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Henry Ford Health System

Henry Ford Health System Publication List – September 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 Web of Science during the month, and then imported into EndNote for formatting. There are **113 unique citations** listed this month, with **11 articles on COVID-19**. Articles are listed first, followed by conference abstracts, books and book chapters, and a bibliography of publications on COVID-19. 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

Miller J, **Fadel RA**, **Tang A**, **Perrotta G**, **Herc E**, **Soman S**, **Nair S**, **Hanna Z**, **Zervos MJ**, **Alangaden G**, **Brar I**, and **Suleyman G**. The Impact of Sociodemographic Factors, Comorbidities and Physiologic Response on 30-day Mortality in COVID-19 Patients in Metropolitan Detroit. *Clin Infect Dis* 2020; Epub ahead of print. PMID: 32945856. Full Text

Henry Ford Hospital, Detroit, MI, USA.
Wayne State University, Detroit, MI, USA.

BACKGROUND: The relationship of health disparities and comorbidities in coronavirus disease 2019 (COVID-19) related outcomes are an ongoing area of interest. This report assesses risk factors associated with mortality in patients presenting with Covid-19 infection and healthcare disparities. METHODS: A retrospective cohort study of consecutive patients presenting to emergency departments within an integrated health system who tested positive for COVID-19 between March 7 and April 30, 2020 in Metropolitan Detroit. The primary outcomes were hospitalization and 30-day mortality. RESULTS: A total of 3,633 patients with mean age of 58 years were included. The majority were female and black non-Hispanic. Sixty-four percent required hospitalization, 56% of whom were black. Hospitalized patients were older, more likely to reside in a low-income area, and had a higher burden of comorbidities. By 30-days, 433 (18.7%) hospitalized patients died. In adjusted analyses, the presence of comorbidities, age >60 years and more severe physiological disturbance were associated with 30-day mortality. Residence in low income areas (odds ratio, 1.02; 95% confidence interval 0.76 - 1.36), and public insurance (odds ratio, 1.24; 95% confidence interval 0.76 - 2.01) were not independently associated with higher risk of mortality. Black female patients had a lower adjusted risk of mortality (odds ratio, 0.46; 95% confidence interval, 0.27 to 0.78). CONCLUSIONS: In this large cohort of COVID-19 patients, those with comorbidities, advanced age, and physiological abnormalities on presentation had higher odds of death. Disparities in income or source of health insurance were not associated with outcomes. Black women had a lower risk of dying.

Anesthesiology

Peleman JR, **Tarwade P**, **Han X**, **Penning DH**, and **Craig JR**. Hemodynamic Changes with 1:1000 Epinephrine on Wrung-Out Pledgets Before and During Sinus Surgery. *Ann Otol Rhinol Laryngol* 2020; Epub ahead of print. PMID: 32945177. Full Text

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BACKGROUND: Intranasal topical 1:1000 epinephrine has been used safely and effectively for hemostasis during endoscopic sinus surgery (ESS). Prior studies assessing hemodynamic changes after intranasal topical epinephrine application have only used soaking wet cottonoid pledgets, and have only assessed for hemodynamic changes before any surgery being performed. OBJECTIVE: The purposes of this study were to determine whether intranasal application of topical 1:1000 epinephrine with wrung-out cottonoid pledgets caused significant hemodynamic changes both before and during ESS, and whether it allowed for adequate hemostasis. METHODS: A prospective evaluation of 30 patients with eosinophilic chronic rhinosinusitis with nasal polyps (CRSwNP) undergoing complete bilateral ESS was conducted. Heart rate, blood pressure (systolic, diastolic, and mean arterial pressure), and electrocardiography changes were recorded at 0, 1, 2, and 5-minute intervals after placing wrung-out epinephrine-saturated pledgets, both before and at the end of ESS. No submucosal epinephrine injections were performed. Estimated blood loss (EBL) and major intraoperative complications were recorded for all cases. RESULTS: There were no significant hemodynamic changes or electrocardiographic abnormalities after placement of wrung-out epinephrine-soaked pledgets both before and after ESS. After bilateral ESS, there were actually mean decreases in heart rate and blood pressure parameters. Mean EBL was 75.8 ± 32.2 mL, and no major intraoperative complications occurred. CONCLUSION: Intranasal application of topical 1:1000 epinephrine via wrung-out cottonoid pledgets was effective for intraoperative hemostasis, and did not cause clinically significant alterations in hemodynamic parameters or cardiovascular events, either before or during ESS in patients with CRSwNP.Level of Evidence: 4.

Behavioral Health Services/Psychiatry

Gautam M, Kaur M, and **Mahr G**. COVID-19-Associated Psychiatric Symptoms in Health Care Workers: Viewpoint From Internal Medicine and Psychiatry Residents. *Psychosomatics* 2020; 61(5):579-581. PMID: 32439184. Full Text

Department of Psychiatry, Henry Ford Hospital/Wayne State University, Detroit, MI.
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Department of Psychiatry, Henry Ford Health System/Wayne State University, Detroit, MI.

Behavioral Health Services/Psychiatry

Jesse MT, Hansen B, Bruschwein H, Chen G, Nonterah C, Peipert JD, Dew MA, Thomas C, Ortega AD, Balliet W, Ladin K, Lerret S, Yaldo A, Coco T, and Mallea J. Findings and Recommendations from the Organ Transplant Caregiver Initiative: Moving Clinical Care and Research Forward. *Am J Transplant* 2020; Epub ahead of print. PMID: 32946643. Full Text

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Psychiatry & Behavioral Neurosciences, Wayne State School of Medicine, Detroit, MI, USA.
Mayo Clinic Hospital, Phoenix, AZ, USA.
Psychiatry and Neurobehavioral Sciences, University of Virginia School of Medicine, Charlottesville, VA, USA.
Memorial Hermann Hospital Transplant Center, Houston, TX, USA.
Department of Psychology, University of Richmond, Richmond, VA, USA.
Department of Psychiatry, Virginia Commonwealth University School of Medicine, Richmond, VA, USA.
Northwestern University Feinberg School of Medicine, Chicago, IL, USA.
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Memorial Transplant Institute, Hollywood, FL, USA.
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Lay-caregivers are essential to the continuum of care in adult organ transplantation. However, we have a limited understanding of the experiences, exigencies, and outcomes associated with lay-caregiving for organ transplant patients. While much discussion and debate has focused on caregiver requirements in relation to transplant candidate selection, little focus has been given to understanding the needs of caregivers themselves. In response to this, the Organ Transplant Caregiver Initiative was created, and a meeting held October 6-7, 2019. Transplant healthcare professionals, researchers, and lay-caregivers discussed the experiences, educational needs, existing research, and research recommendations to improve the experience of lay-caregivers for adult organ transplant

patients. In this report, we summarize the Organ Transplant Caregiver Initiative and meeting findings, providing a preliminary action plan to improve education, research, and advocacy for organ transplant caregivers.

Behavioral Health Services/Psychiatry
Sablaban IM, and **Gautam M**. The diagnosis of severe obsessions in the setting of kratom withdrawal and treatment with lorazepam: Case report. *J Addict Dis* 2020; Epub ahead of print. PMID: 32924857. Request Article

Department of Psychiatry, Henry Ford Hospital/Wayne State University, Detroit, MI, USA.

Commercially available Kratom (Mitragyna speciosa) is a dietary supplement that has gained popularity in the United States for its psychoactive effects and potential medicative properties as an opioid receptor agonist. Likewise, sudden discontinuation may be accompanied by an opioid-like withdrawal. We present the first case in the literature of the withdrawal manifesting in disturbing obsessive thoughts after the substance was used as an opioid replacement treatment by our patient, as well as the first case where lorazepam is utilized for mitigation of these thoughts.

Cardiology/Cardiovascular Research
Afana M, **Altawil M**, **Basir M**, **Alqarqaz M**, **Alaswad K**, **Eng M**, **O'Neill WW**, Lederman RJ, and Greenbaum AB. Transcaval access for the emergency delivery of 5.0 liters per minute mechanical circulatory support in cardiogenic shock. *Catheter Cardiovasc Interv* 2020; Epub ahead of print. PMID: 32902101. Full Text

Division of Cardiology, Henry Ford Health System, Detroit, Michigan, USA.
Center for Structural Heart Disease, Henry Ford Health System, Detroit, Michigan, USA.
Cardiovascular Branch, Division of Intramural Research, National Heart Lung and Blood Institute, National Institutes of Health, Bethesda, Maryland, USA.
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OBJECTIVES: The purpose of this study was to describe the feasibility and early outcomes of transcaval access for delivery of emergency mechanical circulatory support (MCS) in cardiogenic shock. BACKGROUND: Vascular access for implantation of MCS in patients with cardiogenic shock is often challenging due to peripheral arterial disease and vasoconstriction. Transcaval delivery of MCS may be an alternative. We describe a series of patients we implanted an Impella 5.0 device, on-table without CT planning, through a percutaneous transcaval access route. METHODS: Ten patients with progressive or refractory cardiogenic shock underwent Impella 5.0 implantation via transcaval access. Demographic, clinical and procedural variables and in-hospital outcomes were collected. RESULTS: All ten underwent emergency implantation of the 7 mm diameter Impella 5.0 device via transcaval access. Six were women, with median age of 55.5 years (range, 29-69). Cardiogenic shock was attributed to idiopathic nonischemic cardiomyopathy (n = 4), myocarditis (n = 2), ischemic cardiomyopathy (n = 2), heart transplant rejection (n = 1), and unknown etiology (n = 1). Median duration of support was 92.1 hr (range, 21.2-165.4). Seven (70%) survived to device explant, with six (60%) surviving to access port closure and discharge. Among survivors, five recovered heart function and one received destination therapy left ventricular assist device. CONCLUSIONS: Transcaval access is feasible for emergency nonsurgical implantation of the Impella 5.0 device in cardiogenic shock with small or diseased iliofemoral arteries. This allows early institution of higher-flow MCS than conventional femoral artery implantation of the 3.5 L Impella CP device, and enables a bridge-to-recovery or bridge-to-destination strategy.

Cardiology/Cardiovascular Research
Al-Darzi W, **Aurora L**, **Michaels A**, **Cowger J**, **Grafton G**, **Selektor Y**, **Tita C**, **Hannawi B**, **Lanfear D**, **Nemeh HW**, and **Williams CT**. Heart Transplant Recipients with Confirmed 2019 Novel Coronavirus Infection: The Detroit Experience. *Clin Transplant* 2020; e14091. Epub ahead of print. PMID: 32940925. Full Text

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A chronic immunosuppressed state as in solid organ transplant recipients is a reported risk factor for the novel 2019 coronavirus infection. Patients with a history of orthotopic heart transplant (OHT) at a tertiary care transplant center in Detroit, Michigan were retrospectively reviewed from March until May 2020. Clinical parameters and outcomes of 5 OHT recipients and one combined heart-lung recipient with confirmed SARS-CoV-2 were obtained. The cohort was predominately African American males with median age of 59 years (Interquartile Range, 48.25-73.25). All patients were classified as having mild-moderate disease; none required intubation or ICU admission with no deaths. The most common presenting symptoms were fever and shortness of breath 83% (n=5), followed by cough and chills 67% (n=4). All admitted patients (n=5) received hydroxychloroquine and 3 received high dose steroids. Antimetabolites were held for 2 patients (33.3%). The calcineurin inhibitor trough goal was decreased in only 1 patient; 3 other patients, without change in goal, required calcineurin inhibitor dosage reduction. Two patients requiring readmission presented 7 and 23 days after initial symptoms onset. In conclusion, our experience with OHT patients infected by the

SARS-CoV-2 virus did not have an elevated risk of severe infection. Impact of modifying immunosuppression remains unclear.

Cardiology/Cardiovascular Research

Aurora L, **Peterson E**, **Gui H**, **Zeld N**, **McCord J**, Pinto Y, **Cook B**, **Sabbah HN**, **Keoki Williams L**, Snider J, and **Lanfear DE**. Suppression Tumorigenicity 2 (ST2) Turbidimetric Immunoassay Compared to Enzyme-Linked Immunosorbent Assay in Predicting Survival in Heart Failure Patients with Reduced Ejection Fraction. *Clin Chim Acta* 2020; Epub ahead of print. PMID: 32926842. Request Article

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BACKGROUND: Suppressor of tumorigenicity 2 (ST2) is a powerful marker of prognosis and treatment response in heart failure (HF), however, it is an enzyme-linked immunosorbent assay (ELISA) which may be cumbersome and costly. A turbidimetric immunoassay (TIA) that can run on common chemistry analyzers could overcome this. We studied a novel TIA for ST2, comparing it to commercial ST2 (ELISA). METHODS: Patients age ≥18 years meeting Framingham definition for HF were enrolled in a prospective registry (Oct 2007 - March 2015) at Henry Ford Hospital and donated blood samples. Participants with reduced ejection fraction (<50%) and available plasma samples were included and valid ST2 measurements were obtained on the same sample using both TIA and ELISA (N=721). The primary endpoint was all cause death. Correlation between the methods was quantified. The association with survival was tested using unadjusted and adjusted (for MAGGIC score and NTproBNP) Cox models and comparing the Area Under the Curve (AUC). RESULTS: The inter-assay Spearman correlation coefficient was 0.77. Nonparametric regression showed no significant proportional difference (slope = 0.97) and a very small systematic difference (3.2 ng/mL). In univariate analyses both TIA and ELISA ST2 were significant associates of survival with similar effect sizes (HR 4.46 and 3.50, respectively, both p<0.001). In models adjusted for MAGGIC score both ST2 remained significant in Cox models and incrementally improved AUC vs. MAGGIC alone (MAGGIC AUC= 0.757; TIA+MAGGIC AUC=0.786, p=0.025; ELISA+MAGGIC AUC=0.793, p=0.033). In models with both MAGGIC and NTproBNP included, both ST2 still remained significant but did not improve AUC. CONCLUSIONS: A novel TIA method for ST2 quantification correlates highly with ELISA and offers similarly powerful risk-stratification.

Cardiology/Cardiovascular Research

Davies RE, Prasad M, **Alaswad K**, Riley RF, Meraj P, Thompson C, Maran A, Karmpaliotis D, McCabe JM, Kirtane AJ, and Lombardi WL. Training in high-risk coronary procedures and interventions: Recommendations for core competencies. *Catheter Cardiovasc Interv* 2020; Epub ahead of print. PMID: 32915494. Full Text

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Cardiology/Cardiovascular Research

Mirza KK, Xie R, **Cowger J**, Kirklin JK, Meyns B, Gustafsson F, Shaw SM, and Goldstein DJ. Comparative analysis of regional outcomes and adverse events after continuous-flow left ventricular assist device implantation: An IMACS analysis. *J Heart Lung Transplant* 2020; 39(9):904-914. PMID: 32487472. Full Text

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INTRODUCTION: Regional outcomes after implantation of continuous-flow left ventricular assist devices (LVADs) have not been described. We examined differences in patient selection, survival, and adverse events across 3 geographic regions of the world: the Americas, Asia-Pacific, and Europe. METHODS: Using data from The International Society for Heart and Lung Transplantation Mechanically Assisted Circulatory Support registry, all adult patients implanted with a continuous-flow LVADs were included in this International Society for Heart and Lung Transplantation Mechanically Assisted Circulatory Support analysis (n = 15,560), of whom, 9,988 (64%) received axial-flow devices and 5,572 (36%) received centrifugal-flow devices. RESULTS: There were significant interregional differences in the rate of implantation of patients aged >70 years (Americas: 14%, Asia-Pacific: 1%, Europe: 5%; $p < 0.0001$), morbidly obese (Americas: 5%, Asia-Pacific: 1%, Europe: 1%; $p < 0.0001$), male (Americas: 79%, Asia-Pacific: 77%, Europe: 85%; $p < 0.0001$), and implanted as destination therapy (Americas: 48%, Asia-Pacific: 4%, Europe: 22%; $p < 0.0001$). The rates of centrifugal pump usage varied by region (Americas: 30%, Asia-Pacific: 34%, Eu: 74%; $p < 0.0001$). Survival rates varied by region and the type of pump flow, with survival at 12 and 48 months (axial flow vs centrifugal flow) being 82% vs 82% and 52% vs 53 in Americas; 92% vs 86% and 83% vs 74% in Asia-Pacific; and 80% vs 75% and 69% vs 53% in Europe, respectively (regional survival $p < 0.0001$). CONCLUSION: There are marked global differences in LVAD recipient characteristics, device utilization, and post-operative care. These heterogeneities along with differences in patient management and transplantation rates may impact long-term survival. Regional differences in adverse event incidence warrant further investigation.

Cardiology/Cardiovascular Research
Patel S, **Jamoor K**, **Khan A**, and **Maskoun W**. Late onset complete heart block after transcatheter aortic valve replacement treated with permanent his-bundle pacing. *Pacing Clin Electrophysiol* 2020; Epub ahead of print. PMID: 32940376. Full Text

Division of Cardiovascular Disease, Henry Ford Health System.
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Transcatheter aortic valve replacement (TAVR) is a rapidly growing procedure. Conduction disease post TAVR is frequent and routinely monitored for peri-procedurally. Permanent pacemaker placement is relatively common and usually associated with worse outcomes post TAVR. We report a case of very late presenting complete heart block post TAVR treated with His pacing. Our case underscores the need for larger studies to further evaluate the utility of long-term cardiac monitoring post TAVR and outcomes of His bundle pacing in this population. This article is protected by copyright. All rights reserved.

Cardiology/Cardiovascular Research
Qintar M, and Chhatriwalla AK. Update on the Current Status and Indications for Transcatheter Edge-to-Edge Mitral Valve Repair. *Curr Cardiol Rep* 2020; 22(11):135. PMID: 32910371. Full Text

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PURPOSE OF REVIEW: To review the current status and indications of transcatheter edge-to-edge mitral valve repair. RECENT FINDINGS: Mitral regurgitation remains a common valvular disease and can be classified as degenerative (primary) or functional (secondary). Randomized controlled trials have shown that transcatheter edge-to-edge mitral valve repair with MitraClip is successful, safe, and effective in reducing mitral regurgitation. The US Food and Drug Administration approved MitraClip in 2013 for treatment of patients with primary mitral regurgitation at prohibitive surgical risk and in 2019 for secondary mitral regurgitation. Several MitraClip generations exist (NT/R, XT/R, NTW, and XTW) with unique features and considerations. Additional edge-to-edge repair, non-edge-to-edge repair, and transcatheter valve replacement systems are under investigation as stand-alone or adjunctive therapy for patients with mitral regurgitation. Mitral regurgitation remains a significant health burden and many patients are not suitable for surgical repair or replacement. Transcatheter mitral valve therapies can be considered in selected patients and are safe and effective. More research is needed to understand how to best select devices and patients and optimize outcomes.

Cardiology/Cardiovascular Research
Ranka S, Mohananey D, Agarwal N, Verma BR, **Villablanca P**, Mewhort HE, and Ramakrishna H. Chronic Thromboembolic Pulmonary Hypertension-Management Strategies and Outcomes. *J Cardiothorac Vasc Anesth* 2020; 34(9):2513-2523. PMID: 31883688. Full Text

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Chronic thromboembolic pulmonary hypertension (CTEPH) is rare but complex pathophysiological disease with hallmark features of chronic thrombotic mechanical obstruction, right ventricular dysfunction, and secondary pulmonary arteriopathy. It increasingly is being understood that chronic infection/inflammation, abnormal fibrinolysis, and cytokines play an important role in pathogenesis such that only a subset of patients with pulmonary embolism develop CTEPH. Diagnosis remains challenging given the lack of early clinical signs and overlap with other cardiopulmonary conditions. Pulmonary endarterectomy is the surgical procedure of choice with good postoperative survival and functional outcomes, especially when done at high-volume centers with a multidisciplinary approach. There has been a resurgence of balloon pulmonary angioplasty (BPA) as salvage therapy for inoperable CTEPH or in its newfound hybrid role for persistent postoperative pulmonary hypertension with excellent 1-year and 3-year survival. Use of riociguat has shown promising improvements in functional outcomes up to 2 years after initiation. Endothelin receptor antagonists serve a supplemental role postoperatively or in inoperable CTEPH. The role of drug therapy preoperatively or in tandem with BPA is currently under investigation.

Cardiology/Cardiovascular Research
Salih M, Ali SM, Jena N, and **Ananthasubramaniam K**. Review of ultrasound contrast agents in current clinical practice with special focus on DEFINITY(®) in cardiac imaging. *Future Cardiol* 2020; Epub ahead of print. PMID: 32897099. Request Article

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Echocardiography is the most widely used noninvasive modality to evaluate the structure and function of the cardiac muscle in daily practice. However, up to 15-20% of echocardiograms are considered suboptimal. To enable accurate assessment of cardiac function and wall motion abnormality, the use of ultrasound microbubble contrast has shown substantial benefits in cases of salvaging nondiagnostic studies and enhancing the diagnostic accuracy in daily practice. DEFINITY(®) is a perflutren based, lipid shelled microbubble contrast agent, which is US FDA approved for left ventricular opacification. The basis of ultrasound microbubbles, its development, and the clinical role of DEFINITY (characteristics, indications and case examples, side effect profile and existing evidence) is the subject of discussion in this review.

Cardiology/Cardiovascular Research
Simonato M, Whisenant B, Barbosa Ribeiro H, Webb JG, Kornowski R, Guerrero M, Wijeysundera H, Søndergaard L, De Backer O, **Villablanca P**, Rihal C, Eleid M, Kempfert J, Unbehaun A, Erlebach M, Casselman F, Adam M, Montorfano M, Ancona M, Saia F, Ubben T, Meincke F, Napodano M, Codner P, Schofer J, Pelletier M, Cheung A, Shuvy M, Palma JH, Gaia DF, Duncan A, Hildick-Smith D, Veulemans V, Sinning JM, Arbel Y, Testa L, de Weger A, Eltchaninoff H, Hemery T, Landes U, Tchetche D, Dumonteil N, Rodés-Cabau J, Kim WK, Spargias K, Kourkoveli P, Ben-Yehuda O, Campante Teles R, Barbanti M, Fiorina C, Thukkani A, Mackensen GB, Jones N, Presbitero P, Petronio AS, Allali A, Champagnac D, Bleiziffer S, Rudolph T, Iadanza A, Salizzoni S, Agrifoglio M, Nombela-Franco L, Bonaros N, Kass M, Bruschi G, Amabile N, Chhatriwalla A, Messina A, Hirji SA, Andreas M, Welsh R, Schoels W, Hellig F, Windecker S, Stortecky S, Maisano F, Stone GW, and Dvir D. Transcatheter Mitral Valve Replacement After Surgical Repair or Replacement: Comprehensive Mid-Term Evaluation of Valve-in-Valve and Valve-in-Ring Implantation from the VIVID Registry. *Circulation* 2020; Epub ahead of print. PMID: 32975133. Full Text

Background: Mitral valve-in-valve (ViV) and valve-in-ring (ViR) are alternatives to surgical reoperation in patients with recurrent mitral valve failure after previous surgical valve repair or replacement. Our aim was to perform a large-scale analysis examining mid-term outcomes after mitral ViV and ViR. Methods: Patients undergoing mitral ViV and ViR were enrolled in the Valve-in-Valve International Data Registry. Cases were performed between March 2006 and

March 2020. Clinical endpoints are reported according to the Mitral Valve Academic Research Consortium (MVARC) definitions. Significant residual mitral stenosis (MS) was defined as mean gradient ≥10 mmHg and significant residual mitral regurgitation (MR) as ≥ moderate. Results: A total of 1,079 patients (857 ViV, 222 ViR; mean age 73.5 years ± 12.5; 40.8% male) from 90 centers were included. Median STS-PROM score 8.6%; median clinical follow-up 492 days [IQR 76 - 996 days]; median echocardiographic follow-up for patients that survived 1 year 772.5 days [IQR 510 - 1211.75 days]. Four-year Kaplan-Meier survival rate was 62.5% in ViV vs. 49.5% for ViR (p<0.001). Mean gradient across the mitral valve post-procedure was 5.7 ± 2.8 mmHg (≥5mmHg, 61.4% of patients). Significant residual MS occurred in 8.2% of the ViV and 12.0% of the ViR patients (p=0.09). Significant residual MR was more common in ViR patients (16.6% vs. 3.1%; p<0.001) and was associated with lower survival at 4 years (35.1% vs. 61.6%; p=0.02). The rates of MVARC-defined device success were low for both procedures (39.4% total; 32.0% ViR vs. 41.3% ViV; p=0.01), mostly related to having post-procedural mean gradient ≥5mmHg. Correlates for residual MS were smaller true internal diameter, younger age and larger body mass index. The only correlate for residual MR was ViR. Significant residual MS (SHR 4.67; 95% CI 1.74 - 12.56; p=0.002) and significant residual MR (SHR 7.88; 95% CI 2.88 - 21.53; p<0.001) were both independently associated with repeat mitral valve replacement. Conclusions: Significant residual MS and/or MR were not infrequent after mitral ViV and ViR procedures and were both associated with a need for repeat valve replacement. Strategies to improve post-procedural hemodynamics in mitral ViV and ViR should be further explored.

Cardiology/Cardiovascular Research

Tehrani BN, **Basir MB**, and Kapur NK. Acute myocardial infarction and cardiogenic shock: Should we unload the ventricle before percutaneous coronary intervention? *Prog Cardiovasc Dis* 2020; Epub ahead of print. PMID: 32920027. Full Text

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Despite early reperfusion and coordinated systems of care, cardiogenic shock (CS) remains the number one cause of morbidity and in-hospital mortality following acute myocardial infarction (AMI). CS is a complex clinical syndrome that begins with hemodynamic instability and can progress to multi-organ failure and profound hemo-metabolic compromise. To improve outcomes, a clear understanding of the treatment objectives in CS and developing time-sensitive management strategies aimed at stabilizing hemodynamics and restoring myocardial perfusion are critical. Left ventricular (LV) load has been identified as an independent predictor of heart failure and mortality following AMI. Decades of preclinical and clinical research have identified several effective LV unloading strategies. Recent initiatives from single and multi-center registries and more recently the Door to Unload (DTU)-STEMI pilot study have provided valuable insight to developing a standardized treatment approach to AMI, based on early invasive hemodynamics and tailored circulatory support to unload the LV. To follow is a review of the pathophysiology and prevalence of shock, limitations of current therapies, and the pre-clinical and translational basis for incorporating LV unloading into contemporary AMI and shock care.

