artery disease ($p<0.05$ for all). There was no significant difference in all-cause in-hospital mortality (aOR 0.76, $p=0.583$), major bleeding (aOR 0.86, $p=0.367$), pacemaker placement (aOR 0.93, $p=0.771$), acute kidney injury (aOR 0.90, $p=0.642$), home discharge (aOR 1.15, $p=0.367$), and mean length of hospitalization (aOR -0.35, $p=0.550$). Patients with COPD were more likely to be discharged to a skilled nursing facility (aOR 1.80, 95% CI 1.24-2.73, $p=0.007$) compared to non-COPD patients. Conclusion: COPD did not impact in-hospital mortality or post-operative outcomes after TMVr. However, further studies are needed to evaluate the effect of COPD on long-term outcomes after TMVr. [Formula presented]

Cardiology/Cardiovascular Research

Sitammagari K, Kondamareddy D, Dhanireddy BR, Dontaraju V, Desai R, Ninan JK, and **Villablanca P**. Obstructive Sleep Apnea Impacts In-Hospital Outcomes After Transcatheter Mitral Valve Repair: Insights From the National Inpatient Sample. *JACC: Cardiovasc Interv* 2020; 13(4):S58. PMID: Not assigned. Conference Abstract.

Background: Obstructive sleep apnea (OSA) is an independent risk factor for many cardiovascular conditions. However, the association of OSA with outcomes in patients undergoing transcatheter mitral valve repair (TMVr) has not been established. Methods: From January 2011 to September 2015, TMVr procedures among adults were identified using the National Inpatient Sample. The determination of OSA versus non-OSA patients was made by ICD-9 codes. Multivariate linear and logistic regressions were used to calculate odds ratios for primary and secondary outcomes while adjusting for confounders. Results: We identified 5,093 patients who underwent TMVr procedure; of which 458 (8.9%) had documented OSA. Patients with OSA were younger, more likely to be male and had a high burden of comorbidities including diabetes, dyslipidemia, previous coronary artery bypass surgery, chronic pulmonary disease, obesity, liver disease, peripheral vascular disorders, renal failure and coagulopathy ($p<0.05$ for all). There was no significant difference in all-cause in-hospital mortality (aOR 1.18, $p=0.675$) between the two groups. Patients with OSA had higher odds of in-hospital cardiac arrest (aOR 4.41, $p<0.001$), cardiogenic shock (aOR 2.59, $p<0.001$), postoperative myocardial infarction (aOR 6.20, $p<0.001$), acute kidney injury requiring dialysis (aOR 54.47, $p<0.001$), and mechanical ventilation (aOR 2.25, $p<0.001$) as compared to non-OSA patients. Conclusion: In-hospital mortality after TMVr was not influenced by the presence of OSA. However, OSA patients had a significantly higher prevalence of cardiovascular comorbidities and higher in-hospital complications. [Formula presented]

Diagnostic Radiology

Hadied M, Kherallah R, and **Schwartz S**. Partial splenic artery embolization for idiopathic warm autoimmune hemolytic anemia refractory to medical therapy. *J Vasc Interv Radiol* 2020; 31(3):S178. PMID: Not assigned. Conference Abstract.