Cardiology/Cardiovascular Research

Thayer KL, Zweck E, Ayouty M, Garan AR, Hernandez-Montfort J, Mahr C, Morine KJ, Newman S, Jorde L, Haywood JL, Harwani NM, Esposito ML, Davila CD, Wencker D, Sinha SS, Vorovich E, Abraham J, **O'Neill W**, Udelson J, Burkhoff D, and Kapur NK. Invasive Hemodynamic Assessment and Classification of In-Hospital Mortality Risk Among Patients With Cardiogenic Shock. *Circ Heart Fail* 2020; 13(9):e007099. PMID: 32900234. Full Text

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BACKGROUND: Risk stratifying patients with cardiogenic shock (CS) is a major unmet need. The recently proposed Society for Cardiovascular Angiography and Interventions (SCAI) stages as an approach to identify patients at risk for in-hospital mortality remains under investigation. We studied the utility of the SCAI stages and further explored the impact of hemodynamic congestion on clinical outcomes. METHODS: The CS Working Group registry includes patients with CS from 8 medical centers enrolled between 2016 and 2019. Patients were classified by the maximum SCAI stage (B-E) reached during their hospital stay according to drug and device utilization. In-hospital mortality was evaluated for association with SCAI stages and hemodynamic congestion. RESULTS: Of the 1414 patients with CS, the majority were due to decompensated heart failure (50%) or myocardial infarction (MI; 35%). In-hospital mortality was 31% for the total cohort, but higher among patients with MI (41% versus 26%, MI versus heart failure, P<0.0001). Risk for in-hospital mortality was associated with increasing SCAI stage (odds ratio [95% CI], 3.25 [2.63-4.02]) in both MI and heart failure cohorts. Hemodynamic data was available in 1116 (79%) patients. Elevated biventricular filling pressures were common among patients with CS, and right atrial pressure was associated with increased mortality and higher SCAI Stage. CONCLUSIONS: Our findings support an association between the proposed SCAI staging system and in-hospital mortality among patient with heart failure and MI. We further identify that venous congestion is common and identifies patients with CS at high risk for in-hospital mortality. These findings provide may inform future management protocols and clinical studies.

Cardiology/Cardiovascular Research

Vemmou E, **Alaswad K**, Khatri JJ, Nikolakopoulos I, Karacsonyi J, Xenogiannis I, Karmpaliotis D, Garcia S, Burke MN, and Brilakis ES. Patient Radiation Dose During Chronic Total Occlusion Percutaneous Coronary Intervention: Insights From the PROGRESS-CTO Registry. *Circ Cardiovasc Interv* 2020; Epub ahead of print. PMID: 32972204. Full Text

Minneapolis Heart Institute Foundation, MN (E.V., I.N., J.K., I.X., S.G, M.N.B., E.S.B.).
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Center for Individualized and Genomic Medicine Research

Aurora L, **Peterson E**, **Gui H**, **Zeld N**, **McCord J**, Pinto Y, **Cook B**, **Sabbah HN**, **Keoki Williams L**, Snider J, and **Lanfear DE**. Suppression Tumorigenicity 2 (ST2) Turbidimetric Immunoassay Compared to Enzyme-Linked Immunosorbent Assay in Predicting Survival in Heart Failure Patients with Reduced Ejection Fraction. *Clin Chim Acta* 2020; Epub ahead of print. PMID: 32926842. Request Article

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BACKGROUND: Suppressor of tumorigenicity 2 (ST2) is a powerful marker of prognosis and treatment response in heart failure (HF), however, it is an enzyme-linked immunosorbent assay (ELISA) which may be cumbersome and costly. A turbidimetric immunoassay (TIA) that can run on common chemistry analyzers could overcome this. We studied a novel TIA for ST2, comparing it to commercial ST2 (ELISA). METHODS: Patients age ≥18 years meeting Framingham definition for HF were enrolled in a prospective registry (Oct 2007 - March 2015) at Henry Ford Hospital and donated blood samples. Participants with reduced ejection fraction (<50%) and available plasma samples were included and valid ST2 measurements were obtained on the same sample using both TIA and ELISA (N=721). The primary endpoint was all cause death. Correlation between the methods was quantified. The association with survival was tested using unadjusted and adjusted (for MAGGIC score and NTproBNP) Cox models and comparing the Area Under the Curve (AUC). RESULTS: The inter-assay Spearman correlation coefficient was 0.77. Nonparametric regression showed no significant proportional difference (slope = 0.97) and a very small systematic difference (3.2 ng/mL). In univariate analyses both TIA and ELISA ST2 were significant associates of survival with similar effect sizes (HR 4.46 and 3.50, respectively, both p<0.001). In models adjusted for MAGGIC score both ST2 remained significant in Cox models and incrementally improved AUC vs. MAGGIC alone (MAGGIC AUC= 0.757; TIA+MAGGIC AUC=0.786, p=0.025; ELISA+MAGGIC AUC=0.793, p=0.033). In models with both MAGGIC and NTproBNP

included, both ST2 still remained significant but did not improve AUC. CONCLUSIONS: A novel TIA method for ST2 quantification correlates highly with ELISA and offers similarly powerful risk-stratification.

Center for Individualized and Genomic Medicine Research

Gui H, **Levin AM**, Hu D, Sleiman P, **Xiao S**, Mak AC, **Yang M**, Barczak AJ, Huntsman S, Eng C, **Hochstadt S**, **Zhang E**, **Whitehouse K**, **Simons S**, **Cabral W**, **Takriti S**, Abecasis G, Blackwell TW, Kang HM, Nickerson DA, Germer S, **Lanfear DE**, Gilliland F, Gauderman WJ, Kumar R, Erle DJ, Martinez FD, Hakonarson H, Burchard EG, and **Williams LK**. Mapping the 17q12-21.1 Locus for Variants Associated with Early-onset Asthma in African Americans. *Am J Respir Crit Care Med* 2020; Epub ahead of print. PMID: 32966749. Full Text

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RATIONALE: The 17q12-21.1 locus is one of the most highly replicated genetic associations with asthma. Individuals of African descent have lower LD in this region, which could facilitate identifying causal variants. OBJECTIVE: To identify functional variants at 17q12-21.1 associated with early-onset asthma among African American individuals. METHODS AND MEASUREMENTS: We evaluated African American participants from the Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-ethnicity (SAPPHIRE) (n=1,940), the Study of African Americans, Asthma, Genes & Environment (SAGE II) (n=885), and Study of the Genetic Causes of Complex Pediatric Disorders - Asthma (GCPD-A) (n=2,805). Associations with asthma onset at age <5 years were meta-analyzed across cohorts. The lead signal was reevaluated considering haplotypes informed by genetic ancestry (i.e., African vs. European). Both an expression quantitative trait locus (eQTL) analysis and phenome-wide association study (PheWAS) were performed on the lead variant. MAIN RESULTS: The meta-analyzed results from SAPPHIRE, SAGE II, and GCPD-A identified rs11078928 as the top association for early-onset asthma. A haplotype analysis suggested that the asthma association partitioned most closely with rs11078928 genotype. Genetic ancestry did not appear to influence the effect of this variant. In the eQTL analysis, rs11078928 was related to alternative splicing of gasdermin-B (GSDMB) transcripts. The PheWAS of rs11078928 suggested that this variant was predominantly associated with asthma and asthma-associated symptoms. CONCLUSIONS: A splice acceptor polymorphism appears to be a causal variant for asthma at the 17q12-21.1 locus. This variant appears to have the same magnitude of effect in individuals of African and European descent.

Dermatology

Fu C, Peng P, Loschko J, Feng L, Pham P, Cui W, Lee KP, Krug AB, and **Jiang A**. Plasmacytoid dendritic cells cross-prime naive CD8 T cells by transferring antigen to conventional dendritic cells through exosomes. *Proc Natl Acad Sci U S A* 2020; 117(38):23730-23741. PMID: 32879009. Full Text

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Although plasmacytoid dendritic cells (pDCs) have been shown to play a critical role in generating viral immunity and promoting tolerance to suppress antitumor immunity, whether and how pDCs cross-prime CD8 T cells in vivo remain controversial. Using a pDC-targeted vaccine model to deliver antigens specifically to pDCs, we have demonstrated that pDC-targeted vaccination led to strong cross-priming and durable CD8 T cell immunity. Surprisingly, cross-presenting pDCs required conventional DCs (cDCs) to achieve cross-priming in vivo by transferring antigens to cDCs. Taking advantage of an in vitro system where only pDCs had access to antigens, we further demonstrated that cross-presenting pDCs were unable to efficiently prime CD8 T cells by themselves, but conferred antigen-naive cDCs the capability of cross-priming CD8 T cells by transferring antigens to cDCs. Although both cDC1s and cDC2s exhibited similar efficiency in acquiring antigens from pDCs, cDC1s but not cDC2s were required for cross-priming upon pDC-targeted vaccination, suggesting that cDC1s played a critical role in pDC-mediated cross-priming independent of their function in antigen presentation. Antigen transfer from pDCs to cDCs was mediated by previously unreported pDC-derived exosomes (pDCexos), that were also produced by pDCs under various conditions. Importantly, all these pDCexos primed naive antigen-specific CD8 T cells only in the presence of bystander cDCs, similarly to cross-presenting pDCs, thus identifying pDCexo-mediated antigen transfer to cDCs as a mechanism for pDCs to achieve cross-priming. In summary, our data suggest that pDCs employ a unique mechanism of pDCexo-mediated antigen transfer to cDCs for cross-priming.

Dermatology

Lebwohl M, Kircik L, Lacour JP, Liljedahl M, Lynde C, Mørch MH, Papp KA, Perrot JL, **Gold LS**, Takhar A, Thaçi D, Warren RB, and Wollenberg A. Twice-weekly topical calcipotriene / betamethasone dipropionate foam as proactive management of plaque psoriasis increases time in remission and is well tolerated over 52 weeks (PSO-LONG trial). *J Am Acad Dermatol* 2020; Epub ahead of print. PMID: 32950546. Full Text

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BACKGROUND: Topical psoriasis treatment relies on a reactive, rather than long-term proactive, approach to disease relapse. OBJECTIVE: Assess long-term efficacy and safety of proactive psoriasis management with twice-weekly calcipotriene 0.005%/betamethasone dipropionate 0.064% (Cal/BD) foam. METHODS: Phase III trial (NCT02899962) included a 4-week open-label lead-in phase (Cal/BD foam once-daily) and 52-week, randomized, double-blind, maintenance phase. 545 patients achieved treatment success PGA 'clear'/'almost clear', ≥2-grade improvement from baseline) and were randomized to 'proactive' management (Cal/BD foam; n = 272) or 'reactive' management (vehicle foam; n = 273) twice-weekly, with rescue treatment of Cal/BD foam once-daily for 4 weeks upon relapse. Primary endpoint: time to first relapse (PGA ≥'mild'). RESULTS: 251 (46.1%) randomized patients completed the trial. Median time to first relapse: 56 days (proactive), 30 days (reactive). Patients in the proactive group had an additional 41 days in remission compared with the reactive group over 1 year ($P < 0.001$). Number of relapses per year of exposure: 3.1 (proactive), 4.8 (reactive). Cal/BD foam was well tolerated. LIMITATIONS: Maintenance phase dropout rate (53.9%) was within the expected range but provides challenges in statistical analysis. CONCLUSION: Long-term proactive management with Cal/BD foam demonstrated superior efficacy versus reactive management.

Dermatology

Li D, **Peng H**, **Qu L**, Sommar P, Wang A, Chu T, Li X, **Bi X**, **Liu Q**, Sérézal IG, Rollman O, Lohcharoenkal W, Zheng X, Angelstig SE, Grünler J, Pivarcsi A, Sonkoly E, Catrina SB, Xiao C, Ståhle M, **Mi QS**, Zhou L, and Landén NX. miR-19a/b and miR-20a promote wound healing by regulating the inflammatory response of keratinocytes. *J Invest Dermatol* 2020; Epub ahead of print. PMID: 32949564. Full Text

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Persistent and impaired inflammation impedes tissue healing and is characteristic of chronic wounds. A better understanding of the mechanisms controlling wound inflammation is needed. Here we show that in human wound-edge keratinocytes, the expression of miR-17, miR-18a, miR-19a, miR-19b, and miR-20a, which all belong to the miR-17~92 cluster, is upregulated during wound repair. However, their levels are lower in chronic ulcers than acute wounds at the proliferative phase. Conditional knockout of miR-17~92 in keratinocytes as well as injection of miR-19a/b and miR-20a antisense inhibitors into wound-edges enhanced inflammation and delayed wound closure in mice. In contrast, conditional overexpression of the miR-17~92 cluster or miR-19b alone in mice keratinocytes accelerated wound closure in vivo. Mechanistically, miR-19a/b and miR-20a decreased TLR3-mediated NF-κB activation by targeting SHCBP1 and SEMA7A, respectively, reducing the production of inflammatory chemokines/cytokines by keratinocytes. Thus, as crucial regulators of wound inflammation, lack of miR-19a/b and miR-20a may contribute to sustained inflammation and impaired healing in chronic wounds. In line with this, we show that a combinatory treatment with miR-19b and miR-20a improved wound healing in a mouse model of type 2 diabetes.

Dermatology
Lyons AB, and **Hamzavi IH**. Ultraviolet C Induced Skin Reaction from Ultraviolet Germicidal Irradiation of N95 Respirators During the COVID-19 Pandemic. *Photodermatol Photoimmunol Photomed* 2020; Epub ahead of print. PMID: 32974955. Full Text

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With the depletion of personal protective equipment (PPE) during the COVID-19 pandemic, methods for decontamination of N95 filtering facepiece respirators (FFR) are being implemented at institutions throughout the United States. Ultraviolet germicidal irradiation (UVGI) involves administration of ultraviolet C (UVC) irradiation to cause DNA damage to inactivate pathogens on surfaces including FFRs. With the widespread use of this technology may come unintended side effects. We present the case of a patient who developed a skin reaction following UVC exposure from a UVGI device.

Dermatology
Narla S, Azzam M, Townsend S, Vellaichamy G, Marzano AV, Alavi A, Lowes MA, and **Hamzavi IH**. Identifying key components and therapeutic targets of the immune system in hidradenitis suppurativa with an emphasis on neutrophils. *Br J Dermatol* 2020; Epub ahead of print. PMID: 32893875. Full Text

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Hidradenitis suppurativa (HS) is a chronic, inflammatory, recurrent, and debilitating skin disease of the hair follicle unit that typically develops after puberty. The disorder is characterized by comedones, painful inflammatory nodules, abscesses, dermal tunnels, and scarring, with a predilection for intertriginous areas of the body (axillae, inguinal, and anogenital regions). Recruitment of neutrophils to HS lesion sites may play an essential role in the development of the painful inflammatory nodules and abscesses that characterize the disease. This is a review of the major mediators involved in the recruitment of neutrophils to sites of active inflammation including bacterial components (endotoxins, exotoxins, capsule fragments, etc.), the complement pathway anaphylatoxins C3a and C5a, tumor necrosis factor-alpha (TNF- α), interleukin 17 (IL-17), interleukin 8 (CXCL8/IL-8), interleukin 36 (IL-36), interleukin 1 (IL-1), lipocalin-2, leukotriene B4 (LTB4), platelet-activating factor, kallikrein, matrix metalloproteinases (MMPs), and myeloperoxidase inhibitors. Pharmacologic manipulation of the various pathways involved in the process of neutrophil recruitment and activation could allow for successful control and stabilization of HS lesions and the remission of active, severe flares.

Dermatology
Ozog DM, Sexton JZ, **Narla S**, Pretto-Kernahan CD, Mirabelli C, **Lim HW**, **Hamzavi IH**, **Tibbetts RJ**, and **Mi QS**. The Effect of Ultraviolet C Radiation Against Different N95 Respirators Inoculated with SARS-CoV-2. *Int J Infect Dis* 2020; Epub ahead of print. PMID: 32891736. Full Text

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OBJECTIVES: There are currently no studies that have examined whether one dosage can be uniformly applied to different respirator types to effectively decontaminate SARS-CoV-2 on N95 filtering facepiece respirators (FFRs). Health care workers have been using this disinfection method during the pandemic. Our objective was to determine the effect of UVC on SARS-CoV-2 inoculated N95 respirators and whether this was respirator material/model type dependent. METHODS: Four different locations (facepiece and strap) on 5 different N95 FFR models (3 M 1860, 8210, 8511, 9211; Moldex 1511) were inoculated with a 10 µL drop of SARS-CoV-2 viral stock (8 × 10(7) TCID(50)/mL). The outside-facing and wearer-facing surfaces of the respirators were each irradiated with a dose of 1.5 J/cm(2) UVC (254 nm). Viable SARS-CoV-2 was quantified by a median tissue culture infectious dose assay (TCID(50)). RESULTS: UVC delivered using a dose of 1.5 J/cm(2), to each side, was an effective method of decontamination for the facepieces of 3 M 1860 and Moldex 1511, and for the straps of 3 M 8210 and the Moldex 1511. CONCLUSION: This dose is an appropriate decontamination method to facilitate reuse of respirators for healthcare personnel when applied to certain models/materials. In addition, some straps may require additional disinfection to maximize the safety to frontline workers. Implementation of widespread UVC decontamination methods requires a careful consideration of model, material type, design, and fit-testing following irradiation.

Dermatology
Stein Gold L, Alonso-Llamazares J, Lacour JP, Warren RB, Tyring SK, Kircik L, Yamauchi P, and Lebwohl M. PSO-LONG: Design of a Novel, 12-Month Clinical Trial of Topical, Proactive Maintenance with Twice-Weekly Cal/BD Foam in Psoriasis. *Adv Ther* 2020; Epub ahead of print. PMID: 32965655. Full Text

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BACKGROUND: Psoriasis vulgaris is commonly treated with topical corticosteroids and vitamin D analogues. Although potent and super-potent topical corticosteroids are very effective at clearing psoriasis, with short-term reactive treatment durations, symptoms usually recur after treatment discontinuation, necessitating long-term disease management strategies. A foam formulation of calcipotriol and betamethasone dipropionate (Cal/BD foam), consisting of calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g, is approved for the daily treatment of psoriasis for up to 4 weeks. Here, we describe a clinical trial protocol for evaluating the long-term safety and efficacy of twice-weekly Cal/BD foam as a proactive topical maintenance therapy for plaque psoriasis for up to 52 weeks. OBJECTIVE: The aim of this trial was to evaluate the safety and efficacy of Cal/BD foam when applied twice weekly for up to 52 weeks as proactive maintenance therapy, with the goal of preventing or delaying disease relapse as long as possible while minimizing adverse effects. METHODS: Once-daily Cal/BD foam treatment responders from an initial 4-week open-label period were randomized to receive Cal/BD foam or foam vehicle applied to previously cleared plaques twice weekly for up to 52 weeks. In case of relapse, affected subjects in either group received rescue therapy with once-daily Cal/BD foam for 4 weeks on active areas. Thus, the trial (NCT02899962) compared the long-term use of Cal/BD foam in a proactive approach with a conventional, reactive approach. PLANNED OUTCOMES: Efficacy endpoints included the time to first relapse, the number of relapse-free days, and the number of relapses during the maintenance phase. Safety assessments included adverse events, incidence of rebound, local safety and tolerability scores, and effects on calcium metabolism and hypothalamic-pituitary-adrenal axis function. TRIAL REGISTRATION: ClinicalTrials.gov identifier, NCT02899962.

Dermatology
Tisack A, **Jiang A**, and **Veenstra J**. Crusted, ulcerated plaques on the scalp and face. *Clin Exp Dermatol* 2020; Epub ahead of print. PMID: 32959399. Full Text

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Dermatology
Torres AE, **Lyons AB**, **Hamzavi IH**, and **Lim HW**. Response to Commentary on "Role of Phototherapy in the Era of Biologics". *J Am Acad Dermatol* 2020; Epub ahead of print. PMID: 32950547. Full Text

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Dermatology
Umeh ON, **Beekman R**, **D'sa H**, and **Friedman BJ**. Elderly Man With Progressive Nail Atrophy: Challenge. *Am J Dermatopathol* 2020; Epub ahead of print. PMID: 32932300. Full Text

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Diagnostic Radiology
Alanee S, **Deebajah M**, **Taneja K**, **Cole D**, **Pantelic M**, **Peabody J**, **Williamson SR**, **Gupta N**, **Dabaja A**, and **Menon M**. Post prostatectomy Pathologic Findings of Patients with Clinically Significant Prostate Cancer and no Significant PI-RADS Lesions on Preoperative Magnetic Resonance Imaging. *Urology* 2020; Epub ahead of print. PMID: 32946907. Full Text

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OBJECTIVES: We present post-prostatectomy pathology results from a series of prostate cancer (Pca) Gleason grade group ≥ 2 patients who did not have findings suggestive of cancer on preoperative pelvic magnetic resonance imaging (MRI). METHODS: We performed an institutional retrospective study of prostate MRI examinations done from October 2015 to February 2018. We identified patients who underwent prostatectomy for Pca Gleason ≥ 3+4 diagnosed on prostate biopsy with no associated MRI findings suggestive of malignancy and analyzed their post-prostatectomy pathologic findings and MRI imaging results. RESULTS: At our institution, 850 men with Pca received MRI between 2015 and 2018, and 156/850 patients received robotic-assisted radical prostatectomy. Thirty three patients (33/156=21%) had negative MRI for PIRAD 3 or greater but had a biopsy showing significant Pca. Their mean (range) age was 62.7 (50 - 86) years. Their median (interquartile range) PSA, and PSA density were, 4.6 (3.7) ng/mL and 0.12 (0.05) ng/mL/cm2, respectively; all not significantly different from patients with visible lesions on MRI who underwent surgery. On post prostatectomy pathology, 27/33 (82%) men had Pca Gleason score 7 or greater. The most common pattern was infiltrative growth with cancer glands intermingling between benign glands. CONCLUSIONS: We describe the pathologic and imaging findings in an extensive series of men with clinically significant Pca with no significant lesions on preoperative MRI. Our results support the importance of patient counseling on the risk of missing significant Pca on MRI in isolation from other clinical variables.

Diagnostic Radiology

Alexander C, Caras A, Miller WK, **Tahir R**, **Mansour TR**, Medhkour A, and **Marin H**. M2 segment thrombectomy is not associated with increased complication risk compared to M1 segment: A meta-analysis of recent literature. *J Stroke Cerebrovasc Dis* 2020; 29(9):105018. PMID: 32807433. Full Text

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INTRODUCTION: Recent clinical comparisons of M1 and M2 segment endovascular thrombectomy have reached incongruous results in rates of complication and functional outcomes. This study aims to clarify the controversy surrounding this rapidly advancing technique through literature review and meta-analysis. METHODS: A Pubmed search was performed (January 2015-September 2019) using the following keywords: "M2 AND ("stroke" OR "occlusion") AND ("thrombectomy" OR "endovascular")". Safety and clinical outcomes were compared between segments via weighted Student's t-test, Chi-square and odds ratio while study heterogeneity was analyzed using Cochran Q and I(2) tests. RESULTS: Pubmed identified 208 articles and eleven studies were included after full-text analysis, comprising 2,548 M1 and 758 M2 mechanical thrombectomy segment cases. Baseline National Institutes of Health Stroke Scale scores were comparatively lower in patients experiencing an M2 occlusion (16 ± 1.25 vs 13.6 ± 0.96, $p < 0.01$). Patients who underwent M2 mechanical thrombectomy were more likely to experience both good clinical outcomes (modified Rankin Scale 0-2) (48.6% vs 43.5% respectively, OR 1.24; CI 1.05-1.47, $p = 0.01$) and excellent clinical outcomes (modified Rankin Scale 0-1) (34.7% vs. 26.5%%, OR 1.6; CI 1.28-1.99, $p < 0.01$) at 90 days compared to M1 mechanical thrombectomy. Neither recanalization rates (75.3% vs 72.8%, OR 0.92, CI 0.75-1.13, $p = 0.44$) nor symptomatic intracranial hemorrhage rates (5.6% vs 4.9%, OR 0.92; CI 0.61-1.39, $p= 0.7$) were significantly different between M1 and M2 cohorts. Mortality was less frequent in the M2 cohort compared to M1 (16.3% vs 20.7%, OR 0.73; CI 0.57-0.94, $p = 0.01$). M1 and M2 cohorts did not differ in symptom onset-to-puncture (238.1 ± 46.7 vs 239.8 ± 43.9 min respectively, $p=0.488$) nor symptom onset-to recanalization times (318.7 ± 46.6 vs 317.7 ± 71.1 min respectively, $p = 0.772$), though mean operative duration was shorter in the M2 cohort (61.8 ± 25.5 vs 54.6 ± 24 min, $p < 0.01$). CONCLUSIONS: Patients who underwent M2 mechanical thrombectomy had a higher prevalence of good and excellent clinical outcomes compared to the M1 mechanical thrombectomy cohorts. Additionally, our data suggest lower mortality rates in the M2 cohort and symptomatic intracranial hemorrhage rates that are similar to the M1 cohort. Therefore, M2 segment thrombectomy likely does not pose a significantly elevated operative risk and may have a positive impact on patient outcomes.

Diagnostic Radiology

Cho R, **Myers DT**, **Onwubiko IN**, and **Williams TR**. Extraosseous multiple myeloma: imaging spectrum in the abdomen and pelvis. *Abdom Radiol (NY)* 2020; Epub ahead of print. PMID: 32870348. Full Text

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Multiple myeloma represents a subset of plasma cell dyscrasias characterized by the proliferation of plasma cells typically in the bone marrow, representing approximately 1% of all cancers and 15% of hematologic malignancies.