Purpose: While partial splenic artery embolization (PSAE) is a useful procedure that has been performed for a variety of indications including trauma and hypersplenism, it has been rarely described as a treatment for idiopathic warm autoimmune hemolytic anemia (AIHA). Previous reports in the literature are limited to case reports in situations that include the patient being a poor surgical candidate, the inability to transfuse blood during surgery because of autoantibodies, and a patient's refusal of blood products on religious grounds. The purpose of this study is to demonstrate the utility of PSAE in the acute management of AIHA refractory to medical treatment. Materials: A case report describing the management of a 27-year-old male diagnosed with AIHA treated successfully with PSAE as a bridging therapy to definitive surgical splenectomy. Relevant laboratory results and imaging were extracted from the electronic medical record. Results: The patient was diagnosed with AIHA and treated with intravenous solumedrol and rituximab and received 12 units of RBCs at an outside institution. The patient was transferred to our institution after developing antibodies that precluded more transfusions. The decision was made to proceed with PSAE. The first hemoglobin post procedure was 4.5 g/dl, an increase from 2.1 g/dl pre procedure. After embolization, the patient remained in the inpatient setting for eight days. During the inpatient hospitalization the patient's hemoglobin continued to trend upwards until it stabilized around 6 g/dl. Inpatient laboratory workup showed increasing haptoglobin, and decreasing LDH. After discharge, the patient developed persistent pain two months post procedure. An elective splenectomy was scheduled three months after the embolization procedure to address the persistent pain. Six months post embolization procedure and three months postoperatively, the patient is doing well clinically with a hemoglobin of 14 g/dl. Conclusions: In conclusion, this case demonstrates the utility of PSAE as an acute life-saving intervention for poor surgical candidates with idiopathic warm AIHA refractory to medical management.

Diagnostic Radiology

Jaffar S, Gelovani D, Jeakle W, Bacyinski A, Chagas C, and **Morris A**. Targeted case presentations introducing interventional radiology to medical students interested in primary care specialties. *J Vasc Interv Radiol* 2020; 31(3):S206. PMID: Not assigned. Conference Abstract.

Purpose: Interventional radiology (IR) is increasingly utilized through consultation as part of a collaborative health care team. However, formal education in this type of collaboration is limited in medical school curriculum and medical students lack confidence in requesting consultations. Studies have shown that IR interest group presentations and demonstrations increases medical student knowledge and excitement about the field. Our study demonstrates that IR interest group case presentations specific to medical students interested in primary care specialties increases their familiarity with IR, improves medical student collaboration and raises confidence when requesting consults. Materials: Specific cases requiring IR consultation were prepared for internal medicine, family medicine and emergency medicine interest groups. The educational content included an overview of the field of IR, basic principles and techniques of IR, the role of an IR in a multidisciplinary team, IR case presentations specific to the primary care specialty and indications for and benefits of IR consultation. Surveys were administered to students prior to and after the presentation to assess change in knowledge following the presentation using a Likert scale. McNemar's test was used to examine differences in pre- and postsurvey responses. Statistical analyses were conducted using STATA Corp v.14.2. Results: 70 pre-post surveys were completed by first- and second-year medical students (n = 70). There was a statistically significant increase in knowledge and familiarity in all areas from baseline ($P < 0.0016$). Additionally, nearly 33% of first and second year medical students indicated they were interested in 2 or more specialties or undecided (Table 1). Conclusions: Medical students are not exposed to IR and lack confidence when requesting consults for their patients. Increasing medical student familiarity with IR is essential to producing physicians with a broad understanding of the management options at their disposal. Targeted case presentations for preclinical medical students interested in primary care specialties were effective in increasing their familiarity with IR, improving confidence when requesting consults. [Formula presented]

Diagnostic Radiology

Williams P, and **Schwartz S**. Clinical experience with transjugular intrahepatic portosystemic shunt downsizing in patients with severe hepatic encephalopathy. *J Vasc Interv Radiol* 2020; 31(3):S279. PMID: Not assigned. Conference Abstract.

Purpose: The purpose of this study was to evaluate the outcomes of Transjugular Intrahepatic Shunt (TIPS) downsizing in the setting of severe hepatic encephalopathy. Data regarding outcomes and factors influencing these outcomes is relatively scarce. This follows a cohort of patients at a tertiary care center who underwent TIPS revision, in an effort to determine the efficacy and complication rate of the intervention. Materials: A list of patients with underlying cirrhosis undergoing TIPS procedures between 2013-2019 at a large volume tertiary care center was obtained. Data collected included patient demographics, reason for TIPS, whether downsizing occurred, reason for

downsizing, frequency of paracentesis prior to and after downsizing, grade of hepatic encephalopathy prior to and after downsizing, MELD labs prior to and after downsizing, IR technique used for downsizing, whether patients were liver transplant candidates and/or underwent transplantation, and mortality. Results: A total of 195 patients underwent TIPS placement between 2013-2019. Of those, 16 patients required TIPS downsizing using a balloon-expandable covered stent. The mean MELD was 18.4 just prior to downsizing and 17.6 one week after downsizing. The mean portosystemic gradient was 10.5 mm Hg before downsizing and 22.8 mm Hg after downsizing. TIPS downsizing was successful in decreasing the degree of hepatic encephalopathy from an average of grade 2.8 to grade 0.8 encephalopathy. Nine patients died with post-downsizing gradients of 28-29 mm Hg being among the highest. The two patients who survived to transplant within 8 months of their TIPS had pre and post-downsizing MELD scores of 15 or less. Conclusions: The results of the study suggest TIPS downsizing is effective in reducing hepatic encephalopathy. Most patients who were considered transplant candidates undergoing TIPS downsizing did not survive to transplant unless they were transplanted relatively shortly after TIPS, suggesting that TIPS/downsizing served more as short-term bridge to transplant in these patients. Those that died expectedly had higher MELD scores and post-downsizing portosystemic gradients. Limitations of this study are the small patient size and that it was single center.

Hematology-Oncology

Kumar R, Bhandari S, Ngo P, **Singh SRK**, Malapati SJ, and Rojan A. Clinical outcomes of patient migration in locally advanced rectal cancer from community cancer centers: An analysis of the National Cancer Database. *J Clin Oncol* 2020; 38(4). PMID: Not assigned. Conference Abstract.

R. Kumar

Background: With cancer care changing at a rapid pace, patients are becoming increasingly involved with their management and oftentimes migrating to a different facility to seek better care. Our study evaluated the characteristics of such patients who were initially diagnosed at a community cancer center (CCC) and how this affects clinical outcomes. Methods: The National Cancer Database identified 11,977 patients with stage II/III rectal cancer initially diagnosed at a CCC between 2005 and 2015. Clinical characteristics and outcomes between patients who received all of their treatments at the CCC versus those who received part or all of their treatments elsewhere were compared using rank-sum and X tests where appropriate. Cox model was used for survival analysis. Results: Of the total population, 51% were stage II and 49% were stage III. Gender and ethnic distributions were similar between the groups. Approximately 44 % of patients received all their treatment at the CCC and 56% had part or all of their care elsewhere. Patients who migrated were younger (63 vs 65 years, $p<0.001$) and had govt insurance (43.5 vs 35.8%, $p<0.001$). On multivariate analysis, age <65 years (OR 1.12, 95% CI 1.02-1.24), govt insurance (OR 1.17, 95% CI 1.06-1.29), Charlson/Deyo comorbid score <2 (OR 1.29, 95% CI 1.11-1.49), higher income (OR 1.21, 95% CI 1.16-1.27) and Stage III (OR 1.15, 95% CI 1.07-1.24) were associated with higher probability of migration. The treatment characteristics and outcomes are shown in Table. The 5y-OS rate was better in patients who received part or all of their treatment at other institutions (adjusted HR 0.80, 95% CI 0.74-0.86, $p<0.001$). Conclusions: Further studies are needed to provide direction for future strategies to reduce the apparent survival disparities in patients who migrate from CCC. (Table Presented) .

Internal Medicine

Aljabban N, Aljabban J, Gurakar M, **Khorfan K**, Syed SA, Gayar A, Khan H, Hadley D, and Saberi B. Novel therapeutic avenues for cholangiocarcinoma treatment: A meta-analysis. *J Clin Oncol* 2020; 38(4). PMID: Not assigned. Conference Abstract.