Often multiple myeloma is limited to the skeletal system; however, a small percentage (<5%) of patients will develop extraosseous manifestations. We review the current WHO classification of plasma cell dyscrasias and use multimodality imaging including US, CT, MRI, and PET-CT to illustrate the spectrum of extraosseous multiple myeloma in the abdomen and pelvis. Because extraosseous multiple myeloma is associated with a poorer prognosis and decreased survival, it is important for the radiologist to become familiar with a variety of extraosseous manifestations in the abdomen and pelvis, especially in a patient with a known diagnosis of multiple myeloma and the development of an abdominal or pelvic mass.

Diagnostic Radiology

Hadied MO, **Patel PY**, **Cormier P**, **Poyiadji N**, **Salman M**, **Klochko C**, **Nadig J**, **Song T**, **Peterson E**, and **Reeser N**. Interobserver and Intraobserver Variability in the CT Assessment of COVID-19 Based on RSNA Consensus Classification Categories. *Acad Radiol* 2020; Epub ahead of print. PMID: 32948442. Full Text

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PURPOSE: To assess the interobserver and intraobserver agreement of fellowship trained chest radiologists, nonchest fellowship-trained radiologists, and fifth-year radiology residents for COVID-19-related imaging findings based on the consensus statement released by the Radiological Society of North America (RSNA). METHODS: A survey of 70 chest CTs of polymerase chain reaction (PCR)-confirmed COVID-19 positive and COVID-19 negative patients was distributed to three groups of participating radiologists: five fellowship-trained chest radiologists, five nonchest fellowship-trained radiologists, and five fifth-year radiology residents. The survey asked participants to broadly classify the findings of each chest CT into one of the four RSNA COVID-19 imaging categories, then select which imaging features led to their categorization. A 1-week washout period followed by a second survey comprised of randomly selected exams from the initial survey was given to the participating radiologists. RESULTS: There was moderate overall interobserver agreement in each group (κ coefficient range 0.45-0.52 ± 0.02). There was substantial overall intraobserver agreement across the chest and nonchest groups (κ coefficient range 0.61-0.67 ± 0.06) and moderate overall intraobserver agreement within the resident group (κ coefficient 0.58 ± 0.06). For the image features that led to categorization, there were varied levels of agreement in the interobserver and intraobserver components that ranged from fair to perfect kappa values. When assessing agreement with PCR-confirmed COVID status as the key, we observed moderate overall agreement within each group. CONCLUSION: Our results support the reliability of the RSNA consensus classification system for COVID-19-related image findings.

Diagnostic Radiology

Jarvik JG, Meier EN, James KT, Gold LS, Tan KW, Kessler LG, Suri P, Kallmes DF, Cherkin DC, Deyo RA, Sherman KJ, **Halabi SS**, Comstock BA, Luetmer PH, Avins AL, Rundell SD, **Griffith B**, Friedly JL, Lavallee DC, Stephens KA, Turner JA, Bresnahan BW, and Heagerty PJ. The Effect of Including Benchmark Prevalence Data of Common Imaging Findings in Spine Image Reports on Health Care Utilization Among Adults Undergoing Spine Imaging: A Stepped-Wedge Randomized Clinical Trial. *JAMA Netw Open* 2020; 3(9):e2015713. PMID: 32886121. Full Text

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Department of Radiology, Henry Ford Hospital, Detroit, Michigan.
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IMPORTANCE: Lumbar spine imaging frequently reveals findings that may seem alarming but are likely unrelated to pain. Prior work has suggested that inserting data on the prevalence of imaging findings among asymptomatic individuals into spine imaging reports may reduce unnecessary subsequent interventions. OBJECTIVE: To evaluate

the impact of including benchmark prevalence data in routine spinal imaging reports on subsequent spine-related health care utilization and opioid prescriptions. DESIGN, SETTING, AND PARTICIPANTS: This stepped-wedge, pragmatic randomized clinical trial included 250 401 adult participants receiving care from 98 primary care clinics at 4 large health systems in the United States. Participants had imaging of their backs between October 2013 and September 2016 without having had spine imaging in the prior year. Data analysis was conducted from November 2018 to October 2019. INTERVENTIONS: Either standard lumbar spine imaging reports (control group) or reports containing age-appropriate prevalence data for common imaging findings in individuals without back pain (intervention group). MAIN OUTCOMES AND MEASURES: Health care utilization was measured in spine-related relative value units (RVUs) within 365 days of index imaging. The number of subsequent opioid prescriptions written by a primary care clinician was a secondary outcome, and prespecified subgroup analyses examined results by imaging modality. RESULTS: We enrolled 250 401 participants (of whom 238 886 [95.4%] met eligibility for this analysis, with 137 373 [57.5%] women and 105 497 [44.2%] aged >60 years) from 3278 primary care clinicians. A total of 117 455 patients (49.2%) were randomized to the control group, and 121 431 patients (50.8%) were randomized to the intervention group. There was no significant difference in cumulative spine-related RVUs comparing intervention and control conditions through 365 days. The adjusted median (interquartile range) RVU for the control group was 3.56 (2.71-5.12) compared with 3.53 (2.68-5.08) for the intervention group (difference, -0.7%; 95% CI, -2.9% to 1.5%; P = .54). Rates of subsequent RVUs did not differ between groups by specific clinical findings in the report but did differ by type of index imaging (eg, computed tomography: difference, -29.3%; 95% CI, -42.1% to -13.5%; magnetic resonance imaging: difference, -3.4%; 95% CI, -8.3% to 1.8%). We observed a small but significant decrease in the likelihood of opioid prescribing from a study clinician within 1 year of the intervention (odds ratio, 0.95; 95% CI, 0.91 to 1.00; P = .04). CONCLUSIONS AND RELEVANCE: In this study, inserting benchmark prevalence information in lumbar spine imaging reports did not decrease subsequent spine-related RVUs but did reduce subsequent opioid prescriptions. The intervention text is simple, inexpensive, and easily implemented. TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT02015455.

Diagnostic Radiology

Saad H, **Myers DT**, **Song TK**, and **Nadig J**. Radiologic Manifestations of Pulmonary Vein Ablation Complications: A Pictorial Review. *J Thorac Imaging* 2020; Epub ahead of print. PMID: 32960836. Full Text

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In patients with atrial fibrillation refractory to drug therapy and cardioversion, pulmonary vein ablation is an alternative treatment that eradicates arrhythmogenic activity originating in the muscles of the pulmonary veins. While this procedure has a low incidence of significant complications, iatrogenic injuries are possible. Through multimodality pictorial examples utilizing computed tomography, nuclear medicine, fluoroscopy, and chest radiographs, the complications associated with pulmonary vein ablation will be reviewed. Examples of pulmonary vein stenosis, right phrenic nerve injury with associated diaphragmatic paralysis, atrioesophageal fistula, and pericardioesophageal fistula will be illustrated.

Diagnostic Radiology

Zhang R, Tie X, **Qi Z**, **Bevins NB**, Zhang C, Griner D, **Song TK**, **Nadig JD**, Schiebler ML, Garrett JW, Li K, Reeder SB, and Chen GH. Diagnosis of COVID-19 Pneumonia Using Chest Radiography: Value of Artificial Intelligence. *Radiology* 2020; Epub ahead of print. PMID: 32969761. Full Text

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Background Radiologists are proficient in differentiating between chest x-ray radiographs (CXRs) with and without symptoms of pneumonia, but have found it more challenging to differentiate CXRs with COVID-19 pneumonia symptoms from those without. Purpose To develop an artificial intelligence algorithm to differentiate COVID-19 pneumonia from other causes of CXR abnormalities. Materials and Methods In this retrospective study, a deep neural network, CV19-Net, was trained, validated, and tested on CXRs from patients with and without COVID-19 pneumonia. For the COVID-19 positive CXRs, patients with reverse transcriptase polymerase chain reaction positive results for severe acute respiratory syndrome coronavirus 2 with positive pneumonia findings between February 1, 2020 and May 30, 2020 were included. For the non-COVID-19 CXRs, patients with pneumonia who underwent CXR between October 1, 2019 and December 31, 2019 were included. Area under the receiver operating characteristic curve (AUC), sensitivity, and specificity were calculated to characterize diagnostic performance. To benchmark the performance of CV19-Net, a randomly sampled test dataset containing 500 CXRs from 500 patients was evaluated by both the CV19-Net and three experienced thoracic radiologists. Results A total of 2060 patients (5806 CXRs; mean age 62 ± 16, 1059 men) with COVID-19 pneumonia and 3148 patients (5300 CXRs; mean age 64 ± 18, 1578

men) with non-COVID-19 pneumonia were included and split into training + validation and test datasets. For the test set, CV19-Net achieved an AUC of 0.92 (95% confidence interval [CI]: 0.91, 0.93) corresponding to a sensitivity of 88% (95% CI: 87%, 89%) and a specificity of 79% (95% CI: 77%, 80%) using a high sensitivity operating threshold, or a sensitivity of 78% (95% CI: 77%, 79%) and a specificity of 89% (95% CI: 88%, 90%) using a high specificity operating threshold. For the 500 sampled CXRs, CV19-Net achieved an AUC of 0.94 (95% CI: 0.93, 0.96) compared to a 0.85 AUC (95% CI: 0.81, 0.88) of radiologists. Conclusion CV19-Net was able to differentiate COVID-19 related pneumonia from other types of pneumonia with performance exceeding that of experienced thoracic radiologists.

Emergency Medicine

Miller J, **Fadel RA**, **Tang A**, **Perrotta G**, **Herc E**, **Soman S**, **Nair S**, **Hanna Z**, **Zervos MJ**, **Alangaden G**, **Brar I**, and **Suleyman G**. The Impact of Sociodemographic Factors, Comorbidities and Physiologic Response on 30-day Mortality in COVID-19 Patients in Metropolitan Detroit. *Clin Infect Dis* 2020; Epub ahead of print. PMID: 32945856. Full Text

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BACKGROUND: The relationship of health disparities and comorbidities in coronavirus disease 2019 (COVID-19) related outcomes are an ongoing area of interest. This report assesses risk factors associated with mortality in patients presenting with Covid-19 infection and healthcare disparities. METHODS: A retrospective cohort study of consecutive patients presenting to emergency departments within an integrated health system who tested positive for COVID-19 between March 7 and April 30, 2020 in Metropolitan Detroit. The primary outcomes were hospitalization and 30-day mortality. RESULTS: A total of 3,633 patients with mean age of 58 years were included. The majority were female and black non-Hispanic. Sixty-four percent required hospitalization, 56% of whom were black. Hospitalized patients were older, more likely to reside in a low-income area, and had a higher burden of comorbidities. By 30-days, 433 (18.7%) hospitalized patients died. In adjusted analyses, the presence of comorbidities, age >60 years and more severe physiological disturbance were associated with 30-day mortality. Residence in low income areas (odds ratio, 1.02; 95% confidence interval 0.76 - 1.36), and public insurance (odds ratio, 1.24; 95% confidence interval 0.76 - 2.01) were not independently associated with higher risk of mortality. Black female patients had a lower adjusted risk of mortality (odds ratio, 0.46; 95% confidence interval, 0.27 to 0.78). CONCLUSIONS: In this large cohort of COVID-19 patients, those with comorbidities, advanced age, and physiological abnormalities on presentation had higher odds of death. Disparities in income or source of health insurance were not associated with outcomes. Black women had a lower risk of dying.

Emergency Medicine

Morris DC, **Jaehne AK**, **Chopp M**, **Zhang Z**, **Poisson L**, **Chen Y**, **Datta I**, and **Rivers EP**. Proteomic Profiles of Exosomes of Septic Patients Presenting to the Emergency Department Compared to Healthy Controls. *J Clin Med* 2020; 9(9). PMID: 32932765. Full Text

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BACKGROUND: Septic Emergency Department (ED) patients provide a unique opportunity to investigate early sepsis. Recent work focuses on exosomes, nanoparticle-sized lipid vesicles (30-130 nm) that are released into the bloodstream to transfer its contents (RNA, miRNA, DNA, protein) to other cells. Little is known about how early changes related to exosomes may contribute to the dysregulated inflammatory septic response that leads to multi-organ dysfunction. We aimed to evaluate proteomic profiles of plasma derived exosomes obtained from septic ED patients and healthy controls. METHODS: This is a prospective observational pilot study evaluating a plasma proteomic exosome profile at an urban tertiary care hospital ED using a single venipuncture blood draw, collecting 40 cc Ethylenediaminetetraacetic acid (EDTA) blood. MEASUREMENTS: We recruited seven patients in the ED within 6 h of their presentation and five healthy controls. Plasma exosomes were isolated using the Invitrogen Total Exosome Isolation Kit. Exosome proteomic profiles were analyzed using fusion mass spectroscopy and Proteome Discoverer. Principal component analysis (PCA) and differential expression analysis (DEA) for sepsis versus control was performed. RESULTS: PCA of 261 proteins demonstrated septic patients and healthy controls were distributed in two groups. DEA revealed that 62 (23.8%) proteins differed between the exosomes of septic patients and healthy controls, p-value < 0.05. Adjustments using the False Discovery Rate (FDR) showed 23 proteins remained significantly different (FDR < 0.05) between sepsis and controls. Septic patients and controls were classified into two distinct groups by hierarchical clustering using the 62 nominally DE proteins. After adjustment multiple comparisons, three acute phase proteins remained significantly different between patients and controls: Serum amyloid A-1, C-reactive protein and Serum Amyloid A-2. Inflammatory response proteins immunoglobulin heavy constant Δ and Fc-

fragment of IgG binding protein were increased. CONCLUSION: Exosome proteomic profiles of septic ED patients differ from their healthy counterparts with regard to acute phase response and inflammation.

Emergency Medicine
Nowak RM, DeMasi D, Murn A, and Neuenschwander J. Biotin Interference and Laboratory Testing: Possible Implications/Ramifications for Emergency Medicine. *Ann Emerg Med* 2020; 76(3):369-370. PMID: 32828334. Full Text

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Endocrinology and Metabolism
Arya AK, Kumari P, Bhadada SK, Agrawal K, Singh P, Mukherjee S, Sood A, and **Rao SD**. Progressive rise in the prevalence of asymptomatic primary hyperparathyroidism in India: Data from PHPT registry. *J Bone Miner Metab* 2020; Epub ahead of print. PMID: 32894354. Full Text

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INTRODUCTION: Primary hyperparathyroidism (PHPT), a third common endocrine disorder, varies from asymptomatic disease, mostly seen in the West where routine biochemical screening is practiced, to the classical symptomatic disease mostly seen in the Eastern countries. We aimed to compare the demographic, clinical, biochemical measurements in patients with asymptomatic and symptomatic PHPT from the Indian PHPT registry. MATERIAL AND METHODS: Data of PHPT patients from the last 25 years (1995-2019) were analyzed for demographic, clinical presentation and biochemical measurements, and compared these characteristics between asymptomatic and symptomatic PHPT patients. RESULTS: Of the 554 patients, 54 (10%) patients had asymptomatic PHPT. There was a sharp rise in the proportion of asymptomatic PHPT patients of 3% in the first decade to 13% in the second decade of the century ($p = 0.003$). Patients with asymptomatic PHPT were significantly older (50 vs. 42 years; $p < 0.0001$) and had higher mean body mass index (27.8 vs. 23.5 kg/m(2); $p < 0.0001$) compared to the symptomatic PHPT group. In addition, asymptomatic PHPT patients had significantly lower median plasma iPTH (180 vs. 370 pg/mL; $p < 0.0001$), serum alkaline phosphatase (119 vs. 172 IU/L; $p < 0.0001$), and parathyroid adenoma weight (1.0 vs. 2.62 g; $p = 0.006$) compared to the symptomatic PHPT group. CONCLUSION: Although symptomatic PHPT is still most prevalent (> 90%) in India with higher indices of the disease and tumor weights, there is a progressive rise in the prevalence of asymptomatic PHPT patients in the last decade. Improvements in calcium and vitamin D nutrition might account for this change as in the Western series.

Family Medicine
Casadei K, Kiel J, and Freidl M. Triceps Tendon Injuries. *Curr Sports Med Rep* 2020; 19(9):367-372. PMID: 32925376. Full Text

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Triceps tendon injuries are an uncommon clinical entity poorly described in the literature. This review discusses the spectrum of pathology, effective diagnosis, nonsurgical treatment, surgical treatment, rehabilitation, and surgical complications of triceps tendon injuries. Management of triceps tendinopathies depends on the mechanism of injury and the patient's motor examination. Triceps tendinopathies and partial tendon tears with intact strength can be managed conservatively with rest, ice, immobilization, nonsteroidal anti-inflammatory drugs, and physical therapy. If conservative management fails for 6 months or there are strength deficits on examination, surgery should be considered. Based on the current evidence, there are no clear guidelines for "best" surgical approach. Although rare, the most significant surgical complication to be concerned about is rerupture. Rerupture rate is 4.62% among the articles we reviewed.

Global Health Initiative

Maki G, Smith I, Paulin S, **Kaljee L**, Kasambara W, Mlotha J, Chuki P, Rupali P, Singh DR, Bajracharya DC, Barrow L, Johnson E, **Prentiss T**, and **Zervos M**. Feasibility Study of the World Health Organization Health Care Facility-Based Antimicrobial Stewardship Toolkit for Low- and Middle-Income Countries. *Antibiotics (Basel)* 2020; 9(9). PMID: 32872440. Full Text

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Antimicrobial stewardship (AMS) has emerged as a systematic approach to optimize antimicrobial use and reduce antimicrobial resistance. To support the implementation of AMS programs, the World Health Organization developed a draft toolkit for health care facility AMS programs in low- and middle-income countries. A feasibility study was conducted in Bhutan, the Federated States of Micronesia, Malawi, and Nepal to obtain local input on toolkit content and implementation of AMS programs. This descriptive qualitative study included semi-structured interviews with national- and facility-level stakeholders. Respondents identified AMS as a priority and perceived the draft toolkit as a much-needed document to further AMS program implementation. Facilitators for implementing AMS included strong national and facility leadership and clinical staff engagement. Barriers included lack of human and financial resources, inadequate regulations for prescription antibiotic sales, and insufficient AMS training. Action items for AMS implementation included improved laboratory surveillance, establishment of a stepwise approach for implementation, and mechanisms for reporting and feedback. Recommendations to improve the AMS toolkit's content included additional guidance on defining the responsibilities of the committees and how to prioritize AMS programming based on local context. The AMS toolkit was perceived to be an important asset as countries and health care facilities move forward to implement AMS programs.

Hematology/Oncology

Singh SRK, **Thanikachalam K**, and **Donthireddy V**. Desperate times, desperate measures: successful use of chemotherapy in treatment of haemophagocytic lymphohistiocytosis (HLH) due to disseminated histoplasmosis. *BMJ Case Rep* 2020; 13(9). PMID: 32878853. Full Text

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We describe a case of haemophagocytic lymphohistiocytosis (HLH) secondary to disseminated histoplasmosis, which was treated with chemotherapy in addition to standard antifungal therapy. While HLH in the setting of infections is very well described, its treatment in this setting is controversial, with some physicians treating only the underlying infection, whereas others using immune suppression in addition to antimicrobials. To the best of our knowledge, this is the first report documenting the successful treatment of an adult patient with HLH due to disseminated histoplasmosis using etoposide chemotherapy after initial antifungal therapy failed to show improvement.

Hematology/Oncology

Verschraegen CF, Jerusalem G, McClay EF, Iannotti N, Redfern CH, Bennouna J, Chen FL, Kelly K, Mehnert J, Morris JC, Taylor M, Spigel D, **Wang D**, Grote HJ, Zhou D, Munshi N, Bajars M, and Gulley JL. Efficacy and safety of first-line avelumab in patients with advanced non-small cell lung cancer: results from a phase Ib cohort of the JAVELIN Solid Tumor study. *J Immunother Cancer* 2020; 8(2). PMID: 32907924. Full Text

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EMD Serono Research & Development Institute, Inc, Billerica, Massachusetts, USA; a business of Merck KGaA, Darmstadt, Germany.
Genitourinary Malignancies Branch and Laboratory of Tumor Immunology and Biology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA.

INTRODUCTION: Avelumab, an antiprogrammed death ligand-1 antibody, is approved as a monotherapy for treatment of metastatic Merkel cell carcinoma and advanced urothelial carcinoma, and in combination with axitinib for advanced renal cell carcinoma. We report the efficacy and safety of first-line avelumab in advanced non-small cell lung cancer (NSCLC). METHODS: In a phase I expansion cohort of the JAVELIN Solid Tumor trial, patients with treatment-naive, metastatic, or recurrent NSCLC received 10 mg/kg avelumab intravenously every 2 weeks. Endpoints included best overall response, duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety. RESULTS: Overall, 156 patients were enrolled and treated. Median duration of follow-up was 18.6 months (range, 15 to 23 months). The objective response rate was 19.9% (95% CI, 13.9 to 27.0), including complete response in 3 (1.9%) and partial response in 28 (17.9%). Median DOR was 12.0 months (95% CI, 6.9 to not estimable). Median PFS was 4.0 months (95% CI, 2.7 to 5.4) and the 6-month PFS rate was 38.5% (95% CI, 30.7 to 46.3). Median OS was 14.1 months (95% CI, 11.3 to 16.9) and the 12-month OS rate was 56.6% (95% CI, 48.2 to 64.1). Treatment-related adverse events (TRAEs) occurred in 107 patients (68.6%), including grade ≥3 TRAEs in 19 (12.2%). Immune-related adverse events and infusion-related reactions occurred in 31 (19.9%) and 40 patients (25.6%), respectively. No treatment-related deaths occurred. CONCLUSION: Avelumab showed antitumor activity with a tolerable safety profile as a first-line treatment in patients with advanced NSCLC. These data support further investigation of avelumab in the phase III JAVELIN Lung 100 study. TRIAL REGISTRATION DETAILS: ClinicalTrials.gov NCT01772004; registered January 21, 2013.

Hematology/Oncology

Voss MH, Gordon MS, Mita M, Rini B, Makker V, Macarulla T, Smith DC, Cervantes A, Puzanov I, Pili R, **Wang D**, Jalal S, Pant S, Patel MR, Neuwirth RL, Enke A, Shou Y, Sedarati F, Faller DV, and Burris HA, 3rd. Phase 1 study of mTORC1/2 inhibitor sapanisertib (TAK-228) in advanced solid tumours, with an expansion phase in renal, endometrial or bladder cancer. *Br J Cancer* 2020; Epub ahead of print. PMID: 32913286. Full Text

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BACKGROUND: This Phase 1 dose-escalation/expansion study assessed safety/tolerability of sapanisertib, an oral, highly selective inhibitor of mTORC1/mTORC2, in advanced solid tumours. METHODS: Eligible patients received increasing sapanisertib doses once daily (QD; 31 patients), once weekly (QW; 30 patients), QD for 3 days on/4 days off QW (QD × 3dQW; 33 patients) or QD for 5 days on/2 days off QW (QD × 5dQW; 22 patients). In expansion cohorts, 82 patients with renal cell carcinoma (RCC), endometrial or bladder cancer received sapanisertib 5 mg QD (39 patients), 40 mg QW (26 patients) or 30 mg QW (17 patients). RESULTS: Maximum tolerated doses of sapanisertib were 6 mg QD, 40 mg QW, 9 mg QD × 3dQW and 7 mg QD × 5dQW. Frequent dose-limiting toxicities (DLTs) included hyperglycaemia, maculo-papular rash (QD), asthenia and stomatitis (QD × 3dQW/QD × 5dQW); expansion phase doses of 5 mg QD and 30 mg QW were selected based on tolerability beyond the DLT evaluation period. One patient with RCC achieved complete response; nine experienced partial responses (RCC: seven patients; carcinoid tumour/endometrial cancer: one patient each). Sapanisertib pharmacokinetics were time-linear and supported multiple dosing. Pharmacodynamic findings demonstrated treatment-related reductions in TORC1/2 biomarkers. CONCLUSIONS: Sapanisertib demonstrated a manageable safety profile, with preliminary antitumour activity observed in RCC and endometrial cancer. CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, NCT01058707.

Hospital Medicine
Gunasekaran K, Rajasurya V, Devasahayam J, Singh Rahi M, Chandran A, Elango K, and **Talari G**. A Review of the Incidence Diagnosis and Treatment of Spontaneous Hemorrhage in Patients Treated with Direct Oral Anticoagulants. *J Clin Med* 2020; 9(9). PMID: 32942757. Full Text

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Anticoagulation carries a tremendous therapeutic advantage in reducing morbidity and mortality with venous thromboembolism and atrial fibrillation. For over six decades, traditional anticoagulants like low molecular weight heparin and vitamin K antagonists like warfarin have been used to achieve therapeutic anticoagulation. In the past decade, multiple new direct oral anticoagulants have emerged and been approved for clinical use. Since their introduction, direct oral anticoagulants have changed the landscape of anticoagulants. With increasing indications and use in various patients, they have become the mainstay of treatment in venous thromboembolic diseases. The safety profile of direct oral anticoagulants is better or at least similar to warfarin, but several recent reports are focusing on spontaneous hemorrhages with direct oral anticoagulants. This narrative review aims to summarize the incidence of spontaneous hemorrhage in patients treated with direct oral anticoagulants and also offers practical management strategies for clinicians when patients receiving direct oral anticoagulants present with bleeding complications.

Hypertension and Vascular Research
Dalmasso C, Chade AR, **Mendez M**, Giani JF, Bix GJ, Chen KC, and Loria AS. Intrarenal Renin Angiotensin System Imbalance During Postnatal Life Is Associated With Increased Microvascular Density in the Mature Kidney. *Front Physiol* 2020; 11:1046. PMID: 32982785. Full Text

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Environmental stress during early life is an important factor that affects the postnatal renal development. We have previously shown that male rats exposed to maternal separation (MatSep), a model of early life stress, are normotensive but display a sex-specific reduced renal function and exacerbated angiotensin II (AngII)-mediated

vascular responses as adults. Since optimal AngII levels during postnatal life are required for normal maturation of the kidney, this study was designed to investigate both short- and long-term effect of MatSep on (1) the renal vascular architecture and function, (2) the intrarenal renin-angiotensin system (RAS) components status, and (3) the genome-wide expression of genes in isolated renal vasculature. Renal tissue and plasma were collected from male rats at different postnatal days (P) for intrarenal RAS components mRNA and protein expression measurements at P2, 6, 10, 14, 21, and 90 and microCT analysis at P21 and 90. Although with similar body weight and renal mass trajectories from P2 to P90, MatSep rats displayed decreased renal filtration capacity at P90, while increased microvascular density at both P21 and P90 ($p < 0.05$). MatSep increased renal expression of renin, and angiotensin type 1 (AT1) and type 2 (AT2) receptors ($p < 0.05$), but reduced ACE2 mRNA expression and activity from P2-14 compared to controls. However, intrarenal levels of AngII peptide were reduced ($p < 0.05$) possible due to the increased degradation to AngIII by aminopeptidase A. In isolated renal vasculature from neonates, Enriched Biological Pathways functional clusters (EBPfc) from genes changed by MatSep reported to modulate extracellular structure organization, inflammation, and pro-angiogenic transcription factors. Our data suggest that male neonates exposed to MatSep could display permanent changes in the renal microvascular architecture in response to intrarenal RAS imbalance in the context of the atypical upregulation of angiogenic factors.