N. Aljabban

Background: Cholangiocarcinoma (CCA) is a rare cancer of the bile ducts but has been increasing in incidence. The mainstay of treatment of CCA is resection or chemoradiation for more advanced disease, with immunotherapy being an evolving field in treatment. A better understanding of CCA pathogenesis will pave new avenues for treatment. Methods: We employed our STARGEO platform to conduct a meta-analysis of public data from NCBI's Gene Expression Omnibus. We performed meta-analysis with 259 CCA tumor samples against 16 normal intrahepatic duct samples as a control. We then analyzed the signature in Ingenuity Pathway Analysis. Results:Our analysis revealed FXR/RXR and LXR/RXR activation as top canonical pathways. Top upstream regulators identified included HNF1A (with predicted inhibition) and ERBB2 (with predicted activation). The most upregulated genes included several extracellular matrix proteins implicated in cancer including COL1A1, LAMC2 (correlated with poor prognosis in CCA), KRT17 (a keratin implicated in various malignancies but not well described in CCA), and LAMB3 (exerts tumorigenesis through PI3k/Akt signaling). Additionally, we found stark upregulation of the immunophillin FKPBP1A, which is involved in mTOR activation. We also noted upregulation of ubiquitin-associated gene UBASH3B, which inhibits endocytosis in EGFR and has been described in breast cancer but not CCA. From our investigation of immune checkpoint inhibitors, we found upregulation of classically described inhibitors such as CTLA4, TIGIT, and

BTLA. In addition, we found upregulation of SIGLEC7, which has been recently shown to suppress immune function by binding to terminal sialic acid on glycans on the surface of immune cells. Conclusions: Our analysis highlights the possible role of ERBB2 and several extracellular genes in the pathogenesis of CCA. We also identify the role of genes not previously described in CCA such as FKBP1A and UBASH3B. Lastly, our results promote the promise of immunotherapy in CCA treatment.

Orthopedics/Bone and Joint

Singleton IM, **Garfinkel R**, Temkit H, and Belthur MV. Determinants of caregiver satisfaction in pediatric orthopedics. *J Investig Med* 2020; 68(1):A124. PMID: Not assigned. Conference Abstract.

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Purpose of study With healthcare transitioning from volume-based to value-based, patient satisfaction is becoming increasingly tied to physician reimbursement as well as publicly reported. Aside from its use as a quality metric, it is also a key component of patient-centered care. This study investigates determinants of pediatric orthopedic patients' parent or guardian (caregiver) satisfaction with the provider as measured by the Clinician and Group Consumer Assessment of Healthcare Providers and Systems (CG-CAHPS). Methods used This was a prospective cross-sectional study of 200 English-speaking caregivers of pediatric patients that checked into the Phoenix Children's Hospital orthopedic clinic from March 1, 2017 to November 1, 2018. All patients saw the same attending physician. Questionnaires given in clinic included the Newest Vital Sign (NVS) and the Literacy in Musculoskeletal Problems (LiMP) survey to measure general and musculoskeletal health literacy, respectively, demographic information, wait time, Consultation and Relational Empathy Measure (CARE) to measure perceived physician empathy, and CG-CAHPS. Summary of results Of the factors measured, perceived physician empathy correlated the strongest with the caregiver's overall physician satisfaction. Pearson correlation coefficient yielded an r of 0.740 and a p-value of <0.0001. Using multivariable modeling, physician empathy alone accounted for 53% of the variation in satisfaction scores. Other factors such as health literacy as measured by the NVS (r=0.004; p=0.964), LiMP (r=0.013; p=0.879), wait time (r= -0.003; p=0.974), and time spent with the physician (r=0.016; p=0.866) did not independently affect satisfaction. Conclusions The main determinant of caregiver satisfaction with the provider in a pediatric orthopedic setting is perceived physician empathy, accounting for over half of the variation in satisfaction. Health literacy, wait time, and time spent with the physician do not significantly affect satisfaction. This highlights the importance of quality over quantity patient-physician interactions. This is the first study, to our knowledge, that directly correlates pediatric caregivers' perceived physician empathy with provider satisfaction.

Pediatrics

Zoratti E, Panzer A, **Sitarik A**, **Jones K**, **Wegienka G**, **Havstad S**, Lukacs N, Boushey H, **Johnson CC**, Ownby D, and Lynch S. Prenatal Indoor Dog Exposure and Early Life Gut Microbiota in the Microbes, Asthma, Allergy and Pets Birth Cohort. *J Allergy Clin Immunol* 2020; 145(2):AB185. PMID: Not assigned. Conference Abstract.

Rationale: Early-life indoor dog exposure associates with lower atopy and asthma in childhood and may be related to altered gut microbial profiles among dog-exposed infants. Methods: Pregnant women living with either an indoor dog(s) or living in pet-free homes were recruited in southeast Michigan. Stool samples (n=490) were collected from 131 children at five intervals beginning at 1 week until approximately 18 months of age. 16S ribosomal RNA sequencing was used for stool bacterial characterization; community characteristics were compared between infants born into dog-keeping versus pet-free homes. Mixed effect models were fit for alpha diversity longitudinal trajectory analyses. Compositional differences over time were assessed using the first component from a principle coordinates analysis, again subjected to mixed effect modeling. Results were adjusted for potentially confounding covariates. Results: Richness and Faith’s diversity were higher among children from dog-keeping homes (β±SE=12.9±5.9, p=0.029; β±SE=0.83±0.34, p=0.016; respectively). Following adjustment for household income or breastfeeding duration, associations were diminished and often no longer statistically significant. Longitudinal compositional differences were observed using unweighted UniFrac and Canberra metrics (β±SE=0.039±0.017, p=0.021; β±SE=0.026±0.12, p=0.027; respectively) in unadjusted analyses. However, effects were similarly diminished following covariate adjustment. Conclusions: Infants living with dogs have more rich and diverse early-life gut microbial profiles and distinct overall compositions. However, our data indicate this relationship may be at least partially associative rather than causative. Additional work is needed to determine if specific taxa differ by dog exposure after accounting for confounders, which may not be captured by overall diversity metrics.

Pharmacy

Bouwma A, **Mlynarek M**, **Peters M**, **Procopio V**, and **Martz C**. Surgical intensive care unit pain management in the era of intravenous opioid shortages. *Crit Care Med* 2020; 48:23. PMID: Not assigned. Conference Abstract.

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Introduction/Hypothesis: Fentanyl is widely used for the treatment of pain in mechanically ventilated (MV) intensive care unit (ICU) patients, but a shortage of fentanyl forced hospitals to utilize other medications. This study compared pain control in MV patients before and during continuous intravenous infusion (CIVI) fentanyl shortages. Methods: This was a multi-center, IRB approved, quasi-experimental study conducted in surgical ICU (SICU) patients. Patients were included if they were admitted due to trauma or post-procedure, excluding neurologic and cardiac surgeries, and on MV for >24 hours. The before and during shortage groups included patients prior to fentanyl shortages (4/2017-9/2017) who received CIVI fentanyl and during fentanyl shortages (4/2018-9/2018) without CIVI fentanyl administration, respectively. Patients were excluded if they were comfort care, pharmacologically paralyzed, in alcohol withdrawal, or able to verbalize a pain score. Randomization for patient inclusion occurred via a random number generator. The primary outcome was the percentage of Critical-Care Pain Observation Tool (CPOT) scores within goal. Secondary endpoints included the percentage of Richmond Agitation-Sedation Scale scores within goal, time to first CPOT goal, morphine milligram equivalents (MME), ventilator days, ICU length of stay, medications used for pain, agitation, delirium (PAD), rates of CIVI PAD medications, and confusion assessment method for the ICU (CAM-ICU). Data was collected until extubation or up to 7 days on MV. Descriptive statistics, chi-squared, and Mann Whitney U test were used, as appropriate. Results: A total of 164 patients were included (82 patients in the before and during shortage groups respectively). There was no statistically significant difference in the percentage of CPOT scores at goal (79.5% vs. 80.6%; p=0.365) however, the during shortage group did have significantly less oral MME compared to the before group (37.9 MME vs. 240 MME, respectively; $p < 0.001$). There were no statistically significant differences found in other secondary endpoints, with the exception of higher CIVI propofol rates and increased positive CAM-ICU scores in the during shortage group. Conclusions: Patients on MV in the SICU appear to have adequate pain control with less overall MME without CIVI fentanyl utilization.