Infectious Diseases

Gudipati S, **Zervos M**, and **Herc E**. Can the One Health Approach Save Us from the Emergence and Reemergence of Infectious Pathogens in the Era of Climate Change: Implications for Antimicrobial Resistance? *Antibiotics (Basel)* 2020; 9(9). PMID: 32937739. Full Text

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Climate change has become a controversial topic in today's media despite decades of warnings from climate scientists and has influenced human health significantly with the increasing prevalence of infectious pathogens and contribution to antimicrobial resistance. Elevated temperatures lead to rising sea and carbon dioxide levels, changing environments and interactions between humans and other species. These changes have led to the emergence and reemergence of infectious pathogens that have already developed significant antimicrobial resistance. Although these new infectious pathogens are alarming, we can still reduce the burden of infectious diseases in the era of climate change if we focus on One Health strategies. This approach aims at the simultaneous protection of humans, animals and environment from climate change and antimicrobial impacts. Once these relationships are better understood, these models can be created, but the support of our legislative and health system partnerships are critical to helping with strengthening education and awareness.

Infectious Diseases

Maki G, Smith I, Paulin S, **Kaljee L**, Kasambara W, Mlotha J, Chuki P, Rupali P, Singh DR, Bajracharya DC, Barrow L, Johnson E, **Prentiss T**, and **Zervos M**. Feasibility Study of the World Health Organization Health Care Facility-Based Antimicrobial Stewardship Toolkit for Low- and Middle-Income Countries. *Antibiotics (Basel)* 2020; 9(9). PMID: 32872440. Full Text

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Antimicrobial stewardship (AMS) has emerged as a systematic approach to optimize antimicrobial use and reduce antimicrobial resistance. To support the implementation of AMS programs, the World Health Organization developed a draft toolkit for health care facility AMS programs in low- and middle-income countries. A feasibility study was conducted in Bhutan, the Federated States of Micronesia, Malawi, and Nepal to obtain local input on toolkit content and implementation of AMS programs. This descriptive qualitative study included semi-structured interviews with national- and facility-level stakeholders. Respondents identified AMS as a priority and perceived the draft toolkit as a much-needed document to further AMS program implementation. Facilitators for implementing AMS included strong national and facility leadership and clinical staff engagement. Barriers included lack of human and financial resources, inadequate regulations for prescription antibiotic sales, and insufficient AMS training. Action items for AMS implementation included improved laboratory surveillance, establishment of a stepwise approach for implementation, and mechanisms for reporting and feedback. Recommendations to improve the AMS toolkit's content included

additional guidance on defining the responsibilities of the committees and how to prioritize AMS programming based on local context. The AMS toolkit was perceived to be an important asset as countries and health care facilities move forward to implement AMS programs.

Infectious Diseases
Miller J, **Fadel RA**, **Tang A**, **Perrotta G**, **Herc E**, **Soman S**, **Nair S**, **Hanna Z**, **Zervos MJ**, **Alangaden G**, **Brar I**, and **Suleyman G**. The Impact of Sociodemographic Factors, Comorbidities and Physiologic Response on 30-day Mortality in COVID-19 Patients in Metropolitan Detroit. *Clin Infect Dis* 2020; Epub ahead of print. PMID: 32945856. Full Text

Henry Ford Hospital, Detroit, MI, USA.
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BACKGROUND: The relationship of health disparities and comorbidities in coronavirus disease 2019 (COVID-19) related outcomes are an ongoing area of interest. This report assesses risk factors associated with mortality in patients presenting with Covid-19 infection and healthcare disparities. METHODS: A retrospective cohort study of consecutive patients presenting to emergency departments within an integrated health system who tested positive for COVID-19 between March 7 and April 30, 2020 in Metropolitan Detroit. The primary outcomes were hospitalization and 30-day mortality. RESULTS: A total of 3,633 patients with mean age of 58 years were included. The majority were female and black non-Hispanic. Sixty-four percent required hospitalization, 56% of whom were black. Hospitalized patients were older, more likely to reside in a low-income area, and had a higher burden of comorbidities. By 30-days, 433 (18.7%) hospitalized patients died. In adjusted analyses, the presence of comorbidities, age >60 years and more severe physiological disturbance were associated with 30-day mortality. Residence in low income areas (odds ratio, 1.02; 95% confidence interval 0.76 - 1.36), and public insurance (odds ratio, 1.24; 95% confidence interval 0.76 - 2.01) were not independently associated with higher risk of mortality. Black female patients had a lower adjusted risk of mortality (odds ratio, 0.46; 95% confidence interval, 0.27 to 0.78). CONCLUSIONS: In this large cohort of COVID-19 patients, those with comorbidities, advanced age, and physiological abnormalities on presentation had higher odds of death. Disparities in income or source of health insurance were not associated with outcomes. Black women had a lower risk of dying.

Infectious Diseases
Weber DJ, Talbot TR, **Weinmann A**, Mathew T, Heil E, Stenehjem E, Duncan R, Gross A, Stinchfield P, Baliga C, Wagner J, Schaffner W, Echevarria K, and Drees M. Policy statement from the Society for Healthcare Epidemiology of America (SHEA): Only medical contraindications should be accepted as a reason for not receiving all routine immunizations as recommended by the Centers for Disease Control and Prevention. *Infect Control Hosp Epidemiol* 2020; Epub ahead of print. PMID: 32938509. Full Text

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SHEA endorses adhering to the recommendations by the CDC and ACIP for immunizations of all children and adults. All persons providing clinical care should be familiar with these recommendations and should routinely assess immunization compliance of their patients and strongly recommend all routine immunizations to patients. All healthcare personnel (HCP) should be immunized against vaccine-preventable diseases as recommended by the CDC/ACIP (unless immunity is demonstrated by another recommended method). SHEA endorses the policy that immunization should be a condition of employment or functioning (students, contract workers, volunteers, etc) at a healthcare facility. Only recognized medical contraindications should be accepted for not receiving recommended immunizations.

Internal Medicine

Elghazawy H, **Venkatesulu BP**, Verma V, Pushparaji B, Monlezun DJ, Marmagkiolis K, and Iliescu CA. The role of cardio-protective agents in cardio-preservation in breast cancer patients receiving Anthracyclines ± Trastuzumab: a Meta-analysis of clinical studies. *Crit Rev Oncol Hematol* 2020; 153:103006. PMID: 32777728. Full Text

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BACKGROUND: Breast cancer patients often receive cardiotoxic drugs such as anthracyclines (ANT) and Trastuzumab. Numerous trials have tested angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), and beta-blockers (BB) as monotherapy or in combination to reprogram cardiac function dynamics in these patients, but no clear conclusions have been reached thus far, due to evident heterogeneity in the design of clinical studies. METHODS: This PRISMA-guided systematic review and meta-analysis assessed a pooled effect estimate of the potential benefit/harm of ACEi/ARB/BB in breast cancer patients treated with ANT ± Trastuzumab. The protocol was registered on the PROSPERO database. Electronic databases (PubMed, Cochrane Central, Scopus, Web of Science) were searched from inception until February 2019. RESULTS: Twenty-two prospective studies comprising of 2,302 participants were included in the meta-analysis. The 16 studies testing the protective effects of ACEi/ARB/BB after immediate completion of chemotherapy showed a significant lower difference in the mean change of left ventricular ejection fraction (LVEF) in patiens receiving cardio-protective drugs as compared to controls, with a standardized mean difference [SMD = -2.36 (95% CI: -3.23 to -1.49), $p < 0.00001$] favoring the protective role of these drugs. LVEF was evaluated after 6 months after completion of chemotherapy in 3 studies, where ACEi/ARB/BB persistently showed cardio-protective effects as compared to controls [SMD = -6.54 (95% CI: -10.74 to -2.34), $p = 0.002$]. After 1 year from completion of chemotherapy, ACEi/ARB/BB preserved beneficial effects on LVEF vs control [SMD = -5.37 (95% CI: -9.31 to -1.43), $p = 0.008$]. The effect of ACEi/ARB/BB on end-systolic volume (ESV) and end-diastolic volume (EDV) were evaluated immediately after chemotherapy completion and after 1 year. No significant protective effect was apparent. On the other hand, end-diastolic diameter (EDD) was significantly spared in the ACEi/ARB/BB group vs control after chemotherapy completion [SMD = -1.11 (95% CI: -1.88 to -0.35), $p = 0.004$]. Heart failure as a clinical endpoint was assessed in 11 trials. The incidence of heart failure was significantly lower in the ACEi/ARB/BB group as compared to control [Odds ratio = 0.12 (95% CI: 0.03 to 0.45), $p = 0.002$]. CONCLUSION: ACEi/ARB/BB may act as cardioprotective agents in breast cancer patients who undergo ANT ± Trastuzumab. More studies are required to better assess the magnitude of the cardiotoxicity hazards of ANT ± Trastuzumab, with more precise assessment of the effect of ACEi/ARB/BB on cardio-protection.

Internal Medicine

Gui H, **Levin AM**, Hu D, Sleiman P, **Xiao S**, Mak AC, **Yang M**, Barczak AJ, Huntsman S, Eng C, **Hochstadt S**, **Zhang E**, **Whitehouse K**, **Simons S**, **Cabral W**, **Takriti S**, Abecasis G, Blackwell TW, Kang HM, Nickerson DA, Germer S, **Lanfear DE**, Gilliland F, Gauderman WJ, Kumar R, Erle DJ, Martinez FD, Hakonarson H, Burchard EG, and **Williams LK**. Mapping the 17q12-21.1 Locus for Variants Associated with Early-onset Asthma in African Americans. *Am J Respir Crit Care Med* 2020; Epub ahead of print. PMID: 32966749. Full Text

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RATIONALE: The 17q12-21.1 locus is one of the most highly replicated genetic associations with asthma. Individuals of African descent have lower LD in this region, which could facilitate identifying causal variants. OBJECTIVE: To identify functional variants at 17q12-21.1 associated with early-onset asthma among African American individuals. METHODS AND MEASUREMENTS: We evaluated African American participants from the Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-ethnicity (SAPPHIRE) (n=1,940), the Study of African Americans, Asthma, Genes & Environment (SAGE II) (n=885), and Study of the Genetic Causes of Complex Pediatric Disorders - Asthma (GCPD-A) (n=2,805). Associations with asthma onset at age <5 years were meta-analyzed across cohorts. The lead signal was reevaluated considering haplotypes informed by genetic ancestry (i.e., African vs. European). Both an expression quantitative trait locus (eQTL) analysis and phenome-wide association study (PheWAS) were performed on the lead variant. MAIN RESULTS: The meta-analyzed results from SAPPHIRE, SAGE II, and GCPD-A identified rs11078928 as the top association for early-onset asthma. A haplotype analysis suggested that the asthma association partitioned most closely with rs11078928 genotype. Genetic ancestry did not appear to influence the effect of this variant. In the eQTL analysis, rs11078928 was related to alternative splicing of gasdermin-B (GSDMB) transcripts. The PheWAS of rs11078928 suggested that this variant was predominantly associated with asthma and asthma-associated symptoms. CONCLUSIONS: A splice acceptor polymorphism appears to be a causal variant for asthma at the 17q12-21.1 locus. This variant appears to have the same magnitude of effect in individuals of African and European descent.

Internal Medicine

Korpole PR, Al-Bacha S, and **Hamadeh S**. A Case for Biopsy: Injectable Naltrexone-Induced Acute Eosinophilic Pneumonia. *Cureus* 2020; 12(9):e10221. PMID: 32913694. Full Text

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Naltrexone is a semi-synthetic opioid that has competitive antagonist activity at mu opioid receptors. Naltrexone has proven to be efficacious in the treatment of alcohol and opioid dependence, and a long-acting injectable form of naltrexone was developed to overcome non-compliance. Therefore, injectable naltrexone has the potential to become an important medication for the treatment of opiate and alcohol dependence. Acute eosinophilic pneumonia (AEP) is a rare acute respiratory illness of varying severity that may lead to acute respiratory distress syndrome and death. Initially, AEP was thought to be idiopathic; however, it has become apparent that AEP can have identifiable causes including medications, infections, and other inhalational exposures, especially tobacco smoke. AEP is generally a diagnosis of exclusion confirmed by the presence of bronchoalveolar lavage (BAL) fluid eosinophilia. Recognition and elimination of the causative factor for AEP and providing glucocorticoid therapy are key principles in the management of AEP of non-infectious origin. Prognosis is generally excellent if AEP is diagnosed early and managed appropriately, even in patients with acute respiratory failure. The diagnosis of AEP is generally overlooked given the shared clinical attributes with acute lung injury due to other causes, including severe community-acquired pneumonia. A 32-year-old lady presented to the emergency department (ED) with symptoms of dyspnea, chest pain, cough, and subjective fevers since three days. She received a dose of intramuscular Naltrexone for the treatment of alcohol and opiate dependence on the day of symptom onset. Initially, she was noted to be hypoxic, and oxygen supplementation was initiated through a nasal cannula. While in the ED, she was placed on a non-rebreather mask because of worsening hypoxia. Chest imaging showed diffuse bilateral pulmonary infiltrates. Initial laboratory data were pertinent for elevated WBC count with mild peripheral eosinophilia. Antibiotics were administered for the treatment of suspected community-acquired pneumonia. Upon hospital admission, she was started on steroids for the management of suspected eosinophilic pneumonia secondary to injectable naltrexone. Bronchodilator therapy was initiated, and antibiotics were discontinued. The patient's oxygen requirements improved. Pulmonology consultation was requested, and the patient underwent bronchoscopy. BAL studies showed predominance of lymphocytes with no eosinophils. However, lung biopsy showed findings consistent with drug-induced eosinophilic pneumonitis. The patient's hypoxia resolved with steroid therapy. The patient was discharged with a course of oral steroids, albuterol inhaler, and outpatient pulmonology follow-up.

Internal Medicine
Miller J, **Fadel RA**, **Tang A**, **Perrotta G**, **Herc E**, **Soman S**, **Nair S**, **Hanna Z**, **Zervos MJ**, **Alangaden G**, **Brar I**, and **Suleyman G**. The Impact of Sociodemographic Factors, Comorbidities and Physiologic Response on 30-day Mortality in COVID-19 Patients in Metropolitan Detroit. *Clin Infect Dis* 2020; Epub ahead of print. PMID: 32945856. Full Text

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BACKGROUND: The relationship of health disparities and comorbidities in coronavirus disease 2019 (COVID-19) related outcomes are an ongoing area of interest. This report assesses risk factors associated with mortality in patients presenting with Covid-19 infection and healthcare disparities. METHODS: A retrospective cohort study of consecutive patients presenting to emergency departments within an integrated health system who tested positive for COVID-19 between March 7 and April 30, 2020 in Metropolitan Detroit. The primary outcomes were hospitalization and 30-day mortality. RESULTS: A total of 3,633 patients with mean age of 58 years were included. The majority were female and black non-Hispanic. Sixty-four percent required hospitalization, 56% of whom were black. Hospitalized patients were older, more likely to reside in a low-income area, and had a higher burden of comorbidities. By 30-days, 433 (18.7%) hospitalized patients died. In adjusted analyses, the presence of comorbidities, age >60 years and more severe physiological disturbance were associated with 30-day mortality. Residence in low income areas (odds ratio, 1.02; 95% confidence interval 0.76 - 1.36), and public insurance (odds ratio, 1.24; 95% confidence interval 0.76 - 2.01) were not independently associated with higher risk of mortality. Black female patients had a lower adjusted risk of mortality (odds ratio, 0.46; 95% confidence interval, 0.27 to 0.78). CONCLUSIONS: In this large cohort of COVID-19 patients, those with comorbidities, advanced age, and physiological abnormalities on presentation had higher odds of death. Disparities in income or source of health insurance were not associated with outcomes. Black women had a lower risk of dying.

Internal Medicine
Patel S, **Jamoor K**, **Khan A**, and **Maskoun W**. Late onset complete heart block after transcatheter aortic valve replacement treated with permanent his-bundle pacing. *Pacing Clin Electrophysiol* 2020; Epub ahead of print. PMID: 32940376. Full Text

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Transcatheter aortic valve replacement (TAVR) is a rapidly growing procedure. Conduction disease post TAVR is frequent and routinely monitored for peri-procedurally. Permanent pacemaker placement is relatively common and usually associated with worse outcomes post TAVR. We report a case of very late presenting complete heart block post TAVR treated with His pacing. Our case underscores the need for larger studies to further evaluate the utility of long-term cardiac monitoring post TAVR and outcomes of His bundle pacing in this population. This article is protected by copyright. All rights reserved.

Nephrology
Cotiguala L, Masood A, Park JM, **Samaniego-Picota MD**, Kaul DR, and Naik AS. Increasing Net Immunosuppression after BK Polyoma Virus Infection. *Transpl Infect Dis* 2020:e13472. PMID: 32959930. Full Text

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BACKGROUND: Reducing immunosuppression can effectively treat BK viremia (BKV) and BK nephropathy, but has been associated with increased risks for acute rejection and development of donor specific antibodies (DSA). To date there have been no systematic evaluations of re-escalating immunosuppression in transplant patients with resolving BKV. Importantly, the safety of this approach and impact on graft survival is unclear. METHODS: We performed a single center retrospective review of kidney transplant recipients between July 2011 and June 2013 who had immunosuppression reduction after developing BKV (plasma PCR ≥1,000 copies/mL). Changes in immunosuppression and patient outcomes were tracked until occurrence of a complication event: biopsy-proven

acute rejection (BPAR), detection of de novo DSA, or recurrent BKV. Patients were grouped according to whether or not net immunosuppression was eventually increased. RESULTS: Out of 88 patients with BKV, 44 (50%) had net immunosuppression increased while the other 44 did not. Duration of viremia, peak viremia, induction and sensitization status were similar between the two groups. In a Kaplan-Meier analysis, increasing immunosuppression was associated with less BPAR (p=0.001) and a trend towards less de novo DSA development (p=0.06). Death-censored graft survival (p=0.27) was not different between the two groups. In the net immunosuppression increase group, recurrent BKV occurred in 22.7% without any BKV-related graft losses. CONCLUSION: These findings support potential benefits of increasing immunosuppression in patients with low-level or resolved BKV, but prospective trials are needed to better understand such an approach.

Nephrology

Miller J, **Fadel RA**, **Tang A**, **Perrotta G**, **Herc E**, **Soman S**, **Nair S**, **Hanna Z**, **Zervos MJ**, **Alangaden G**, **Brar I**, and **Suleyman G**. The Impact of Sociodemographic Factors, Comorbidities and Physiologic Response on 30-day Mortality in COVID-19 Patients in Metropolitan Detroit. *Clin Infect Dis* 2020; Epub ahead of print. PMID: 32945856. Full Text

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BACKGROUND: The relationship of health disparities and comorbidities in coronavirus disease 2019 (COVID-19) related outcomes are an ongoing area of interest. This report assesses risk factors associated with mortality in patients presenting with Covid-19 infection and healthcare disparities. METHODS: A retrospective cohort study of consecutive patients presenting to emergency departments within an integrated health system who tested positive for COVID-19 between March 7 and April 30, 2020 in Metropolitan Detroit. The primary outcomes were hospitalization and 30-day mortality. RESULTS: A total of 3,633 patients with mean age of 58 years were included. The majority were female and black non-Hispanic. Sixty-four percent required hospitalization, 56% of whom were black. Hospitalized patients were older, more likely to reside in a low-income area, and had a higher burden of comorbidities. By 30-days, 433 (18.7%) hospitalized patients died. In adjusted analyses, the presence of comorbidities, age >60 years and more severe physiological disturbance were associated with 30-day mortality. Residence in low income areas (odds ratio, 1.02; 95% confidence interval 0.76 - 1.36), and public insurance (odds ratio, 1.24; 95% confidence interval 0.76 - 2.01) were not independently associated with higher risk of mortality. Black female patients had a lower adjusted risk of mortality (odds ratio, 0.46; 95% confidence interval, 0.27 to 0.78). CONCLUSIONS: In this large cohort of COVID-19 patients, those with comorbidities, advanced age, and physiological abnormalities on presentation had higher odds of death. Disparities in income or source of health insurance were not associated with outcomes. Black women had a lower risk of dying.

Nephrology

Naik AS, Le D, Aqeel J, Wang SQ, Chowdhury M, Walters LM, Cibrik DM, **Samaniego M**, and Wiggins RC. Podocyte stress and detachment measured in urine are related to mean arterial pressure in healthy humans. *Kidney Int* 2020; 98(3):699-707. PMID: 32739208. Full Text

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Hypertension-associated progressive glomerulosclerosis is a significant driver of both de novo and all-cause chronic kidney disease leading to end-stage kidney failure. The progression of glomerular disease proceeds via continuing depletion of podocytes from the glomeruli into the ultrafiltrate. To non-invasively assess injury patterns associated with mean arterial pressure (MAP), we conducted an observational study of 87 healthy normotensive individuals who were cleared for living kidney donation. Urine pellet podocin and aquaporin2 mRNAs normalized to the urine creatinine concentration (UPod:Creat ratio and UAqp2:Creat ratio) were used as markers of podocyte detachment and tubular injury, respectively. The ratio of two podocyte mRNA markers, podocin to nephrin (UPod:Neph) as well as the ratio of podocin to the tubular marker aquaporin2 (UPod:Aqp2) estimated the relative rates of podocyte stress and glomerular vs. tubular injury. The MAP was positively correlated with the UPod:Neph and UPod:Aqp2, thereby confirming the relationship of MAP with podocyte stress and the preferential targeting of the glomerulus by higher MAP. In multivariable linear regression analysis, both UPod:Neph and UPod:Creat, but not UAqp2:Creat or proteinuria, were both significantly related to a range of normal MAP (70 to 110 mm Hg). Systolic, as opposed to diastolic or pulse pressure was associated with UPod:Creat. Thus, higher podocyte stress and detachment into the

urine are associated with MAP even in a relatively "normal" range of MAP. Hence, urine pellet mRNA monitoring can potentially identify progression risk before the onset of overt hypertension, proteinuria or chronic kidney disease.

Nephrology
Singh N, Tandukar S, Zibari G, Naseer MS, Amiri HS, and **Samaniego M**. Successful Simultaneous Pancreas and Kidney Transplant in a Patient Post-COVID-19 Infection. *Kidney Int* 2020; Epub ahead of print. PMID: 32946881. Full Text

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Neurology
Francoeur CL, Lee J, Dangayach N, Gidwani U, and **Mayer SA**. Non-invasive cerebral perfusion monitoring in cardiac arrest patients: a prospective cohort study. *Clin Neurol Neurosurg* 2020; 196:105970. PMID: 32505869. Full Text

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OBJECTIVES: To determine if non-invasive cerebral perfusion estimation provided by a new acousto-optic technology can be used as a reliable predictor of neurological outcome. PATIENTS AND METHODS: We performed a prospective, observational cohort study of consecutive comatose patients successfully resuscitated from out-of-hospital cardiac arrest. Patients were monitored using c-FLOW (Ornim Medical) from critical care unit admission up to 72 h, full awakening, or death. Primary outcome was favourable neurological outcome at hospital discharge, defined as a Cerebral Performance Category score of 1 or 2. RESULTS: A total of 21 patients were enrolled, without any loss to follow-up. Mean perfusion index over the monitoring period was not associated with functional outcome at hospital discharge (OR 1.03 [0.93, 1.17]). Adjustment for initial rhythm, time to return of spontaneous circulation and Glasgow coma scale motor score did not significantly alter the results (OR 1.06 [0.99, 1.12]). Mean perfusion index showed a poor discriminative value with an area under the curve of 0.60 for functional outcome (0.64 for survival). Correlation between the probes was weak (Pearson coefficient 0.35). CONCLUSION: Cerebral perfusion monitoring using a c-FLOW device in survivors of cardiac arrest is feasible, but reliability of the information provided has yet to be demonstrated. In our cohort, we were unable to identify any association between the perfusion index and clinical outcomes at discharge. As such, clinical management of cardiac arrest patients based on non-invasive perfusion index is not supported and should be limited to research protocols. The trial was registered with ClinicalTrials.gov, number NCT02575196.

Neurology
Grover KM, and **Sripathi N**. Myasthenia Gravis and Pregnancy. *Muscle Nerve* 2020; Epub ahead of print. PMID: 32929722. Full Text

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Neurology

Liu X, **Fan B**, **Chopp M**, and **Zhang Z**. Epigenetic Mechanisms Underlying Adult Post Stroke Neurogenesis. *Int J Mol Sci* 2020; 21(17). PMID: 32867041. Full Text

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Stroke remains the leading cause of adult disability. Post-stroke neurogenesis contributes to functional recovery. As an intrinsic neurorestorative process, it is important to elucidate the molecular mechanism underlying stroke-induced neurogenesis and to develop therapies designed specifically to augment neurogenesis. Epigenetic mechanisms include DNA methylation, histone modification and its mediation by microRNAs and long-non-coding RNAs. In this review, we highlight how epigenetic factors including DNA methylation, histone modification, microRNAs and long-non-coding RNAs mediate stroke-induced neurogenesis including neural stem cell self-renewal and cell fate determination. We also summarize therapies targeting these mechanisms in the treatment of stroke.