Public Health Sciences

Zoratti E, Panzer A, **Sitarik A**, **Jones K**, **Wegienka G**, **Havstad S**, Lukacs N, Boushey H, **Johnson CC**, Ownby D, and Lynch S. Prenatal Indoor Dog Exposure and Early Life Gut Microbiota in the Microbes, Asthma, Allergy and Pets Birth Cohort. *J Allergy Clin Immunol* 2020; 145(2):AB185. PMID: Not assigned. Conference Abstract.

Rationale: Early-life indoor dog exposure associates with lower atopy and asthma in childhood and may be related to altered gut microbial profiles among dog-exposed infants. Methods: Pregnant women living with either an indoor dog(s) or living in pet-free homes were recruited in southeast Michigan. Stool samples (n=490) were collected from 131 children at five intervals beginning at 1 week until approximately 18 months of age. 16S ribosomal RNA sequencing was used for stool bacterial characterization; community characteristics were compared between infants born into dog-keeping versus pet-free homes. Mixed effect models were fit for alpha diversity longitudinal trajectory analyses. Compositional differences over time were assessed using the first component from a principle coordinates analysis, again subjected to mixed effect modeling. Results were adjusted for potentially confounding covariates. Results: Richness and Faith's diversity were higher among children from dog-keeping homes (β±SE=12.9±5.9, p=0.029; β±SE=0.83±0.34, p=0.016; respectively). Following adjustment for household income or breastfeeding duration, associations were diminished and often no longer statistically significant. Longitudinal compositional differences were observed using unweighted UniFrac and Canberra metrics (β±SE=0.039±0.017, p=0.021; β±SE=0.026±0.12, p=0.027; respectively) in unadjusted analyses. However, effects were similarly diminished following covariate adjustment. Conclusions: Infants living with dogs have more rich and diverse early-life gut microbial profiles and distinct overall compositions. However, our data indicate this relationship may be at least partially associative rather than causative. Additional work is needed to determine if specific taxa differ by dog exposure after accounting for confounders, which may not be captured by overall diversity metrics.

Surgery

Ivanics T, **Williams P**, **Nasser H**, **Leonard-Murali S**, **Schwartz S**, and **Lin J**. Contemporary Management of Chronic Indwelling Inferior Vena Cava Filters: A Single-Institution Experience. *J Vasc Surg-Venous L* 2020; 8(2):325-327. PMID: Not assigned. Conference Abstract.

Objective: Despite increasing retrieval rates of the inferior vena cava (IVC) filter, less than one-third are removed within the recommended time. Prolonged filter dwell times may increase the technical difficulty of retrieval and filter-related complications. We sought to evaluate contemporary outcomes of patients with chronic indwelling IVC filters at a tertiary care center. Methods: From 2015 to 2019, a retrospective analysis was performed of all patients who were referred for removal of prolonged IVC filter with a dwell time >6 years. Descriptive analyses were used to evaluate patient characteristics and procedural outcome by electronic medical records. Data were expressed as the mean and standard deviation, median with interquartile range (IQR), or number and percentage, as appropriate. Results: During the study period, a total of 45 patients were identified with a median filter dwell time of 9.0 years (IQR, 6-13 years); 32 patients underwent removal of IVC filter and 13 patients refused retrieval. The median age of patients was 55.3 years (IQR, 42.6-66.5 years); the majority were female (55.6%) and white (60.5%). Comorbidities included history of venous thromboembolism (80%), hypercoagulable state (13.3%), hypertension (55.6%), diabetes (24.4%), hyperlipidemia (31.1%), chronic kidney disease (11.1%), and active smoking status (11.1%). IVC filters removed