Neurology

Morris DC, **Jaehne AK**, **Chopp M**, **Zhang Z**, **Poisson L**, **Chen Y**, **Datta I**, and **Rivers EP**. Proteomic Profiles of Exosomes of Septic Patients Presenting to the Emergency Department Compared to Healthy Controls. *J Clin Med* 2020; 9(9). PMID: 32932765. Full Text

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BACKGROUND: Septic Emergency Department (ED) patients provide a unique opportunity to investigate early sepsis. Recent work focuses on exosomes, nanoparticle-sized lipid vesicles (30-130 nm) that are released into the bloodstream to transfer its contents (RNA, miRNA, DNA, protein) to other cells. Little is known about how early changes related to exosomes may contribute to the dysregulated inflammatory septic response that leads to multi-organ dysfunction. We aimed to evaluate proteomic profiles of plasma derived exosomes obtained from septic ED patients and healthy controls. METHODS: This is a prospective observational pilot study evaluating a plasma proteomic exosome profile at an urban tertiary care hospital ED using a single venipuncture blood draw, collecting 40 cc Ethylenediaminetetraacetic acid (EDTA) blood. MEASUREMENTS: We recruited seven patients in the ED within 6 h of their presentation and five healthy controls. Plasma exosomes were isolated using the Invitrogen Total Exosome Isolation Kit. Exosome proteomic profiles were analyzed using fusion mass spectroscopy and Proteome Discoverer. Principal component analysis (PCA) and differential expression analysis (DEA) for sepsis versus control was performed. RESULTS: PCA of 261 proteins demonstrated septic patients and healthy controls were distributed in two groups. DEA revealed that 62 (23.8%) proteins differed between the exosomes of septic patients and healthy controls, p-value < 0.05. Adjustments using the False Discovery Rate (FDR) showed 23 proteins remained significantly different (FDR < 0.05) between sepsis and controls. Septic patients and controls were classified into two distinct groups by hierarchical clustering using the 62 nominally DE proteins. After adjustment multiple comparisons, three acute phase proteins remained significantly different between patients and controls: Serum amyloid A-1, C-reactive protein and Serum Amyloid A-2. Inflammatory response proteins immunoglobulin heavy constant Δ and Fc-fragment of IgG binding protein were increased. CONCLUSION: Exosome proteomic profiles of septic ED patients differ from their healthy counterparts with regard to acute phase response and inflammation.

Neurology

Syed MJ, Lisak RP, **Delly F**, and Zutshi D. Reply from the authors: Myasthenic crises in COVID-19. *J Neurol Sci* 2020; 417:117061. PMID: 32741591. Full Text

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Neurology

Venkat P, **Zacharek A**, **Landschoot-Ward J**, **Wang F**, **Culmone L**, **Chen Z**, **Chopp M**, and **Chen J**. Exosomes derived from bone marrow mesenchymal stem cells harvested from type two diabetes rats promotes neurorestorative effects after stroke in type two diabetes rats. *Exp Neurol* 2020; 334:113456. PMID: 32889008. Full Text

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BACKGROUND AND PURPOSE: Diabetes elevates the risk of stroke, promotes inflammation, and exacerbates vascular and white matter damage post stroke, thereby hindering long term functional recovery. Here, we investigated the neurorestorative effects and the underlying therapeutic mechanisms of treatment of stroke in type 2 diabetic rats (T2DM) using exosomes harvested from bone marrow stromal cells obtained from T2DM rats (T2DM-MSC-Exo). METHODS: T2DM was induced in adult male Wistar rats using a combination of high fat diet and Streptozotocin. Rats were subjected to transient 2 h middle cerebral artery occlusion (MCAo) and 3 days later randomized to one of the following treatment groups: 1) phosphate-buffered-saline (PBS, i.v), 2) T2DM-MSC-Exo, (3 × 10(11), i.v), 3) T2DM-MSC-Exo with miR-9 over expression (miR9+/+-T2DM-MSC-Exo, 3 × 10(11), i.v) or 4) MSC-Exo derived from normoglycemic rats (Nor-MSC-Exo) (3 × 10(11), i.v). T2DM sham control group is included as reference. Rats were sacrificed 28 days after MCAo. RESULTS: T2DM-MSC-Exo treatment does not alter blood glucose, lipid levels, or lesion volume, but significantly improves neurological function and attenuates post-stroke weight loss compared to PBS treated as well as Nor-MSC-Exo treated T2DM-stroke rats. Compared to PBS treatment, T2DM-MSC-Exo treatment of T2DM-stroke rats significantly 1) increases tight junction protein ZO-1 and improves blood brain barrier (BBB) integrity; 2) promotes white matter remodeling indicated by increased axon and myelin density, and increases oligodendrocytes and oligodendrocyte progenitor cell numbers in the ischemic border zone as well as increases primary cortical neuronal axonal outgrowth; 3) decreases activated microglia, M1 macrophages, and inflammatory factors MMP-9 (matrix mettaloproteinase-9) and MCP-1 (monocyte chemoattractant protein-1) expression in the ischemic brain; and 4) decreases miR-9 expression in serum, and increases miR-9 target ABCA1 (ATP-binding cassette transporter 1) and IGFR1 (Insulin-like growth factor 1 receptor) expression in the brain. MiR9+/+-T2DM-MSC-Exo treatment significantly increases serum miR-9 expression compared to PBS treated and T2DM-MSC-Exo treated T2DM stroke rats. Treatment of T2DM stroke with miR9+/+-T2DM-MSC-Exo fails to improve functional outcome and attenuates T2DM-MSC-Exo treatment induced white matter remodeling and anti-inflammatory effects in T2DM stroke rats. CONCLUSIONS: T2DM-MSC-Exo treatment for stroke in T2DM rats promotes neurorestorative effects and improves functional outcome. Down regulation of miR-9 expression and increasing its target ABCA1 pathway may contribute partially to T2DM-MSC-Exo treatment induced white matter remodeling and anti-inflammatory responses.

Neurosurgery

Alexander C, Caras A, Miller WK, **Tahir R**, **Mansour TR**, Medhkour A, and **Marin H**. M2 segment thrombectomy is not associated with increased complication risk compared to M1 segment: A meta-analysis of recent literature. *J Stroke Cerebrovasc Dis* 2020; 29(9):105018. PMID: 32807433. Full Text

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INTRODUCTION: Recent clinical comparisons of M1 and M2 segment endovascular thrombectomy have reached incongruous results in rates of complication and functional outcomes. This study aims to clarify the controversy surrounding this rapidly advancing technique through literature review and meta-analysis. METHODS: A Pubmed search was performed (January 2015-September 2019) using the following keywords: "M2 AND ("stroke" OR "occlusion") AND ("thrombectomy" OR "endovascular")". Safety and clinical outcomes were compared between segments via weighted Student's t-test, Chi-square and odds ratio while study heterogeneity was analyzed using Cochran Q and I(2) tests. RESULTS: Pubmed identified 208 articles and eleven studies were included after full-text analysis, comprising 2,548 M1 and 758 M2 mechanical thrombectomy segment cases. Baseline National Institutes of Health Stroke Scale scores were comparatively lower in patients experiencing an M2 occlusion (16 ± 1.25 vs 13.6 ± 0.96, p < 0.01). Patients who underwent M2 mechanical thrombectomy were more likely to experience both good clinical outcomes (modified Rankin Scale 0-2) (48.6% vs 43.5% respectively, OR 1.24; CI 1.05-1.47, p = 0.01) and excellent clinical outcomes (modified Rankin Scale 0-1) (34.7% vs. 26.5%%, OR 1.6; CI 1.28-1.99, p < 0.01) at 90 days compared to M1 mechanical thrombectomy. Neither recanalization rates (75.3% vs 72.8%, OR 0.92, CI 0.75-1.13, p = 0.44) nor symptomatic intracranial hemorrhage rates (5.6% vs 4.9%, OR 0.92; CI 0.61-1.39, p= 0.7) were significantly different between M1 and M2 cohorts. Mortality was less frequent in the M2 cohort compared to M1 (16.3% vs 20.7%, OR 0.73; CI 0.57-0.94, p = 0.01). M1 and M2 cohorts did not differ in symptom onset-to-puncture (238.1 ± 46.7 vs 239.8 ± 43.9 min respectively, p=0.488) nor symptom onset-to recanalization times (318.7 ± 46.6 vs 317.7 ± 71.1 min respectively, p = 0.772), though mean operative duration was shorter in the M2 cohort (61.8 ± 25.5

vs 54.6 ± 24 min, p < 0.01). CONCLUSIONS: Patients who underwent M2 mechanical thrombectomy had a higher prevalence of good and excellent clinical outcomes compared to the M1 mechanical thrombectomy cohorts. Additionally, our data suggest lower mortality rates in the M2 cohort and symptomatic intracranial hemorrhage rates that are similar to the M1 cohort. Therefore, M2 segment thrombectomy likely does not pose a significantly elevated operative risk and may have a positive impact on patient outcomes.

Neurosurgery
Saadmim F, Forhad T, Sikder A, Ghann W, **M MA**, Sitther V, Ahammad AJS, Subhan MA, and Uddin J. Enhancing the Performance of Dye Sensitized Solar Cells Using Silver Nanoparticles Modified Photoanode. *Molecules* 2020; 25(17). PMID: 32899213. Full Text

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In this study, silver nanoparticles were synthesized, characterized, and applied to a dye-sensitized solar cell (DSSC) to enhance the efficiency of solar cells. The synthesized silver nanoparticles were characterized with UV-Vis spectroscopy, dynamic light scattering, transmission electron microscopy, and field emission scanning electron microscopy. The silver nanoparticles infused titanium dioxide film was also characterized by Fourier transform infrared and Raman spectroscopy. The performance of DSSC fabricated with silver nanoparticle-modified photoanode was compared with that of a control group. The current and voltage characteristics of the devices as well as the electrochemical impedance measurements were also carried out to assess the performance of the fabricated solar cells. The solar-to-electric efficiency of silver nanoparticles based DSSC was 1.76%, which is quite remarkable compared to the 0.98% realized for DSSC fabricated without silver nanoparticles.

Neurosurgery
Schwalb JM. Commentary: Impact of Spinal Cord Stimulation on Opioid Dose Reduction: A Nationwide Analysis. *Neurosurgery* 2020; Epub ahead of print. PMID: 32888297. Full Text

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Neurosurgery
Zervos TM, **Bazydlo M**, **Tundo K**, **Macki M**, and **Rock J**. Risk Factors Associated With Symptomatic Deep Vein Thrombosis Following Elective Spine Surgery: A Case Control Study. *World Neurosurg* 2020; Epub ahead of print. PMID: 32889183. Full Text

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BACKGROUND: Few studies provide insight into risk factors (RFs) associated with postoperative deep vein thrombosis (DVT) following elective spinal surgery. DVTs are detrimental in this population due to the risk of pulmonary embolization or surgical site hemorrhage with treatment. OBJECTIVE: Elective spine surgery patients have a low incidence of DVT, thus, a case-control study was selected to investigate RFs associated with postoperative symptomatic DVT. METHODS: Cases were matched to controls in a 1:2 ratio based on surgery type. Risk of having a prior DVT and choice of subcutaneous heparin dosing following surgery was analyzed in a multivariate regression model with other potentially confounding variables. RESULTS: 195 patients were included in this study. Independent of patient age, history of DVT was associated with postoperative symptomatic DVT (OR 4.09, 95% CI 1.22-13.78). Two versus three times daily postoperative heparin dosing (OR 1.56, 95% CI 0.32-7.56), surgery length (OR 1.32, 95% CI 0.98-1.79), and patient age (OR 1.04, 95% CI 1.0-1.08) were not statistically significant, independent RFs. Older age and longer length of surgery trended toward association with DVT without reaching significance. Length of stay (LOS) was increased from 3-5 days (P<0.001) in DVT patients compared to controls. CONCLUSIONS: These results suggest that patients with a history of DVT undergoing elective spinal surgery are at higher risk of developing symptomatic DVT postoperatively resulting in significantly increased LOS. Further study on

additional preoperative screening and medical optimization in elective spine surgery patients may help reduce the rate of symptomatic postoperative DVT.

Nursing
Simanovski J, and Ralph J. Readmissions After Lung Transplantation. *Prog Transplant* 2020; Epub ahead of print. PMID: 32912114. Full Text

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Lung transplantation has evolved to become an acceptable therapy for individuals with end-stage lung disease. Readmissions rates after lung transplantation remain high as compared to other medical surgical populations. The purpose of this review is to synthesize the current body of knowledge about patterns, risk factors, and outcomes of readmissions after lung transplantation. The literature revealed that the most common admission diagnoses linked to lung transplant readmissions are infections followed by tachyarrhythmias, airway complications, surgical complications, rejection, thromboembolic events, gastrointestinal complications, and renal dysfunction. Risk factors for these readmissions include male gender, longer intensive care unit stay, reintubation, prolonged chest tube air leak, frailty, and discharge to a long-term care facility. Outcomes of multiple readmissions after lung transplantation are associated with decreased survival and increased risk of mortality. Further research is needed to better understand which readmission diagnoses are preventable and whether multidisciplinary interventions can reduce readmission rates among patients after lung transplantation.

Ophthalmology and Eye Care Services
Hamid MS, **Steen DW**, **Ormsby AH**, Lin X, and **Le KH**. Inflamed nonlimbal scleral dermoid masquerading as nodular scleritis. *J aapos* 2020; Epub ahead of print. PMID: 32931936. Full Text

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Orthopaedics/Bone and Joint
Bell KL, Detweiler M, Yayac M, Penna S, and Chen AF. Preoperative Opioid Use Increases the Cost of Care in Total Joint Arthroplasty. *J Am Acad Orthop Surg* 2020; Epub ahead of print. PMID: 32925386. Full Text

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INTRODUCTION: Predictors of financial costs related to total joint arthroplasty (TJA) have become increasingly important becuase payment methods have shifted from fee for service to bundled payments. The purpose of this study was to assess the relationship between preoperative opioid use and cost of care in primary TJA. METHODS: A retrospective study was conducted in Medicare patients who underwent elective unilateral primary total knee or hip arthroplasty between 2015 and 2018. Preoperative opioid usage, comorbidities, length of stay, and demographic information were obtained from chart review. The total episode-of-care (EOC) cost data was obtained from the Centers of Medicare and Medicaid Services based on Bundled Payments for Care Improvement Initiative Model 2, including index hospital and 90-day postacute care costs. Patients were grouped based on preoperative opioid usage. Costs were compared between groups, and multivariate linear regression analyses were performed to analyze whether preoperative opioid usage influenced the cost of TJA care. Analyses were risk-adjusted for patient risk factors, including comorbidities and demographics. RESULTS: A total of 3,211 patients were included in the study. Of the 3,211 TJAs, 569 of 3,211 patients (17.7%) used preoperative opioids, of which 242 (42.5%) only used tramadol. EOC costs were significantly higher for opioid and tramadol users than nonopioid users ($19,229 versus $19,403 versus $17,572, $P < 0.001$). Multivariate regression predicted that the use of preoperative opioids in TJA was associated with increased EOC costs by $789 for opioid users (95% confidence interval [CI] $559 to $1,019, $P < 0.001$) and $430 for tramadol users (95% CI $167 to $694, $P = 0.001$). Total postacute care costs were also increased by 70% for opioid users (95% CI 44% to 102%, $P < 0.001$) and 48% for tramadol users (95% CI 22% to 80%, $P < 0.001$). DISCUSSION: This study demonstrated that preoperative opioid usage was associated with higher cost of care in TJA. Limiting preoperative opioid use for pain management before TJA could contribute to cost savings within a bundled model.

Orthopaedics/Bone and Joint

Jelsema TR, **Tam AC**, and **Moeller JL**. Injectable Ketorolac and Corticosteroid Use in Athletes: A Systematic Review. *Sports Health* 2020; Epub ahead of print.:1941738120946008. PMID: 32877323. Full Text

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CONTEXT: The use of injectable medications to help athletes quickly return to the field of play after injury is common. Understanding the effects and risks of these medications will help providers make informed decisions regarding their use in this patient population. OBJECTIVE: To evaluate the utilization, efficacy, and adverse effects of injectable ketorolac and corticosteroids in athletes. DATA SOURCES: This systematic review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A systematic search of the literature was performed using multiple databases (PubMed, Embase, Cochrane, Web of Science, and ClinicalTrials.gov). Secondary references were appraised for relevant articles. No randomized controlled trials or other prospective studies were identified. Articles included retrospective database reviews and physician survey studies. STUDY SELECTION: A total of 6 studies met the inclusion and exclusion criteria and were reviewed by 2 independent reviewers with a third consulted in the case of disagreement, which was not needed. STUDY DESIGN: Systematic review. LEVEL OF EVIDENCE: Level 5. DATA EXTRACTION: Two reviewers recorded rate of use, effectiveness of treatment, and reported side effect data. RESULTS: Most studies centered around the football athlete, either professional or collegiate. Professional football game day use of intramuscular ketorolac declined from 93.3% (28/30) in 2002 to 48% in 2016. Collegiate football game day use of intramuscular ketorolac declined from 62% in 2008 to 26% in 2016. Game day corticosteroid injection was far lower than ketorolac usage. Both medications were reported to be effective with few adverse events. CONCLUSION: Use of injectable ketorolac is common but declining in professional and college football. Pain control efficacy is good, and risk of adverse events is low. The incidence of injectable corticosteroid use in athletes is unknown. Use of injectable corticosteroids in athletes allows for early return to sport activities with no reported complications.

Orthopaedics/Bone and Joint

McDonald M, **Ward L**, Sorenson B, **Wortham H**, Jarski R, and **El-Yussif E**. The Effect of a 6am-9am Dedicated Orthopaedic Trauma Room on Hip Fracture Outcomes in a Community Level II Trauma Center. *J Orthop Trauma* 2020; Epub ahead of print. PMID: 32956207. Full Text

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OBJECTIVE: To assess the outcomes of elderly hip fracture surgeries performed 12 months before and 12 months after the implementation of a daily 6am-9am DOTR at a Level II community trauma center. DESIGN: Retrospective cohort study SETTING:: Level II academic trauma center PATIENTS:: A total of 431 consecutive trauma patients undergoing surgical management of isolated low energy hip fractures from January 1, 2018, to December 31, 2019. INTERVENTION: Implementation of a 6am-9am DOTR Monday through Friday MAIN OUTCOME MEASURES:: Time to surgery, number of cases performed after-hours, surgical time, 90-day morbidity and mortality, and time to therapy. RESULTS: Retrospective analysis showed that despite a 24% increase in surgical hip fracture volume, implementation of a part-time DOTR led to a decrease in after-hours surgery (32.4% vs. 19.6%; P=0.008) and patients requiring the intensive care unit postoperatively (7% vs. 3.8%; P=0.036). Surgeries performed after-hours were longer compared to surgeries performed during the daytime (82.0 minutes vs. 68 minutes; P=0.003) and had more complications (pneumonia, pulmonary embolism and surgical site infection; P=0.002, 0.047, 0.024, respectively). CONCLUSIONS: Our results show that a part-time DOTR in a community Level II hospital is associated with improvement in patient care. LEVEL OF EVIDENCE: Therapeutic Level III. See Instructions for Authors for a complete description of levels of evidence.

Orthopaedics/Bone and Joint

Moeller JL, and Galasso L. Pelvic Region Avulsion Fractures in Adolescent Athletes: A Series of 242 Cases. *Clin J Sport Med* 2020; Epub ahead of print. PMID: 32941369. Full Text

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OBJECTIVE: The objective of this descriptive study was to evaluate pelvic region avulsion fractures in adolescents, including age of injury, location of injury, activity and mechanism at time of injury, treatments used, duration of treatment, and outcomes. DESIGN: This was a retrospective chart review of patients who presented with pelvic region avulsion fracture over a 19-year period. SETTING: Private practice, primary care sports medicine clinic.

PATIENTS: All patients younger than 20 years of age diagnosed with an acute pelvic region avulsion fracture. INTERVENTIONS: There was no set intervention protocol. A variety of interventions and combination of interventions were used and determined by the treating physician on a case-by-case basis. MAIN OUTCOME MEASURES: Clearance for return toward sport activities. RESULTS: Of the 242 cases, 162 were male. Soccer was the most common sport at the time of injury, and running/sprinting was the most common mechanism. Males were generally older at presentation and were more likely than females to have anterior inferior iliac spine injuries, whereas females were more likely to have iliac crest avulsions. Conservative treatment was effective in all cases. Males were treated for a shorter duration than females, but this difference was not statistically significant. CONCLUSIONS: Pelvic avulsion fractures are a rare injury in adolescent athletes. Males are twice as likely to experience these injuries and are older at presentation compared to females. Conservative management leads to successful outcomes in most cases.

Orthopaedics/Bone and Joint
Umeh ON, **Beekman R**, **D'sa H**, and **Friedman BJ**. Elderly Man With Progressive Nail Atrophy: Challenge. *Am J Dermatopathol* 2020; Epub ahead of print. PMID: 32932300. Full Text

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Otolaryngology
Dhillon VK, Randolph GW, Stack BC, Jr., Lindeman B, Bloom G, Sinclair CF, Woodson G, Brooks JA, Childs LF, Esfandiari NH, Evangelista L, Guardiani E, Quintanilla-Dieck L, Naunheim MR, Shindo M, **Singer M**, Tolley N, Angelos P, Kupfer R, Banuchi V, Liddy W, and Tufano RP. Immediate and partial neural dysfunction after thyroid and parathyroid surgery: Need for recognition, laryngeal exam, and early treatment. *Head Neck* 2020; Epub ahead of print. PMID: 32954575. Full Text

BACKGROUND: Laryngeal dysfunction after thyroid and parathyroid surgery requires early recognition and a standardized approach for patients that present with voice, swallowing, and breathing issues. The Endocrine Committee of the American Head and Neck Society (AHNS) convened a panel to define the terms "immediate vocal fold paralysis" and "partial neural dysfunction" and to provide clinical consensus statements based on review of the literature, integrated with expert opinion of the group. METHODS: A multidisciplinary expert panel constructed the manuscript and recommendations for laryngeal dysfunction after thyroid and parathyroid surgery. A meta-analysis was performed using the literature and published guidelines. Consensus was achieved using polling and a modified Delphi approach. RESULTS: Twenty-two panelists achieved consensus on five statements regarding the role of early identification and standardization of evaluation for patients with "immediate vocal fold paralysis" and "partial neural dysfunction" after thyroid and parathyroid surgery. CONCLUSION: After endorsement by the AHNS Endocrine Section and Quality of Care Committee, it received final approval from the AHNS Council.

Otolaryngology
Krane NA, Fagin A, **Ghanem TA**, Cannady SB, Petrisor D, and Wax MK. Simultaneous maxillary and mandibular reconstruction with a single Osteocutaneous fibula free flap: A description of three cases. *Microsurgery* 2020; Epub ahead of print. PMID: 32956515. Full Text

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Large defects that comprise both the maxilla and mandible prove to be difficult reconstructive endeavors and commonly require two free tissue transfers. Three cases are presented to discuss an option for simultaneous reconstruction of maxillary and mandibular defects using a single osteocutaneous fibula free flap. The first case describes a 16-year-old male with a history of extensive facial trauma sustained in a boat propeller accident resulting in a class IId maxillary and 5 cm mandibular defect status post three failed reconstructive surgeries; the second, a 33-year-old male with recurrent rhabdomyosarcoma of the muscles of mastication with resultant hemi-mandibulectomy and class IId maxillary defects; and lastly, a 48-year-old male presenting after a failed scapular free flap to reconstruct defects resulting from a self-inflicted gunshot wound, which included a 5 cm defect of the right mandibular body and 4.5 cm defect of the inferior maxillary bone. In all cases, a single osteocutaneous fibula free flap was used in two bone segments; one to obturate the maxillary defect and restore alveolar bone and the other to reconstruct the

mandibular defect. The most recent patient was able to undergo implantable dental rehabilitation. Postoperatively, the free flaps were viable and masticatory function was restored in all patients during a follow-up range of 2-4 years.

Otolaryngology
Lechner MG, Bernardo AC, Lampe A, Praw SS, **Tam SH**, and Angell TE. Changes in Stage Distribution and Disease-Specific Survival in Differentiated Thyroid Cancer with Transition to American Joint Committee on Cancer 8th Edition: A Systematic Review and Meta-Analysis. *Oncologist* 2020; Epub ahead of print. PMID: 32864832. Full Text

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BACKGROUND: Recent revision significantly changed the American Joint Committee on Cancer (AJCC) staging criteria for differentiated thyroid cancer (DTC). To quantitatively evaluate resulting changes in patient stage distribution and the associated disease-specific survival (DSS) incorporating diverse populations, we performed a meta-analysis of studies comparing the AJCC 7th edition (AJCC-7) with 8th edition (AJCC-8) staging for DTC. MATERIALS AND METHODS: After PROSPERO registration (#CRD42019123657), publications in English reporting DSS of DTC with AJCC-7 and AJCC-8 from inception to June 2019 were identified by search of MEDLINE and PubMed. Random-effects meta-analyses were conducted to compare differences in survival between AJCC-7 and AJCC-8. Pooled hazard ratios, 10-year DSS, and corresponding interval estimates were calculated for AJCC subgroups. Differences in survival between editions were assessed using subgroup analysis with nonoverlapping confidence intervals indicating statistical significance. RESULTS: Final analysis included six studies with 10,850 subjects and median follow-up from 55 to 148 months. Use of AJCC-8 shifted classification to earlier stages: stage I, from 60% to 81%; stage II, from 5% to 13%; stage III, from 21% to 2%; stage IV, from 10% to 3%. Ten-year DSS was significantly lower in AJCC-8 versus AJCC-7 in patients with stage II (88.6%, 95% confidence interval [CI] 82.7-94.6% vs. 98.1%, 95% CI 96.6-99.6%, respectively) and stage III disease (70.5%, 95% CI 59.1-83.9% vs. 96.8%, 95% CI 94.1-99.64%, respectively). CONCLUSION: Meta-analysis of revised AJCC staging for DTC, incorporating diverse populations, demonstrates redistribution of patients toward earlier clinical stages and better stratification of disease-specific mortality risk, specifically among patients now classified with stage II and III disease. IMPLICATIONS FOR PRACTICE: This study provides updated estimates of disease-specific survival for patients with differentiated thyroid cancer determined by the American Joint Committee on Cancer staging system that are generalizable to broader populations and support improved stratification using the recently revised criteria.

Otolaryngology
Peleman JR, **Tarwade P**, **Han X**, **Penning DH**, and **Craig JR**. Hemodynamic Changes with 1:1000 Epinephrine on Wrung-Out Pledgets Before and During Sinus Surgery. *Ann Otol Rhinol Laryngol* 2020; Epub ahead of print. PMID: 32945177. Full Text

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BACKGROUND: Intranasal topical 1:1000 epinephrine has been used safely and effectively for hemostasis during endoscopic sinus surgery (ESS). Prior studies assessing hemodynamic changes after intranasal topical epinephrine application have only used soaking wet cottonoid pledgets, and have only assessed for hemodynamic changes before any surgery being performed. OBJECTIVE: The purposes of this study were to determine whether intranasal application of topical 1:1000 epinephrine with wrung-out cottonoid pledgets caused significant hemodynamic changes both before and during ESS, and whether it allowed for adequate hemostasis. METHODS: A prospective evaluation of 30 patients with eosinophilic chronic rhinosinusitis with nasal polyps (CRSwNP) undergoing complete bilateral ESS was conducted. Heart rate, blood pressure (systolic, diastolic, and mean arterial pressure), and electrocardiography changes were recorded at 0, 1, 2, and 5-minute intervals after placing wrung-out epinephrine-saturated pledgets, both before and at the end of ESS. No submucosal epinephrine injections were performed. Estimated blood loss (EBL) and major intraoperative complications were recorded for all cases. RESULTS: There were no significant hemodynamic changes or electrocardiographic abnormalities after placement of wrung-out epinephrine-soaked pledgets both before and after ESS. After bilateral ESS, there were actually mean decreases in heart rate and blood pressure parameters. Mean EBL was 75.8 ± 32.2 mL, and no major intraoperative complications occurred.

CONCLUSION: Intranasal application of topical 1:1000 epinephrine via wrung-out cottonoid pledgets was effective for intraoperative hemostasis, and did not cause clinically significant alterations in hemodynamic parameters or cardiovascular events, either before or during ESS in patients with CRSwNP. Level of Evidence: 4.

Otolaryngology

Wang X, Langer EM, Daniel CJ, Janghorban M, **Wu V**, Wang XJ, and Sears RC. Altering MYC phosphorylation in the epidermis increases the stem cell population and contributes to the development, progression, and metastasis of squamous cell carcinoma. *Oncogenesis* 2020; 9(9):79. PMID: 32895364. Full Text

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cMYC (MYC) is a potent oncoprotein that is subject to post-translational modifications that affect its stability and activity. Here, we show that Serine 62 phosphorylation, which increases MYC stability and oncogenic activity, is elevated while Threonine 58 phosphorylation, which targets MYC for degradation, is decreased in squamous cell carcinoma (SCC). The oncogenic role of MYC in the development of SCC is unclear since studies have shown in normal skin that wild-type MYC overexpression can drive loss of stem cells and epidermal differentiation. To investigate whether and how altered MYC phosphorylation might affect SCC development, progression, and metastasis, we generated mice with inducible expression of MYC(WT) or MYC(T58A) in the basal layer of the skin epidermis. In the T58A mutant, MYC is stabilized with constitutive S62 phosphorylation. When challenged with DMBA/TPA-mediated carcinogenesis, MYC(T58A) mice had accelerated development of papillomas, increased conversion to malignant lesions, and increased metastasis as compared to MYC(WT) mice. In addition, MYC(T58A)-driven SCC displayed stem cell gene expression not observed with MYC(WT), including increased expression of Lgr6, Sox2, and CD34. In support of MYC(T58A) enhancing stem cell phenotypes, its expression was associated with an increased number of BrdU long-term label-retaining cells, increased CD34 expression in hair follicles, and increased colony formation from neonatal keratinocytes. Together, these results indicate that altering MYC phosphorylation changes its oncogenic activity-instead of diminishing establishment and/or maintenance of epidermal stem cell populations like wild-type MYC, pS62-MYC enhances these populations and, under carcinogenic conditions, pS62-MYC expression results in aggressive tumor phenotypes.

Pathology and Laboratory Medicine

Agaimy A, Bonert M, Naqvi A, Wang C, Trpkov K, Dettmar P, Wintzer HO, Stoehr R, Hes O, **Williamson SR**, Gibson IW, and Hartmann A. Langerhans Cell Histiocytosis Associated With Renal Cell Carcinoma Is a Neoplastic Process: Clinicopathologic and Molecular Study of 7 Cases. *Am J Surg Pathol* 2020; Epub ahead of print. PMID: 32910018. Full Text

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Langerhans cell histiocytosis (LCH) is a rare histiocytic disorder composed of Langerhans cells admixed with reactive mononuclear and granulocytic cells, associated with prominent eosinophils. LCH is considered a neoplasm, driven in most cases by oncogenic RAS/RAF/MEK/ERK pathway mutations. The disease predominantly affects children. Urinary system involvement has rarely been reported in a multisystem disease setting. We describe 7 patients who presented with LCH occurring within (6 cases) or after (1 case) a resected clear cell (n=6) or clear cell papillary (n=1) renal cell carcinoma (RCC), identified prospectively in our routine and consultation files (2012 to 2019). The patients included 5 women and 2 men, with a median age of 54 years (range, 39 to 73 y), none with a history of LCH or LCH

manifestations before the time of RCC diagnosis. The median size of the RCC was 3.5 cm (range, 1.8 to 8.3 cm). Treatment included partial (5 cases), or radical (2 cases) nephrectomy. All RCCs on gross examination showed at least focal cystic changes and were low grade (World Health Organization [WHO]/International Society of Urologic Pathologists [ISUP] grade 1 to 2). The LCH foci were detected as incidental histological finding within the resected RCC in all six cases and they were limited to few high-power fields (<2 mm) in 5 of 6 cases, but in the sixth case, they occupied almost the entire clear cell papillary RCC (2 cm nodule). No LCH manifestations were detected in the normal kidney or in perinephric fat. The seventh patient developed LCH within inguinal deep soft tissue followed by systemic manifestations 6 years after clear cell RCC. Langerhans cell immunophenotype was supported by the reactivity for S-100, CD1a, and langerin and by the negative pankeratin. Successful pyrosequencing of microdissected LCH DNA revealed the V600E BRAF mutation in all 6 cases of LCH within RCC. To our knowledge, only 3 similar cases were published since 1980; the only case tested for BRAF mutation showed wild-type BRAF. This is the first study analyzing the morphologic and genetic features of a cohort of LCH associated with RCC. In our experience, these cases may be underrecognized in practice, or may erroneously be diagnosed as RCC dedifferentiation or high-grade sarcomatoid transformation. Finally, the detection of BRAF mutation further confirms that LCH in this setting is indeed a neoplasm, rather than a reactive lesion.

Pathology and Laboratory Medicine

Alanee S, **Deebajah M**, **Taneja K**, **Cole D**, **Pantelic M**, **Peabody J**, **Williamson SR**, **Gupta N**, **Dabaja A**, and **Menon M**. Post prostatectomy Pathologic Findings of Patients with Clinically Significant Prostate Cancer and no Significant PI-RADS Lesions on Preoperative Magnetic Resonance Imaging. *Urology* 2020; Epub ahead of print. PMID: 32946907. Full Text

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OBJECTIVES: We present post-prostatectomy pathology results from a series of prostate cancer (Pca) Gleason grade group ≥ 2 patients who did not have findings suggestive of cancer on preoperative pelvic magnetic resonance imaging (MRI). METHODS: We performed an institutional retrospective study of prostate MRI examinations done from October 2015 to February 2018. We identified patients who underwent prostatectomy for Pca Gleason ≥ 3+4 diagnosed on prostate biopsy with no associated MRI findings suggestive of malignancy and analyzed their post-prostatectomy pathologic findings and MRI imaging results. RESULTS: At our institution, 850 men with Pca received MRI between 2015 and 2018, and 156/850 patients received robotic-assisted radical prostatectomy. Thirty three patients (33/156=21%) had negative MRI for PIRAD 3 or greater but had a biopsy showing significant Pca. Their mean (range) age was 62.7 (50 - 86) years. Their median (interquartile range) PSA, and PSA density were, 4.6 (3.7) ng/mL and 0.12 (0.05) ng/mL/cm2, respectively; all not significantly different from patients with visible lesions on MRI who underwent surgery. On post prostatectomy pathology, 27/33 (82%) men had Pca Gleason score 7 or greater. The most common pattern was infiltrative growth with cancer glands intermingling between benign glands. CONCLUSIONS: We describe the pathologic and imaging findings in an extensive series of men with clinically significant Pca with no significant lesions on preoperative MRI. Our results support the importance of patient counseling on the risk of missing significant Pca on MRI in isolation from other clinical variables.

Pathology and Laboratory Medicine

Aurora L, **Peterson E**, **Gui H**, **Zeld N**, **McCord J**, Pinto Y, **Cook B**, **Sabbah HN**, **Keoki Williams L**, Snider J, and **Lanfear DE**. Suppression Tumorigenicity 2 (ST2) Turbidimetric Immunoassay Compared to Enzyme-Linked Immunosorbent Assay in Predicting Survival in Heart Failure Patients with Reduced Ejection Fraction. *Clin Chim Acta* 2020; Epub ahead of print. PMID: 32926842. Request Article

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BACKGROUND: Suppressor of tumorigenicity 2 (ST2) is a powerful marker of prognosis and treatment response in heart failure (HF), however, it is an enzyme-linked immunosorbent assay (ELISA) which may be cumbersome and

costly. A turbidimetric immunoassay (TIA) that can run on common chemistry analyzers could overcome this. We studied a novel TIA for ST2, comparing it to commercial ST2 (ELISA). METHODS: Patients age ≥18 years meeting Framingham definition for HF were enrolled in a prospective registry (Oct 2007 - March 2015) at Henry Ford Hospital and donated blood samples. Participants with reduced ejection fraction (<50%) and available plasma samples were included and valid ST2 measurements were obtained on the same sample using both TIA and ELISA (N=721). The primary endpoint was all cause death. Correlation between the methods was quantified. The association with survival was tested using unadjusted and adjusted (for MAGGIC score and NTproBNP) Cox models and comparing the Area Under the Curve (AUC). RESULTS: The inter-assay Spearman correlation coefficient was 0.77. Nonparametric regression showed no significant proportional difference (slope = 0.97) and a very small systematic difference (3.2 ng/mL). In univariate analyses both TIA and ELISA ST2 were significant associates of survival with similar effect sizes (HR 4.46 and 3.50, respectively, both p<0.001). In models adjusted for MAGGIC score both ST2 remained significant in Cox models and incrementally improved AUC vs. MAGGIC alone (MAGGIC AUC= 0.757; TIA+MAGGIC AUC=0.786, p=0.025; ELISA+MAGGIC AUC=0.793, p=0.033). In models with both MAGGIC and NTproBNP included, both ST2 still remained significant but did not improve AUC. CONCLUSIONS: A novel TIA method for ST2 quantification correlates highly with ELISA and offers similarly powerful risk-stratification.

Pathology and Laboratory Medicine

Cho R, **Myers DT**, **Onwubiko IN**, and **Williams TR**. Extraosseous multiple myeloma: imaging spectrum in the abdomen and pelvis. *Abdom Radiol (NY)* 2020; Epub ahead of print. PMID: 32870348. Full Text

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Multiple myeloma represents a subset of plasma cell dyscrasias characterized by the proliferation of plasma cells typically in the bone marrow, representing approximately 1% of all cancers and 15% of hematologic malignancies. Often multiple myeloma is limited to the skeletal system; however, a small percentage (<5%) of patients will develop extraosseous manifestations. We review the current WHO classification of plasma cell dyscrasias and use multimodality imaging including US, CT, MRI, and PET-CT to illustrate the spectrum of extraosseous multiple myeloma in the abdomen and pelvis. Because extraosseous multiple myeloma is associated with a poorer prognosis and decreased survival, it is important for the radiologist to become familiar with a variety of extraosseous manifestations in the abdomen and pelvis, especially in a patient with a known diagnosis of multiple myeloma and the development of an abdominal or pelvic mass.

Pathology and Laboratory Medicine

Hamid MS, **Steen DW**, **Ormsby AH**, Lin X, and **Le KH**. Inflamed nonlimbal scleral dermoid masquerading as nodular scleritis. *J aapos* 2020; Epub ahead of print. PMID: 32931936. Full Text

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Pathology and Laboratory Medicine

Ozog DM, Sexton JZ, **Narla S**, Pretto-Kernahan CD, Mirabelli C, **Lim HW**, **Hamzavi IH**, **Tibbetts RJ**, and **Mi QS**. The Effect of Ultraviolet C Radiation Against Different N95 Respirators Inoculated with SARS-CoV-2. *Int J Infect Dis* 2020; Epub ahead of print. PMID: 32891736. Full Text

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OBJECTIVES: There are currently no studies that have examined whether one dosage can be uniformly applied to different respirator types to effectively decontaminate SARS-CoV-2 on N95 filtering facepiece respirators (FFRs). Health care workers have been using this disinfection method during the pandemic. Our objective was to determine the effect of UVC on SARS-CoV-2 inoculated N95 respirators and whether this was respirator material/model type dependent. METHODS: Four different locations (facepiece and strap) on 5 different N95 FFR models (3 M 1860, 8210, 8511, 9211; Moldex 1511) were inoculated with a 10 µL drop of SARS-CoV-2 viral stock (8 × 10(7) TCID(50)/mL). The outside-facing and wearer-facing surfaces of the respirators were each irradiated with a dose of 1.5 J/cm(2) UVC (254 nm). Viable SARS-CoV-2 was quantified by a median tissue culture infectious dose assay (TCID(50)). RESULTS: UVC delivered using a dose of 1.5 J/cm(2), to each side, was an effective method of decontamination for the facepieces of 3 M 1860 and Moldex 1511, and for the straps of 3 M 8210 and the Moldex 1511. CONCLUSION: This dose is an appropriate decontamination method to facilitate reuse of respirators for healthcare personnel when applied to certain models/materials. In addition, some straps may require additional disinfection to maximize the safety to frontline workers. Implementation of widespread UVC decontamination methods requires a careful consideration of model, material type, design, and fit-testing following irradiation.

Pathology and Laboratory Medicine
Umeh ON, **Beekman R**, **D'sa H**, and **Friedman BJ**. Elderly Man With Progressive Nail Atrophy: Challenge. *Am J Dermatopathol* 2020; Epub ahead of print. PMID: 32932300. Full Text

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Pathology and Laboratory Medicine
Wheeler SE, Peck Palmer OM, Greene DN, Park JY, **Winston-McPherson G**, Amukele TK, and Pérez-Stable EJ. Examining Laboratory Medicine's Role in Eliminating Health Disparities. *Clin Chem* 2020; Epub ahead of print. PMID: 32888006. Full Text

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Pathology and Laboratory Medicine
Yuan L, Oshilaja O, Sierk A, Zhang G, Booth CN, Brainard J, and Dyhdalo KS. Metastatic breast cancer diagnosed on cervical cytology. *Cytopathology* 2020; Epub ahead of print. PMID: 32789952. Full Text

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Pharmacy
Stuart MM, **Smith ZR**, **Payter KA**, **Martz CR**, **To L**, **Swiderek JL**, **Coba VE**, and **Peters MA**. Pharmacist-driven discontinuation of antipsychotics for ICU delirium: A quasi-experimental study. *JACCP Journal of the American College of Clinical Pharmacy* 2020; 3(6):1009-1014. PMID: Not assigned. Full Text

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Introduction: The use of antipsychotics reduces the duration of intensive care unit (ICU) delirium. Continuation of antipsychotics prescribed for ICU delirium at hospital discharge has been an increasingly reported phenomenon with risk factors for continuation upon discharge identified. Objective: To evaluate a pharmacist-driven discontinuation protocol on the rate of patients with an antipsychotic continued at hospital discharge for ICU delirium. Methods: This was a single-center, retrospective quasi-experimental study of patients admitted to the medical, surgical, or cardiac ICU started on antipsychotics for delirium. A protocol was developed for pharmacists to discontinue scheduled antipsychotics once delirium had resolved. The pre- and post-protocol groups included patients between November 2015 to April 2016 and November 2017 to April 2018, respectively. The primary outcome was the rate of antipsychotic continuation at hospital discharge in the pre- and postprotocol groups. Secondary outcomes were related to antipsychotic use and adverse events. Chi-square, Fisher's exact test, Mann-Whitney U test, and t-test were used as appropriate. Results: A total of 158 patients were included. There were no differences in baseline demographics including age, gender, ICU type, baseline QTc, ICU length of stay (LOS) or hospital LOS (25 [13, 34] vs 19 [13, 30] days; P >.05). There was a significant reduction in the rate of antipsychotics continued at hospital discharge with 26 (32.9%) and 6 (7.6%) patients having therapy continued in the pre- and postprotocol groups, respectively (P <.001). No differences were noted in antipsychotic continuation upon transfer to floor, QTc prolongation, or recurrence of delirium within 7 days of antipsychotic discontinuation. Conclusions: Implementation of a pharmacist-driven antipsychotic discontinuation protocol for delirium was associated with a significant decrease in antipsychotic continuation at hospital discharge. The protocol did not result in a significantly higher incidence of QTc prolongation or recurrence of delirium. Future studies are needed to assess antipsychotic discontinuation in the ICU setting.

Public Health Sciences

Averin A, Silvia A, **Lamerato L**, Richert-Boe K, **Kaur M**, Sundaresan D, Shah N, Hatfield M, Lawrence T, Lyman GH, and Weycker D. Risk of chemotherapy-induced febrile neutropenia in patients with metastatic cancer not receiving granulocyte colony-stimulating factor prophylaxis in US clinical practice. *Support Care Cancer* 2020; Epub ahead of print. PMID: 32880732. Full Text

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OBJECTIVES: To evaluate the use of granulocyte colony-stimulating factor (G-CSF) prophylaxis in US patients with selected metastatic cancers and chemotherapy-induced febrile neutropenia (FN) incidence and associated outcomes among the subgroup who did not receive prophylaxis. METHODS: This retrospective cohort study was conducted at four US health systems and included adults with metastatic cancer (breast, colorectal, lung, non-Hodgkin lymphoma [NHL]) who received myelosuppressive chemotherapy (2009-2017). Patients were stratified by FN risk level based on risk factors and chemotherapy (low/unclassified risk, intermediate risk without any risk factors, intermediate risk with ≥ 1 risk factor [IR + 1], high risk [HR]). G-CSF use was evaluated among all patients stratified by FN risk, and FN/FN-related outcomes were evaluated among patients who did not receive first-cycle G-CSF prophylaxis. RESULTS: Among 1457 metastatic cancer patients, 20.5% and 28.1% were classified as HR and IR + 1, respectively. First-cycle G-CSF prophylaxis use was 48.5% among HR patients and 13.9% among IR + 1 patients. In the subgroup not receiving first-cycle G-CSF prophylaxis, FN incidence in cycle 1 was 7.8% for HR patients and 4.8% for IR + 1 patients; during the course, corresponding values were 16.9% and 15.9%. Most (> 90%) FN episodes required hospitalization, and mortality risk ranged from 7.1 to 26.9% across subgroups. CONCLUSION: In this retrospective study, the majority of metastatic cancer chemotherapy patients for whom G-CSF prophylaxis is recommended did not receive it; FN incidence in this subgroup was notably high. Patients with elevated FN risk should be carefully identified and managed to ensure appropriate use of supportive care.

Public Health Sciences

Gui H, **Levin AM**, Hu D, Sleiman P, **Xiao S**, Mak AC, **Yang M**, Barczak AJ, Huntsman S, Eng C, **Hochstadt S**, **Zhang E**, **Whitehouse K**, **Simons S**, **Cabral W**, **Takriti S**, Abecasis G, Blackwell TW, Kang HM, Nickerson DA, Germer S, **Lanfear DE**, Gilliland F, Gauderman WJ, Kumar R, Erle DJ, Martinez FD, Hakonarson H, Burchard EG, and **Williams LK**. Mapping the 17q12-21.1 Locus for Variants Associated with Early-onset Asthma in African Americans. *Am J Respir Crit Care Med* 2020; Epub ahead of print. PMID: 32966749. Full Text

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RATIONALE: The 17q12-21.1 locus is one of the most highly replicated genetic associations with asthma. Individuals of African descent have lower LD in this region, which could facilitate identifying causal variants. OBJECTIVE: To identify functional variants at 17q12-21.1 associated with early-onset asthma among African American individuals. METHODS AND MEASUREMENTS: We evaluated African American participants from the Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-ethnicity (SAPPHIRE) (n=1,940), the Study of African Americans, Asthma, Genes & Environment (SAGE II) (n=885), and Study of the Genetic Causes of Complex Pediatric Disorders - Asthma (GCPD-A) (n=2,805). Associations with asthma onset at age <5 years were meta-analyzed across cohorts. The lead signal was reevaluated considering haplotypes informed by genetic ancestry (i.e., African vs. European). Both an expression quantitative trait locus (eQTL) analysis and phenome-wide association study (PheWAS) were performed on the lead variant. MAIN RESULTS: The meta-analyzed results from SAPPHIRE, SAGE II, and GCPD-A identified rs11078928 as the top association for early-onset asthma. A haplotype analysis suggested that the asthma association partitioned most closely with rs11078928 genotype. Genetic ancestry did not appear to influence the effect of this variant. In the eQTL analysis, rs11078928 was related to alternative splicing of gasdermin-B (GSDMB) transcripts. The PheWAS of rs11078928 suggested that this variant was predominantly associated with asthma and asthma-associated symptoms. CONCLUSIONS: A splice acceptor polymorphism appears to be a causal variant for asthma at the 17q12-21.1 locus. This variant appears to have the same magnitude of effect in individuals of African and European descent.

Public Health Sciences

Li P, Liu R, Lin J, and Ji Y. TEPI-2 and UBI: designs for optimal immuno-oncology and cell therapy dose finding with toxicity and efficacy. *J Biopharm Stat* 2020; 1-14. Epub ahead of print. PMID: 32951518. Request Article

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Conventional dose finding designs in oncology drug development target on the identification of the maximum tolerated dose (MTD), with the assumption that the MTD has the most potential of clinical activity among those identified tolerable dose levels. However, immuno-oncology (I-O) and cell therapy area, may lack dose-efficacy monotonicity, posing significant challenges in the statistical designs for dose finding trials. A desirable design should empower the trial to identify the right dose level with tolerable toxicity and acceptable efficacy. Such dose is called as optimal biological dose (OBD), which is more appropriate to be considered as the primary objective of the first-in-human trial in I-O and cell therapy than MTD. We propose two model-assisted designs in this setting: the toxicity and efficacy probability interval-2 (TEPI-2) design and the utility-based interval (UBI) design that incorporate the toxicity and efficacy outcomes simultaneously and identify a dose that has high probability of acceptable efficacy with manageable toxicity. The proposed designs can generate decision tables before trial starts to facilitate practical and easy-to-implement applications. Through simulation studies, our proposed novel designs demonstrate superior performance in accuracy, efficiency, and safety. Additionally, they can reduce the number of patients and shorten clinical development timeline. We also illustrate the advantages of proposed methods by redesigning a CAR T-cell therapy phase I clinical trial for multiple myeloma and summarize our recommendations in the discussion section.

Public Health Sciences

Miller J, **Fadel RA**, **Tang A**, **Perrotta G**, **Herc E**, **Soman S**, **Nair S**, **Hanna Z**, **Zervos MJ**, **Alangaden G**, **Brar I**, and **Suleyman G**. The Impact of Sociodemographic Factors, Comorbidities and Physiologic Response on 30-day Mortality in COVID-19 Patients in Metropolitan Detroit. *Clin Infect Dis* 2020; Epub ahead of print. PMID: 32945856. Full Text

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BACKGROUND: The relationship of health disparities and comorbidities in coronavirus disease 2019 (COVID-19) related outcomes are an ongoing area of interest. This report assesses risk factors associated with mortality in patients presenting with Covid-19 infection and healthcare disparities. METHODS: A retrospective cohort study of consecutive patients presenting to emergency departments within an integrated health system who tested positive for COVID-19 between March 7 and April 30, 2020 in Metropolitan Detroit. The primary outcomes were hospitalization and 30-day mortality. RESULTS: A total of 3,633 patients with mean age of 58 years were included. The majority were female and black non-Hispanic. Sixty-four percent required hospitalization, 56% of whom were black. Hospitalized patients were older, more likely to reside in a low-income area, and had a higher burden of comorbidities. By 30-days, 433 (18.7%) hospitalized patients died. In adjusted analyses, the presence of comorbidities, age >60 years and more severe physiological disturbance were associated with 30-day mortality. Residence in low income areas (odds ratio, 1.02; 95% confidence interval 0.76 - 1.36), and public insurance (odds ratio, 1.24; 95% confidence interval 0.76 - 2.01) were not independently associated with higher risk of mortality. Black female patients had a lower adjusted risk of mortality (odds ratio, 0.46; 95% confidence interval, 0.27 to 0.78). CONCLUSIONS: In this large cohort of COVID-19 patients, those with comorbidities, advanced age, and physiological abnormalities on presentation had higher odds of death. Disparities in income or source of health insurance were not associated with outcomes. Black women had a lower risk of dying.