included 12 (26.7%) Günther Tulip (Cook Medical, Bloomington, Ind), 5 (11.1%) Celect (Cook), 4 (8.9%) G2 (Bard, Murray Hill, NJ), 2 (4.4%) Greenfield (Boston Scientific, Marlborough, Mass), 1 (2.2%) Simon Nitinol (Bard), 1 (2.2%) OptEase (Cordis, Bridgewater, NJ), and 1 (2.2%) Recovery (Bard). The most common indication for filter placement was high risk despite anticoagulation (52.4%), followed by venous thromboembolism prophylaxis (21.4%) and inability to be anticoagulated (19.0%). The majority of the patients were symptomatic (66.7%). If symptomatic, the most common reason for retrieval was filter migration (62.1%), and chief complaint was pain (51.7%). The time from first clinic visit or consultation until IVC filter removal was a median of 34.0 days (IQR, 14.8-62.8 days). Retrieval success was 95% (standard deviation, 0.20), with a median length of stay of 0 days. Most retrievals were performed through an endovascular approach, and interventional radiology performed the majority of retrievals (n = 24 [75.0%]). None of the patients who underwent retrieval (n = 32) developed a postprocedural complication (Table). Conclusions: Despite prolonged dwell times, IVC filter retrieval can be performed safely and effectively in carefully selected patients at a tertiary referral center. [Formula presented]

Surgery

Rteil A, **Lin J**, **Weaver M**, **Ahsan S**, **Lee A**, and **Kabbani L**. Socioeconomic Status and Clinical Stage of Patients Presenting for Treatment of Varicose Veins. *J Vasc Surg-Venous L* 2020; 8(2):328. PMID: Not assigned. Conference Abstract.

Objective: The association between socioeconomic status (SES) and chronic venous insufficiency has not been rigorously studied. This study aimed to determine the influence of SES on the clinical stage of patients presenting for chronic venous disease therapy. Methods: By use of the local Vascular Quality Initiative Varicose Vein Registry at our tertiary referral center, all patients undergoing therapy for varicose veins between January 2015 and June 2019 were queried. SES was quantified using the Neighborhood Deprivation Index (NDI). This is a standardized and reproducible index used in research that summarizes eight domains of socioeconomic deprivation. It is based on census tract data derived from the patients' addresses at the time of the operation. The higher the number, the worse the patients' SES is. The association between SES and severity of the vein disease at presentation was studied with bivariate analysis of variance and linear regression analysis. Results: A total of 449 patients had complete SES and Clinical, Etiology, Anatomy, and Pathophysiology (CEAP) class data and were included in the study. The mean age was 58 years; 67% were female, and 60% were white. CEAP class included the following: C2, 22%; C3, 50%; C4, 15%; C5, 5%; and C6, 8%. The average NDI was 0.03 (minimum, −1.45; maximum, 2.89). There was a linear correlation between the CEAP class at presentation and the NDI ($P < .05$; Fig). SES was not associated with history of deep venous thrombosis, prior vein treatment, use of compression therapy, or Venous Clinical Severity Score. Conclusions: CEAP class at presentation for treatment of chronic venous disease is associated with SES. This may reflect that patients with a lower SES wait longer before seeking medical therapy for venous disease. [Formula presented]

Books and Book Chapters

Hypertension and Vascular Research

Munukutla S, **Pan G**, and **Palaniyandi SS**. Aldehyde Dehydrogenase (ALDH) 2 in Diabetic Heart Diseases. *Adv Exp Med Biol* 2019; 1193:155-174. PMID: 31368103. Request Book Chapter

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A major pathophysiological mechanism behind the development of diabetic heart diseases is oxidative stress mediated by toxic reactive aldehydes such as 4-hydroxynonenal (4HNE). Aldehyde dehydrogenase (ALDH) 2 is a mitochondrial enzyme that has been found to detoxify these deleterious aldehydes and thereby mitigate cardiac damage. Furthermore, its protective role in cellular signaling reverses aberrations caused by hyperglycemia, thereby protecting cardiac function. This chapter assesses the role of ALDH2 in diabetic heart diseases by examining preclinical studies where ALDH2 activity is perturbed in both decreased and increased directions. In doing so, issues in improving ALDH2 activity in select human populations are elucidated, and further research directions are discussed.