Public Health Sciences

Morris DC, **Jaehne AK**, **Chopp M**, **Zhang Z**, **Poisson L**, **Chen Y**, **Datta I**, and **Rivers EP**. Proteomic Profiles of Exosomes of Septic Patients Presenting to the Emergency Department Compared to Healthy Controls. *J Clin Med* 2020; 9(9). PMID: 32932765. Full Text

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BACKGROUND: Septic Emergency Department (ED) patients provide a unique opportunity to investigate early sepsis. Recent work focuses on exosomes, nanoparticle-sized lipid vesicles (30-130 nm) that are released into the bloodstream to transfer its contents (RNA, miRNA, DNA, protein) to other cells. Little is known about how early changes related to exosomes may contribute to the dysregulated inflammatory septic response that leads to multi-organ dysfunction. We aimed to evaluate proteomic profiles of plasma derived exosomes obtained from septic ED patients and healthy controls. METHODS: This is a prospective observational pilot study evaluating a plasma proteomic exosome profile at an urban tertiary care hospital ED using a single venipuncture blood draw, collecting 40 cc Ethylenediaminetetraacetic acid (EDTA) blood. MEASUREMENTS: We recruited seven patients in the ED within 6 h of their presentation and five healthy controls. Plasma exosomes were isolated using the Invitrogen Total Exosome Isolation Kit. Exosome proteomic profiles were analyzed using fusion mass spectroscopy and Proteome Discoverer. Principal component analysis (PCA) and differential expression analysis (DEA) for sepsis versus control was performed. RESULTS: PCA of 261 proteins demonstrated septic patients and healthy controls were distributed in two groups. DEA revealed that 62 (23.8%) proteins differed between the exosomes of septic patients and healthy controls, p-value < 0.05. Adjustments using the False Discovery Rate (FDR) showed 23 proteins remained significantly different (FDR < 0.05) between sepsis and controls. Septic patients and controls were classified into two distinct groups by hierarchical clustering using the 62 nominally DE proteins. After adjustment multiple comparisons, three acute phase proteins remained significantly different between patients and controls: Serum amyloid A-1, C-reactive protein and Serum Amyloid A-2. Inflammatory response proteins immunoglobulin heavy constant Δ and Fc-fragment of IgG binding protein were increased. CONCLUSION: Exosome proteomic profiles of septic ED patients differ from their healthy counterparts with regard to acute phase response and inflammation.

Public Health Sciences

Peleman JR, **Tarwade P**, **Han X**, **Penning DH**, and **Craig JR**. Hemodynamic Changes with 1:1000 Epinephrine on Wrung-Out Pledgets Before and During Sinus Surgery. *Ann Otol Rhinol Laryngol* 2020; Epub ahead of print. PMID: 32945177. Full Text

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BACKGROUND: Intranasal topical 1:1000 epinephrine has been used safely and effectively for hemostasis during endoscopic sinus surgery (ESS). Prior studies assessing hemodynamic changes after intranasal topical epinephrine application have only used soaking wet cottonoid pledgets, and have only assessed for hemodynamic changes before any surgery being performed. OBJECTIVE: The purposes of this study were to determine whether intranasal application of topical 1:1000 epinephrine with wrung-out cottonoid pledgets caused significant hemodynamic changes both before and during ESS, and whether it allowed for adequate hemostasis. METHODS: A prospective evaluation of 30 patients with eosinophilic chronic rhinosinusitis with nasal polyps (CRSwNP) undergoing complete bilateral ESS was conducted. Heart rate, blood pressure (systolic, diastolic, and mean arterial pressure), and electrocardiography changes were recorded at 0, 1, 2, and 5-minute intervals after placing wrung-out epinephrine-saturated pledgets, both before and at the end of ESS. No submucosal epinephrine injections were performed. Estimated blood loss (EBL) and major intraoperative complications were recorded for all cases. RESULTS: There were no significant hemodynamic changes or electrocardiographic abnormalities after placement of wrung-out epinephrine-soaked pledgets both before and after ESS. After bilateral ESS, there were actually mean decreases in heart rate and blood pressure parameters. Mean EBL was 75.8 ± 32.2 mL, and no major intraoperative complications occurred. CONCLUSION: Intranasal application of topical 1:1000 epinephrine via wrung-out cottonoid pledgets was effective for intraoperative hemostasis, and did not cause clinically significant alterations in hemodynamic parameters or cardiovascular events, either before or during ESS in patients with CRSwNP.Level of Evidence: 4.

Public Health Sciences
Peters RM, El-Masri M, and **Cassidy-Bushrow AE**. Self-Reported Sensory Gating and Stress-Related Hypertension. *Nurs Res* 2020; 69(5):339-346. PMID: 32865945. Full Text

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BACKGROUND: Increasing evidence views hypertension as a stress-induced disorder. Stressors must be "gated" by the brain before any inflammatory or immune processes that contribute to hypertension are initiated. No studies were found that examined sensory gating in relation to hypertension. OBJECTIVES: The aim of the study was to determine if disturbances in self-reported sensory gating could differentiate normotensive from hypertensive young adults. METHODS: A nonmatched, case-control design was used. We administered an online survey to 163 young adult participants. Participants were predominantly female, in their mid-20s, well educated, and approximately evenly distributed by race and hypertension status. The Sensory Gating Inventory (SGI) measured gating disturbances. RESULTS: The mean SGI scores were significantly higher among persons diagnosed with hypertension, reflecting a moderate effect size of sensory gating. After adjusting for confounders, however, the normotensive and hypertensive groups were not significantly different on their SGI scores. DISCUSSION: With an observed moderate effect size of 0.35, but low power, more research is warranted regarding the role of gating disturbances in the development of stress-induced hypertension. Clinically, the SGI may be important for screening patients who would benefit from ambulatory blood pressure monitoring to identify persons with masked hypertension.

Public Health Sciences
Sitarik AR, **Havstad SL**, **Johnson CC**, **Jones K**, **Levin AM**, Lynch SV, Ownby DR, Rundle AG, **Straughen JK**, **Wegienka G**, **Woodcroft KJ**, Yong GJM, and **Cassidy-Bushrow AE**. Association between cesarean delivery types and obesity in preadolescence. *Int J Obes (Lond)* 2020; 44(10):2023-2034. PMID: 32873910. Request Article

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BACKGROUND/OBJECTIVES: The association between mode of delivery and childhood obesity remains inconclusive. Because few studies have separated C-section types (planned or unplanned C-section), our objective was to assess how these subtypes relate to preadolescent obesity. SUBJECTS/METHODS: The study consisted of 570 maternal-child pairs drawn from the WHEALS birth cohort based in Detroit, Michigan. Children were followed-up at 10 years of age where a variety of anthropometric measurements were collected. Obesity was defined based on

BMI percentile (≥95th percentile), as well as through Gaussian finite mixture modeling on the anthropometric measurements. Risk ratios (RRs) and 95% confidence intervals (CIs) for obesity comparing planned and unplanned C-sections to vaginal deliveries were computed, which utilized inverse probability weights to account for loss to follow-up and multiple imputation for covariate missingness. Mediation models were fit to examine the mediation role of breastfeeding. RESULTS: After adjusting for marital status, maternal race, prenatal tobacco smoke exposure, maternal age, maternal BMI, any hypertensive disorders during pregnancy, gestational diabetes, prenatal antibiotic use, child sex, parity, and birthweight z-score, children born via planned C-section had 1.77 times higher risk of obesity (≥95th percentile), relative to those delivered vaginally ((95% CI) = (1.16, 2.72); p = 0.009). No association was found comparing unplanned C-section to vaginal delivery (RR (95% CI) = 0.75 (0.45, 1.23); p = 0.25). The results were similar but slightly stronger when obesity was defined by anthropometric class (RR (95% CI) = 2.78 (1.47, 5.26); p = 0.002). Breastfeeding did not mediate the association between mode of delivery and obesity. CONCLUSIONS: These findings indicate that children delivered via planned C-section-but not unplanned C-section-have a higher risk of preadolescent obesity, suggesting that partial labor or membrane rupture (typically experienced during unplanned C-section delivery) may offer protection. Additional research is needed to understand the biological mechanisms behind this effect, including whether microbiological differences fully or partially account for the association.

Public Health Sciences

Zervos TM, **Bazydlo M**, **Tundo K**, **Macki M**, and **Rock J**. Risk Factors Associated With Symptomatic Deep Vein Thrombosis Following Elective Spine Surgery: A Case Control Study. *World Neurosurg* 2020; Epub ahead of print. PMID: 32889183. Full Text

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BACKGROUND: Few studies provide insight into risk factors (RFs) associated with postoperative deep vein thrombosis (DVT) following elective spinal surgery. DVTs are detrimental in this population due to the risk of pulmonary embolization or surgical site hemorrhage with treatment. OBJECTIVE: Elective spine surgery patients have a low incidence of DVT, thus, a case-control study was selected to investigate RFs associated with postoperative symptomatic DVT. METHODS: Cases were matched to controls in a 1:2 ratio based on surgery type. Risk of having a prior DVT and choice of subcutaneous heparin dosing following surgery was analyzed in a multivariate regression model with other potentially confounding variables. RESULTS: 195 patients were included in this study. Independent of patient age, history of DVT was associated with postoperative symptomatic DVT (OR 4.09, 95% CI 1.22-13.78). Two versus three times daily postoperative heparin dosing (OR 1.56, 95% CI 0.32-7.56), surgery length (OR 1.32, 95% CI 0.98-1.79), and patient age (OR 1.04, 95% CI 1.0-1.08) were not statistically significant, independent RFs. Older age and longer length of surgery trended toward association with DVT without reaching significance. Length of stay (LOS) was increased from 3-5 days (P<0.001) in DVT patients compared to controls. CONCLUSIONS: These results suggest that patients with a history of DVT undergoing elective spinal surgery are at higher risk of developing symptomatic DVT postoperatively resulting in significantly increased LOS. Further study on additional preoperative screening and medical optimization in elective spine surgery patients may help reduce the rate of symptomatic postoperative DVT.

Plastic Surgery

Venkatesh KP, **Ambani SW**, Arakelians ARL, Johnson JT, and Solari MG. Head and Neck Microsurgeon Practice Patterns and Perceptions Regarding Venous Thromboembolism Prophylaxis. *J Reconstr Microsurg* 2020; 36(8):549-555. PMID: 32408367. Request Article

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BACKGROUND: Patients undergoing head and neck (H&N) microvascular reconstruction comprise a population at high risk for venous thromboembolism (VTE). Free flap and VTE thromboprophylaxis may coincide but tend to vary from surgeon to surgeon. This study identifies VTE prophylaxis patterns and perceptions among H&N microsurgeons in the United States. METHODS: An online survey on VTE prophylaxis practice patterns and perceptions was emailed to 172 H&N microsurgeons in the United States using an anonymous link. RESULTS: There were 74 respondents (43% response rate). These surgeons completed residencies in otolaryngology (59%), plastic surgery (31%), and oral maxillofacial surgery (7%). Most underwent fellowship training (95%) and have practiced at an academic center (97%) for at least 6 years (58%), performing an average of 42 ± 31 H&N free flap cases per year (range = 1-190). Most adhered to general VTE prophylaxis guidelines (69%) while 11% did not and 20% were unsure. Nearly all surgeons (99%) would provide prophylactic anticoagulation, mostly in the form of subcutaneous heparin

(51%) or enoxaparin (44%); 64% additionally used aspirin, while 4% used aspirin alone. The majority of surgeons (68%) reported having postoperative VTE complications, with six surgeons (8%) reporting patient deaths due to pulmonary embolism. A third of the surgeons have encountered VTE prophylaxis-related adverse bleeding events, but most still believe that chemoprophylaxis is important for VTE prevention (92%). While 35% of surgeons were satisfied with their current practice, most would find it helpful to have official prophylactic anticoagulation guidelines specific to H&N free flap cases. CONCLUSION: The majority of microsurgeons experienced postoperative VTE complications after H&N free flap reconstruction despite the routine use of prophylactic anticoagulation. Though bleeding events are a concern, most surgeons believe chemoprophylaxis is important for VTE prevention and would welcome official guidelines specific to this high-risk population.

Pulmonary and Critical Care Medicine

Stuart MM, **Smith ZR**, **Payter KA**, **Martz CR**, **To L**, **Swiderek JL**, **Coba VE**, and **Peters MA**. Pharmacist-driven discontinuation of antipsychotics for ICU delirium: A quasi-experimental study. *JACCP Journal of the American College of Clinical Pharmacy* 2020; 3(6):1009-1014. PMID: Not assigned. Full Text

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Introduction: The use of antipsychotics reduces the duration of intensive care unit (ICU) delirium. Continuation of antipsychotics prescribed for ICU delirium at hospital discharge has been an increasingly reported phenomenon with risk factors for continuation upon discharge identified. Objective: To evaluate a pharmacist-driven discontinuation protocol on the rate of patients with an antipsychotic continued at hospital discharge for ICU delirium. Methods: This was a single-center, retrospective quasi-experimental study of patients admitted to the medical, surgical, or cardiac ICU started on antipsychotics for delirium. A protocol was developed for pharmacists to discontinue scheduled antipsychotics once delirium had resolved. The pre- and post-protocol groups included patients between November 2015 to April 2016 and November 2017 to April 2018, respectively. The primary outcome was the rate of antipsychotic continuation at hospital discharge in the pre- and postprotocol groups. Secondary outcomes were related to antipsychotic use and adverse events. Chi-square, Fisher's exact test, Mann-Whitney U test, and t-test were used as appropriate. Results: A total of 158 patients were included. There were no differences in baseline demographics including age, gender, ICU type, baseline QTc, ICU length of stay (LOS) or hospital LOS (25 [13, 34] vs 19 [13, 30] days; P >.05). There was a significant reduction in the rate of antipsychotics continued at hospital discharge with 26 (32.9%) and 6 (7.6%) patients having therapy continued in the pre- and postprotocol groups, respectively (P <.001). No differences were noted in antipsychotic continuation upon transfer to floor, QTc prolongation, or recurrence of delirium within 7 days of antipsychotic discontinuation. Conclusions: Implementation of a pharmacist-driven antipsychotic discontinuation protocol for delirium was associated with a significant decrease in antipsychotic continuation at hospital discharge. The protocol did not result in a significantly higher incidence of QTc prolongation or recurrence of delirium. Future studies are needed to assess antipsychotic discontinuation in the ICU setting.

Radiation Oncology

Liu SW, Woody NM, Wei W, Appachi S, Contrera KJ, Tsai JC, **Ghanem AI**, Matia B, Joshi NP, Geiger JL, Ku JA, Burkey BB, Scharpf J, Prendes BL, Caudell JJ, Dunlap NE, Adelstein DJ, Porceddu S, Liu H, **Siddiqui F**, Lee NY, Koyfman S, and Lamarre ED. Evaluating compliance with process-related quality metrics and survival in oral cavity squamous cell carcinoma: Multi-institutional oral cavity collaboration study. *Head Neck* 2020; Epub ahead of print. PMID: 32918373. Full Text

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BACKGROUND: Process-related measures have been proposed as quality metrics in head and neck cancer care. A recent single-institution study identified four key metrics associated with increased survival. This study sought to validate the association of these quality metrics with survival in a multi-institutional cohort. METHODS: Multicenter retrospective study of patients with oral cavity squamous cell (1/2005-1/2015). Baseline patient and disease characteristics and compliance with quality metrics was evaluated. Association between compliance with quality metrics with overall survival (OS), disease-free survival (DFS), and disease-specific survival (DSS) was evaluated using Cox proportional hazards models. RESULTS: Failure to comply with two or more of the quality metrics was associated with worse OS, DFS, and DSS. Adherence to all or all but one of the quality metrics was found to be

associated with improved survival. CONCLUSIONS: Process-related quality metrics are associated with increased survival in patients with oral cavity squamous cell carcinoma in a multi-institutional cohort.

Radiation Oncology

Shumway DA, Kapadia N, **Walker EM**, Griffith KA, Do TT, Feng M, Boike T, Helfrich Y, **DePalma B**, Gillespie EF, Miller A, Hayman J, Jagsi R, and Pierce LJ. Development of an Illustrated Scale for Acute Radiation Dermatitis in Breast Cancer Patients. *Pract Radiat Oncol* 2020; Epub ahead of print. PMID: 32947041. Request Article

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PURPOSE: Scales for rating acute radiation dermatitis (ARD) have not been validated despite decades of clinical use, and little is known regarding the relationship between toxicity scores and patient-reported symptoms. Skin tone also complicates assessment of ARD, and as such we sought to design an illustrated scale to consistently describe ARD across several skin tone types in breast cancer patients undergoing radiation (RT). METHODS: Patients undergoing RT for breast cancer were enrolled on a prospective study with photographs obtained at 2-week intervals. Photographs were clustered according to the apparent severity of acute radiation dermatitis and a descriptive photonumeric scale was developed. Four clinically experienced raters used both the illustrated photonumeric scale and the CTCAE to independently score the collection of photographs in two independent sessions. RESULTS: Among 80 unique patients with 192 photographs, 47 patients (59%) completed questionnaires about their symptoms during RT. Physicians completed toxicity forms at the point-of-care for 52 patients (65%). Photonumeric ratings compared against patient reports of dry and moist desquamation demonstrated high specificity (95% and 93%, respectively) and negative predictive value (84% and 92%), indicating correct identification of patients who did not report dry or moist desquamation. The sensitivity and positive predictive value for separate measures of dry and moist desquamation were considerably lower. A combined measure of any desquamation (dry or moist) portrayed higher diagnostic accuracy, resulting in 72% sensitivity, 93% specificity, 75% PPV, and 92% NPV. Photonumeric ratings of dry or moist desquamation were significantly associated with patient reports of itching, burning/stinging, hurting, and swelling. CONCLUSION: The xxx scale for acute radiation dermatitis is a simple grading rubric that is distinguished by characterization of its intra- and inter-rater reliability and diagnostic accuracy, correlation with patient-reported symptoms of bother and pain, and applicability across the spectrum of skin pigmentation.

Rehabilitation Services

Pepin ME, and **Chan D**. Applying a clinical decision-making model to a patient with severe shoulder pain ultimately diagnosed as neuralgic amyotrophy. *Physiother Theory Pract* 2020; 1-12. Epub ahead of print. PMID: 32892675. Request Article

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Shoulder symptoms are often encountered in physical therapy and a myriad of etiologies can cause these symptoms, either locally or remotely. The purpose of this case report is to describe the physical therapist's differential diagnostic process for a patient with acute and severe onset of shoulder pain. Case Description: The patient was a 37-year-old female with sudden onset of right shoulder pain that awakened her at night. Pain was associated with decreased range of motion and shoulder weakness. Faced with an uncertain diagnosis, the physical therapist followed a systematic approach to clinical decision-making. Outcomes: Neuralgic amyotrophy was the primary diagnostic hypothesis but other causes of shoulder pain could not be ruled out. Conclusion: The clinical decision-making process helped the physical therapist narrow down the differential diagnosis list and make a decision to send the patient for further testing. Magnetic resonance imaging and electromyogram confirmed the diagnosis of neuralgic amyotrophy.

Sleep Medicine

Cheng P, Cuellar R, Johnson DA, **Kalmbach DA**, **Joseph CL**, **Cuamatzi Castelan A**, **Sagong C**, Casement MD, and **Drake CL**. Racial discrimination as a mediator of racial disparities in insomnia disorder. *Sleep Health* 2020; Epub ahead of print. PMID: 32928711. Full Text

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STUDY OBJECTIVES: Racial and ethnic minorities are more likely to suffer from insomnia that is more severe; however, few studies have examined mechanisms by which racial disparities in severity of insomnia disorder may arise. One potential mechanism for disparities in insomnia severity is perceived discrimination. This study tested discrimination as a mediator in the relationship between race and insomnia. METHODS: Participants were recruited from communities in the Detroit metropolitan area and were diagnosed with insomnia disorder using the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition). The final sample included 1,458 individuals. Insomnia symptom severity was assessed via the Insomnia Severity Index and self-reported racial discrimination was evaluated using a single item. Racial discrimination was tested as a mediator in the relationship between race and insomnia symptom severity. Individuals were categroized as either White or a racial minority (i.e., non White individuals), with sensitivity analyses examining Black individuals and non-Black racial minority groups. RESULTS: Consistent with our hypothesis, racial discrimination was a significant mediator accounting for 57.3% of the relationship between race and insomnia symptom severity. Sensitivity analyses indicated that the indirect effect of racial discrimination was stronger in the non-Black racial minority group compared to Black individuals. CONCLUSIONS: These results provide support that racial discrimination is likely an important mechanism by which racial and ethnic sleep disparities exist. Implications for prevention, intervention, and treatment of insomnia in racial minorities to reduce health disparities are discussed.

Sleep Medicine
Cheng P, Walch O, Huang Y, Mayer C, **Sagong C**, **Cuamatzi Castelan A**, Burgess HJ, **Roth T**, Forger DB, and **Drake CL**. Predicting circadian misalignment with wearable technology: Validation of wrist-worn actigraphy and photometry in night shift workers. *Sleep* 2020; Epub ahead of print. PMID: 32918087. Full Text

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STUDY OBJECTIVES: A critical barrier to successful treatment of circadian misalignment in shift workers is determining circadian phase in a clinical or field setting. Light and movement data collected passively from wrist actigraphy can generate predictions of circadian phase via mathematical models; however, these models have largely been tested in non-shift working adults. This study tested the feasibility and accuracy of actigraphy in predicting dim light melatonin onset (DLMO) in fixed-night shift workers. METHODS: A sample of 45 night shift workers wore wrist actigraphs before completing DLMO in the laboratory (17.0 days ± 10.3 SD). DLMO was assessed via 24 hourly saliva samples in dim light (&10 lux). Data from actigraphy were provided as input to a mathematical model to generate predictions of circadian phase. Agreement was assessed and compared to average sleep timing on non-workdays as a proxy of DLMO. Model code and a prototype assessment tool are available open source. RESULTS: Model predictions of DLMO showed good concordance with in-lab DLMO, with a Lin's concordance coefficient of 0.70, which was twice as high as agreement using average sleep timing as a proxy of DLMO. The absolute mean error of the predictions was 2.88 hours, with 76% and 91% of the predictions falling with 2 and 4 hours, respectively. CONCLUSION: This study is the first to demonstrate the use of wrist actigraphy-based estimates of circadian phase as a clinically useful and valid alternative to in-lab measurement of DLMO in fixed night shift workers. Future research should explore how additional predictors may impact accuracy.

Sleep Medicine
Kalmbach DA, **Cheng P**, **Roth T**, **Sagong C**, and **Drake CL**. Objective sleep disturbance is associated with poor response to cognitive and behavioral treatments for insomnia in postmenopausal women. *Sleep Med* 2020; 73:82-92. PMID: 32799029. Full Text

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STUDY OBJECTIVES: To determine whether insomnia patients with objective sleep disturbance are less responsive to cognitive and behavioral treatments than those without objective sleep disturbance, characterize effects of insomnia therapy on objective sleep, and determine whether reductions in nocturnal cognitive arousal correspond to changes in objective sleep. METHODS: Secondary analysis of a single-site, randomized controlled trial. 113 postmenopausal women (56.40 ± 5.34 years) with menopause-related insomnia disorder were randomized to three treatment conditions: cognitive-behavioral therapy for insomnia (CBTI), sleep restriction therapy (SRT), or sleep

education control. Primary outcomes were the Insomnia Severity Index (ISI) and polysomnography (PSG) sleep parameters and were collected at pretreatment, posttreatment, and six-month follow-up. RESULTS: Patients with lower pretreatment PSG sleep efficiency had lower rates of insomnia remission after active treatment relative to those with higher sleep efficiency (37.8% vs 61.8%). Neither CBTI and SRT produced clinically meaningful effects on PSG sleep. Exploratory analyses revealed that reductions in nocturnal cognitive arousal were associated with decreases in PSG sleep latency, but not wake after sleep onset. CONCLUSIONS: Our findings support an emerging literature suggesting that insomnia patients with objective sleep disturbance may have blunted response to insomnia therapy. Research is needed to enhance treatments to better improve insomnia in patients with objective sleep disturbance. A lack of observed CBTI and SRT effects on PSG sleep suggests that these therapies may be presently ill-designed to improve objective sleep. Nocturnal cognitive arousal may represent an entry point to improve objective sleep latency in insomnia. NAME: Behavioral Treatment of Menopausal Insomnia: Sleep and Daytime Outcomes. URL: clinicaltrials.gov. Registration: NCT01933295.

Surgery

Docimo S, Jr., Jacob B, **Seras K**, and Ghanem O. Closed Facebook groups and COVID-19: an evaluation of utilization prior to and during the pandemic. *Surg Endosc* 2020; Epub ahead of print. PMID: 32926250. Full Text

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BACKGROUND: Surgical education was limited during the COVID-19 pandemic due to redeployment, limited clinical activity, and cancelation of elective procedures and educational conferences. Closed Facebook groups became a tool for surgical education while upholding social distancing guidelines. We aim to evaluate the use of Online Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) closed Facebook groups, during and prior to the COVID-19 pandemic. METHODS: Institutional Review Board evaluation and written consent was not indicated as the data does not pertain to any human subjects. Data files pertaining to new membership activity, posts, comments and reactions of eight closed Facebook groups. The pandemic group was defined as March 19th to April 30, 2020. The pre-pandemic group was defined as February 6th, to March 18th, 2020. The percentage increase of new memberships, posts, comments and reactions were calculated for each period. A two-tailed t-test, using a significance level of 0.05 was used to evaluate significance. RESULTS: A statistically significant increase in membership during the pandemic period was noted for each group. In regards to posts, the Flex Endo, Acute Care, Colorectal, Foregut, and Bariatric groups were noted to have a statistically significant increase in the pandemic period. Colorectal and Bariatric groups were the only two groups that were noted to have a significant increase in comments in the pandemic period. For reactions, Flex Endo, Colorectal, Foregut, and Bariatric groups were noted to have experienced a significant increase during the pandemic. CONCLUSIONS: The COVID-19 pandemic halted surgical education at all levels. The membership and utilization of closed Facebook groups increased significantly in many instances, demonstrating the importance of internet-based surgical education now and into the future. Further development of internet-based curriculums is warranted.

Surgery

Hans SS, **Lee MM**, and Jain N. Ureteral stenosis following iliac artery stenting. *J Vasc Surg Cases Innov Tech* 2020; 6(3):469-472. PMID: 32923750. Full Text

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Ureteral complications after open aortoiliac reconstruction for aneurysmal and occlusive disease have been reported previously. However, ureteral complications from endovascular interventions for iliac artery disease are relatively rare. We describe a case of left ureteral stenosis resulting in hydroureteronephrosis after multiple endovascular interventions involving the left common and external iliac arteries. The intraoperative findings during robotic ureterolysis revealed significant peri-iliac fibrosis and scarring in the area of the iliac stents. This case illustrates that, although uncommon, ureteral stenosis may occur after iliac stenting owing to peristent fibrosis.

Surgery

Morris DC, **Jaehne AK**, **Chopp M**, **Zhang Z**, **Poisson L**, **Chen Y**, **Datta I**, and **Rivers EP**. Proteomic Profiles of Exosomes of Septic Patients Presenting to the Emergency Department Compared to Healthy Controls. *J Clin Med* 2020; 9(9). PMID: 32932765. Full Text

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BACKGROUND: Septic Emergency Department (ED) patients provide a unique opportunity to investigate early sepsis. Recent work focuses on exosomes, nanoparticle-sized lipid vesicles (30-130 nm) that are released into the bloodstream to transfer its contents (RNA, miRNA, DNA, protein) to other cells. Little is known about how early changes related to exosomes may contribute to the dysregulated inflammatory septic response that leads to multi-organ dysfunction. We aimed to evaluate proteomic profiles of plasma derived exosomes obtained from septic ED patients and healthy controls. METHODS: This is a prospective observational pilot study evaluating a plasma proteomic exosome profile at an urban tertiary care hospital ED using a single venipuncture blood draw, collecting 40 cc Ethylenediaminetetraacetic acid (EDTA) blood. MEASUREMENTS: We recruited seven patients in the ED within 6 h of their presentation and five healthy controls. Plasma exosomes were isolated using the Invitrogen Total Exosome Isolation Kit. Exosome proteomic profiles were analyzed using fusion mass spectroscopy and Proteome Discoverer. Principal component analysis (PCA) and differential expression analysis (DEA) for sepsis versus control was performed. RESULTS: PCA of 261 proteins demonstrated septic patients and healthy controls were distributed in two groups. DEA revealed that 62 (23.8%) proteins differed between the exosomes of septic patients and healthy controls, p-value < 0.05. Adjustments using the False Discovery Rate (FDR) showed 23 proteins remained significantly different (FDR < 0.05) between sepsis and controls. Septic patients and controls were classified into two distinct groups by hierarchical clustering using the 62 nominally DE proteins. After adjustment multiple comparisons, three acute phase proteins remained significantly different between patients and controls: Serum amyloid A-1, C-reactive protein and Serum Amyloid A-2. Inflammatory response proteins immunoglobulin heavy constant Δ and Fc-fragment of IgG binding protein were increased. CONCLUSION: Exosome proteomic profiles of septic ED patients differ from their healthy counterparts with regard to acute phase response and inflammation.

Surgery

Nasser H, **Ivanics T**, and **Carlin AM**. Factors influencing the choice between laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass. *Surg Endosc* 2020; Epub ahead of print. PMID: 32909206. Full Text

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BACKGROUND: While laparoscopic sleeve gastrectomy (LSG) continues to be the most commonly performed bariatric operation, several variables influence surgeons' practice patterns and patients' decision-making in the type of bariatric procedure to perform. The aim of this study was to evaluate patient factors that influence the decision between laparoscopic Roux-en-Y gastric bypass (LRYGB) versus LSG. METHODS: The Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP) database was queried for patients undergoing LSG and LRYGB between 2015 and 2017. Univariate analysis and multivariate logistic regression were used to evaluate factors associated with performing LRYGB compared to LSG. RESULTS: A total of 252,117 (72.3%) LSG and 96,677 (27.7%) LRYGB cases were identified. Patients undergoing LSG were younger (44.3 ± 12.0 vs 45.2 ± 11.8 years; p < 0.01) and had a lower body mass index (BMI; 45.1 ± 7.8 vs 46.2 ± 8.1 kg/m(2); p < 0.01). Most of the patients were females (79.4%), white (73.0%), with an American Society of Anesthesiology (ASA) class ≤ 3 (96.4%). The factors associated with undergoing LRYGB compared to LSG were diabetes mellitus, gastroesophageal reflux disease, BMI ≥ 50 kg/m(2), ASA class > 3, obstructive sleep apnea, hypertension, and hyperlipidemia. However, patients with kidney disease, black race, chronic steroid use, age ≥ 60 years, recent smoking history, chronic obstructive pulmonary disease, and coronary artery disease were more likely to undergo LSG. CONCLUSIONS: The decision to perform LRYGB is primarily driven by obesity-associated comorbidities and higher BMI, whereas LSG is more likely to be performed in higher risk patients.

Surgery

Simanovski J, and Ralph J. Readmissions After Lung Transplantation. *Prog Transplant* 2020; Epub ahead of print. PMID: 32912114. Full Text

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Lung transplantation has evolved to become an acceptable therapy for individuals with end-stage lung disease. Readmissions rates after lung transplantation remain high as compared to other medical surgical populations. The purpose of this review is to synthesize the current body of knowledge about patterns, risk factors, and outcomes of readmissions after lung transplantation. The literature revealed that the most common admission diagnoses linked to lung transplant readmissions are infections followed by tachyarrhythmias, airway complications, surgical complications, rejection, thromboembolic events, gastrointestinal complications, and renal dysfunction. Risk factors

for these readmissions include male gender, longer intensive care unit stay, reintubation, prolonged chest tube air leak, frailty, and discharge to a long-term care facility. Outcomes of multiple readmissions after lung transplantation are associated with decreased survival and increased risk of mortality. Further research is needed to better understand which readmission diagnoses are preventable and whether multidisciplinary interventions can reduce readmission rates among patients after lung transplantation.

Surgery

Stuart MM, **Smith ZR**, **Payter KA**, **Martz CR**, **To L**, **Swiderek JL**, **Coba VE**, and **Peters MA**. Pharmacist-driven discontinuation of antipsychotics for ICU delirium: A quasi-experimental study. *JACCP Journal of the American College of Clinical Pharmacy* 2020; 3(6):1009-1014. PMID: Not assigned. Full Text

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Introduction: The use of antipsychotics reduces the duration of intensive care unit (ICU) delirium. Continuation of antipsychotics prescribed for ICU delirium at hospital discharge has been an increasingly reported phenomenon with risk factors for continuation upon discharge identified. Objective: To evaluate a pharmacist-driven discontinuation protocol on the rate of patients with an antipsychotic continued at hospital discharge for ICU delirium. Methods: This was a single-center, retrospective quasi-experimental study of patients admitted to the medical, surgical, or cardiac ICU started on antipsychotics for delirium. A protocol was developed for pharmacists to discontinue scheduled antipsychotics once delirium had resolved. The pre- and post-protocol groups included patients between November 2015 to April 2016 and November 2017 to April 2018, respectively. The primary outcome was the rate of antipsychotic continuation at hospital discharge in the pre- and postprotocol groups. Secondary outcomes were related to antipsychotic use and adverse events. Chi-square, Fisher's exact test, Mann-Whitney U test, and t-test were used as appropriate. Results: A total of 158 patients were included. There were no differences in baseline demographics including age, gender, ICU type, baseline QTc, ICU length of stay (LOS) or hospital LOS (25 [13, 34] vs 19 [13, 30] days; P >.05). There was a significant reduction in the rate of antipsychotics continued at hospital discharge with 26 (32.9%) and 6 (7.6%) patients having therapy continued in the pre- and postprotocol groups, respectively (P <.001). No differences were noted in antipsychotic continuation upon transfer to floor, QTc prolongation, or recurrence of delirium within 7 days of antipsychotic discontinuation. Conclusions: Implementation of a pharmacist-driven antipsychotic discontinuation protocol for delirium was associated with a significant decrease in antipsychotic continuation at hospital discharge. The protocol did not result in a significantly higher incidence of QTc prolongation or recurrence of delirium. Future studies are needed to assess antipsychotic discontinuation in the ICU setting.

Urology

Ahlawat R, **Sood A**, **Jeong W**, Ghosh P, Keeley J, **Abdollah F**, Kher V, **Olson P**, **Farah G**, **Wurst H**, **Bhandari M**, and **Menon M**. Robotic Kidney Transplantation with Regional Hypothermia Versus Open Kidney Transplantation for Patients with End-Stage Renal Disease: An Ideal Stage 2B Study. *J Urol* 2020; Epub ahead of print. PMID: 32941100. Full Text

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PURPOSE: To report on comparative effectiveness of minimally invasive versus traditional open kidney transplantation. MATERIALS AND METHODS: We undertook a prospective cohort study of 654 patients who underwent open or robotic kidney transplantation at a single tertiary care hospital between January 2013 and December 2015. Primary outcome was delayed graft function (DGF), defined as the need for dialysis within 1-week of surgery. Secondary outcomes included postoperative complications, pain, graft rejection, and graft and patient survival. Non-parsimonious propensity score and Ding-VanderWeele analytical methods were utilized to adjust for confounding bias. RESULTS: Within the 1:3 matched cohort (robotic n=126, open n=378; well-matched with standardized mean difference ~10%), the robotic approach was associated with lower rates of wound infections (0% vs 4%, p=0.023) and symptomatic lymphoceles (0% vs 7% at 36 months, p=0.003), as well as, reduced postoperative pain, requirement for narcotic analgesia and blood loss. There were no differences among the two groups, robotic versus open, with respect to graft function (DGF 0% vs 2.4%, p=0.081), hospital stay (median 8 days for both, p=0.647), graft rejection (16.2% vs 18.6% at 36 months, p=0.643), and graft (95.2% vs 96.3% at 36 months, p=0.266) and overall survival (94.5% vs 98.1% at 36 months, p=0.307). Ding-VanderWeele analysis suggested minimal influence of unknown confounders on study findings. CONCLUSIONS: Robotic kidney transplantation with regional hypothermia was associated with a lower rate of postoperative complications, and improved patient comfort, in comparison to open kidney transplantation. Graft function, and graft and overall survival were comparable among the two techniques.

Urology
Alanee S, **Deebajah M**, **Taneja K**, **Cole D**, **Pantelic M**, **Peabody J**, **Williamson SR**, **Gupta N**, **Dabaja A**, and **Menon M**. Post prostatectomy Pathologic Findings of Patients with Clinically Significant Prostate Cancer and no Significant PI-RADS Lesions on Preoperative Magnetic Resonance Imaging. *Urology* 2020; Epub ahead of print. PMID: 32946907. Full Text

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OBJECTIVES: We present post-prostatectomy pathology results from a series of prostate cancer (Pca) Gleason grade group ≥ 2 patients who did not have findings suggestive of cancer on preoperative pelvic magnetic resonance imaging (MRI). METHODS: We performed an institutional retrospective study of prostate MRI examinations done from October 2015 to February 2018. We identified patients who underwent prostatectomy for Pca Gleason ≥ 3+4 diagnosed on prostate biopsy with no associated MRI findings suggestive of malignancy and analyzed their post-prostatectomy pathologic findings and MRI imaging results. RESULTS: At our institution, 850 men with Pca received MRI between 2015 and 2018, and 156/850 patients received robotic-assisted radical prostatectomy. Thirty three patients (33/156=21%) had negative MRI for PIRAD 3 or greater but had a biopsy showing significant Pca. Their mean (range) age was 62.7 (50 - 86) years. Their median (interquartile range) PSA, and PSA density were, 4.6 (3.7) ng/mL and 0.12 (0.05) ng/mL/cm2, respectively; all not significantly different from patients with visible lesions on MRI who underwent surgery. On post prostatectomy pathology, 27/33 (82%) men had Pca Gleason score 7 or greater. The most common pattern was infiltrative growth with cancer glands intermingling between benign glands. CONCLUSIONS: We describe the pathologic and imaging findings in an extensive series of men with clinically significant Pca with no significant lesions on preoperative MRI. Our results support the importance of patient counseling on the risk of missing significant Pca on MRI in isolation from other clinical variables.

Urology
Arora S, **Bronkema C**, Porter JR, Mottrie A, Dasgupta P, Challacombe B, Rha KH, Ahlawat RK, Capitanio U, Yuvaraja TB, Rawal S, Moon DA, Sivaraman A, Maes KK, Porpiglia F, Gautam G, Turkeri L, **Bhandari M**, **Jeong W**, **Menon M**, **Rogers CG**, and **Abdollah F**. Omission of cortical renorrhaphy during robotic partial nephrectomy: a Vattikuti Collective Quality Initiative (VCQI) database analysis. *Urology* 2020; Epub ahead of print. PMID: 32941944. Full Text

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OBJECTIVES: To analyze the outcomes of patients in whom cortical (outer) renorrhaphy (CR) was omitted during robotic partial nephrectomy (RPN). METHODS: We analyzed 1453 patients undergoing RPN, from 2006-2018, within a large multi-institutional database. Patients having surgery for bilateral tumors (n=73) were excluded. CR and no-CR groups were compared in terms of operative and ischemia time, estimated blood loss (EBL), complications, surgical margins, hospital stay, change in estimated glomerular filtration rate (eGFR), and need of angioembolization. Inverse probability of treatment weighting with Firth correction for center code was performed to account for selection bias. RESULTS: CR was omitted in 120 patients (8.7%);1260 (91.3%) patients underwent both inner layer and CR. There

was no difference in intraoperative complications (7.4% CR;8.9% no-CR group; p=0.6), postoperative major complications (1% and 2.8% in CR and no-CR groups, respectively; p=0.2), or median drop in eGFR (7.3 vs 10.4 ml/min/m(2)). The no-CR group had a higher incidence of minor complications (26.7% vs 5.5% in CR group; p<0.001). EBL was 100 mL (IQR 50-200) in both groups (p=0.6). Angioembolization was needed in 0.7% patients in CR vs. 1.4% in no-CR group (p=0.4). Additionally, there was no difference in median operative time (168 vs. 162 min;p=0.2) or ischemia time (18 vs. 17 min; p=0.7). CONCLUSIONS: In selected patients with renal masses, single layer renorrhaphy does not significantly improve operative time, ischemia time, or eGFR after RPN. There is a higher incidence of minor complications, but not major perioperative complications after no-CR technique.

Urology
Elsayed AS, Gibson S, Jing Z, Wijburg C, Wagner AA, Mottrie A, Dasgupta P, **Peabody J**, Hussein AA, and Guru KA. Rates and Patterns of Recurrences, and Survival Outcomes after Robot-Assisted Radical Cystectomy: Results from the International Robotic Cystectomy Consortium. *J Urol* 2020; Epub ahead of print. PMID: 32945729. Full Text

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INTRODUCTION AND OBJECTIVES: There have been concerns about higher incidence of local and retroperitoneal recurrences after robot-assisted radical cystectomy (RARC) compared to open radical cystectomy. We sought to report and detail relapses following RARC utilizing a multinational database. METHODS: A retrospective review of the International Robotic Cystectomy Consortium was performed. Data were reviewed for demographics, perioperative, pathologic and oncologic outcomes. Relapse rates and patterns were analyzed. Kaplan Meier curves were used to depict relapse-free (RFS), local recurrence-free (LRFS), distant metastases-free survival (DMFS), and overall survival (OS). Kaplan Meier curves were further stratified by disease stage, lymph node status, and margins. Multivariate stepwise Cox regression models were used to identify variables associated with RFS, LRFS, DMFS and OS. RESULTS: Of 2107 patients, 521 (25%) relapsed. Mean age was 68 ± 10 years, with a median follow up of 26 (IQR 11-55) months for the study cohort. Local recurrences were observed in 11% and distant metastases in 18%. Early oncologic failure (within 3 months) occurred in 4%. The most common sites of local recurrence and distant metastases were the pelvis (5%) and lungs (6%) respectively. Abdominal wall/port-site metastases occurred in 1.2% and peritoneal carcinomatosis in 1.2%. The 5-year RFS, LRFS, DMFS, and OS were 66%, 84%, 74%, and 60% respectively. Patient with higher disease stage, pN+ve, and positive soft tissue surgical margins demonstrated worse RFS, LRFS, DMFS, and OS (log rank p<0.01 for all comparisons). Multivariate regression models identified that node positive status and disease stage (≥pT3) were significantly associated with RFS, LRFS, DMFS, and OS (p<0.01). CONCLUSION: Disease stage remains the main variable associated with disease relapse and survival following RC. RARC was not associated with different patterns or higher relapse rates in comparison to historic open radical cystectomy data.

Urology
Kovacevic L, Lu H, **Kovacevic N**, Thomas R, and Lakshmanan Y. Cystatin C, Neutrophil Gelatinase-associated Lipocalin, and Lysozyme C: Urinary Biomarkers for Detection of Early Kidney Dysfunction in Children With Urolithiasis. *Urology* 2020; 143:221-226. PMID: 32505622. Full Text

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OBJECTIVE: To screen for the presence of biomarkers involved in tubular injury and kidney damage in children with urolithiasis (RS), and to validate these proteins by ELISA. METHODS: Prospective-controlled pilot study of children with urolithiasis and their age- and gender-matched controls (HC). Initial screening test was done by quantitative proteomic comparison of pooled urine from RS versus HC, using liquid chromatography-mass spectrometry. Proteins of interest were selected using the following criteria: (1) ≥5 spectral counts; (2) ≥2-fold difference in spectral counts; and (3) ≤.05 P value for the Fisher's Exact Test. Validation was performed by ELISA testing. Statistical analysis was performed by Student t-test and Mann-Whitney U test. RESULTS: Proteomic analysis identified 3 proteins of interest, Cystatin C (CYTC), neutrophil gelatinase-associated lipocalin (NGAL) and lysozyme C that were significantly over-represented in RS group versus HC. ELISA analysis revealed significantly increased urinary levels of CYTC and

NGAL, and nearly significantly increased urinary levels of lysozyme C in RS group (N = 24) compared to controls (N = 13). Subgroup analysis showed significantly higher urinary levels of CYTC in both hypercalciuria (N = 14) and hypocitraturia (N = 10) versus HC (P <.05). CONCLUSION: Children with urolithiasis showed significant increase in urinary CYTC and NGAL irrespective of their normal serum creatinine. These biomarkers indicate tubular injury and early kidney damage and represent valid tools for early screening when traditional tests are normal.

Conference Abstracts

Hematology/Oncology
Carducci MA, **Wang D**, Habermehl C, Bödding M, Rohdich F, Stinchi S, Karpenko O, Gimmi C, and LoRusso P. A multicenter, open-label, dose-escalation, first-in-man study of MetAP2 inhibitor M8891 in patients with advanced solid tumours. *Annals of Oncology* 2020; 31:S486. Conference Abstract.

Background: Methionine aminopeptidase 2 (MetAP2) removes N-terminal Met residues from nascent proteins. MetAP2 inhibition affects protein functionality, which directly affects tumour and endothelial cells, leading to cell cycle arrest and anti-angiogenesis. M8891, a first-in-class, orally available, selective, reversible MetAP2 inhibitor, has anti-angiogenic and anti-tumour effects in preclinical models. We report preliminary results from a phase 1, open-label, dose-escalation study of M8891 alone in patients with advanced solid tumours (NCT03138538). Methods: Patients with biopsy-accessible, histologically confirmed advanced solid tumours received M8891 once daily (QD) in 21-day cycles until disease progression or unacceptable toxicity. Dose escalation aims to determine the maximum tolerated dose, recommended Phase 2 dose, safety, tolerability and pharmacokinetic (PK)/pharmacodynamic profile. Methionyl-elongation factor 1α (a MetAP2 substrate) is a biomarker of target engagement in tumours. Results: Of 24 patients enrolled across six dose levels (7, 12, 20, 35, 60, 80 mg QD), common adverse events were nausea, abdominal pain, constipation, vomiting and Grade 1–2 lipase increases. Transaminase increases were mainly due to underlying disease. Although platelet count reduced and thrombocytopenia was observed (n=10; ≤Grade 4), no bleeding events were reported. Two dose-limiting toxicities occurred at 60 and 80 mg QD (both Grade 4 thrombocytopenia). Exposure increased dose-proportionally up to 35 mg QD, but less than dose-proportionally above 35 mg QD. At steady state (Day 1–15), the M8891 accumulation ratio (AUC) was 1.8–2.9, in line with a half-life of ~30 hours and QD dosing. Target engagement, observed at 7 mg QD, increased dose-dependently, along with exposure. No objective tumour responses were observed in these preliminary data. Conclusions: M8891 has a manageable safety profile, and a favourable PK profile with high exposure and low inter-patient variability. Dose/exposure-dependent target engagement was observed in tumours. Dose selection will be based on safety and exposure; cohort expansion at 35 mg is ongoing. Indication-based cohort in preparation. Clinical trial identification: NCT03138538.

Hematology/Oncology
Dziadziuszko R, Zhang Q, Li X, Paul SM, Sugidono M, Mocci S, Kinkolykh A, Shames DS, Archer V, Mathisen MS, Jin DX, **Gadgeel SM**, Peters S, and Mok T. Blood-based genomic profiling of advanced non-small cell lung cancer (aNSCLC) patients (pts) from blood first assay screening trial (BFAST) and comparison with real-world data (RWD). *Annals of Oncology* 2020; 31:S845-S846. Conference Abstract.

Background: BFAST (NCT03178552) is an ongoing global study evaluating the relationship between blood-based next-generation sequencing (NGS) detection of actionable genetic alterations in circulating tumour DNA and activity of targeted therapies and immunotherapy in pts with 1L aNSCLC. The natural history Cohort Z is non-interventional and collects RWD for pts not receiving treatment as part of the trial. We present BFAST screened pts' characteristics and prevalence of genomic alterations detected in blood. Methods: BFAST pts were screened using Foundation Medicine, Inc. (FMI)'s liquid biopsy assay (FoundationACT). Demographics and genomic alteration prevalence of 5847 BFAST screened pts (as of 31 Dec 2019) were compared with a concurrent cohort of 3784 aNSCLC pts from the de-identified Flatiron Health-FMI Clinico-Genomic Database (CGDB) of FMI-tested US pts who were treated in the Flatiron Health network. ~80% of these pts were tissue-tested, including 1293 "BFAST-like" pts who were tested before 1L treatment and were ECOG PS 0–2 at testing. Results: The prevalence of genomic alterations was similar in BFAST-screened and concurrent CGDB pts, with the exception of KRAS and PIK3CA alterations, which were higher in CGDB pts (Table). BFAST pts were younger (median age 66 vs 70 yrs) with a higher proportion of Asian (20 vs 4%), male (59 vs 50%) and ECOG PS 0–1 pts (91 vs 67%), and fewer smokers (69 vs 83%). Conclusions: To our knowledge, BFAST is the first blood-based NGS genomic survey of a large cohort of 1L aNSCLC pts in a global clinical trial setting. The prevalence of genomic alterations was generally similar to CGDB, despite the use of blood assays vs predominantly tissue assays. Future comparisons of BFAST Cohort Z, CGDB tissue- and blood-tested pts, and their clinical outcome, will provide insights into the value of blood-based NGS testing in global trial and community settings [Formula presented]. Clinical trial identification: NCT03178552.

Hematology/Oncology
Gadgeel SM, Yan M, Paul SM, Mathisen M, Mocci S, Assaf ZJ, Patel R, Sokol ES, Mok T, Peters S, Paz-Ares L, and Dziadziuszko R. Blood first assay screening trial (BFAST) in patients (pts) with 1L NSCLC: ALK+ cohort updated biomarker analyses. *Annals of Oncology* 2020; 31:S841. Conference Abstract.

Background: BFAST (NCT03178552) is a global, multi-cohort study evaluating the relationship between blood-based next-generation sequencing (NGS) detection of actionable genetic alterations in circulating tumour DNA and activity of targeted therapies/immunotherapy in pts with 1L advanced NSCLC. In the ALK+ cohort, investigator-assessed objective response rate (ORR) was 87.4% and 12-month progression-free survival (PFS) rate was 78.4% with alectinib. We present updated ALK+ cohort biomarker analyses (median follow-up: 18.2 months). Methods: Pts aged ≥18 with stage III/IV ALK+ NSCLC (detected by blood-based NGS) received oral alectinib 600mg twice daily. Pre-treatment plasma samples were analysed for: co-occurring genetic alterations, ALK allele frequency, EML4 variants; their association with clinical outcomes was explored (adjusted [adj.] for sex, disease stage, performance and smoking status). Results: Of detected ALK fusions, 84% were EML4-ALK fusions. The most common EML4 variants (V) were V1 (34%) and V3 (33%), and the most common co-mutation was TP53 (44%). Pts with wild-type TP53 had improved 12-month PFS rate vs pts with mutated TP53 (89.4 vs 63.2%, respectively; adj. hazard ratio [HR] 0.31; 95% CI 0.14–0.68; P=.004). Worse 12-month PFS rate was seen for high (73.8%) vs low (81.5%) ALK allele frequency (50% allele cut-off [5.56 copies/mL; range: 0.43–686.28 copies/ml]: adj. HR 0.49; 95% CI 0.22–1.09; p=.08). No significant difference was seen in 12 month PFS rate between EML4 (78.9%) and non-EML4 (71.4%) fusions (adj. HR 0.91; 95% CI 0.33–2.49; p=.846) or EML4 V1 (87.5%) and V3 (74.1%) (adj. HR 0.53; 95% CI 0.18–1.55; p=.244). No significant difference in ORR was observed among the categories analysed. Conclusions: Molecular heterogeneity in ALK+ NSCLC may influence clinical efficacy of ALK inhibitors such as alectinib. Larger, more mature datasets are needed to identify and validate additional biomarkers predictive of limited benefit from ALK inhibitors. Clinical trial identification: NCT03178552.

Hematology/Oncology
Hamilton EP, Barve MA, Tolcher AW, Buscema J, Papadopoulos KP, Zarwan C, Anderson CK, Doroshow D, **Wang D**, Huebner D, Jansen VM, Jarlenski D, Mosher R, Kaufman J, Moore KN, and Richardson DL. Safety and efficacy of XMT-1536 in ovarian cancer: A subgroup analysis from the phase I expansion study of XMT-1536, a NaPi2b antibody-drug conjugate. *Annals of Oncology* 2020; 31:S627-S628. Conference Abstract.

Background: XMT-1536 is a first-in-class ADC targeting NaPi2b, the sodium-dependent phosphate transport protein, broadly expressed in solid tumors such as serous epithelial ovarian cancer. XMT-1536 is being evaluated in patients (pts) with ovarian cancer and non-small cell lung adenocarcinoma in a phase I study (NCT03319628) and has shown a favorable safety profile and evidence of clinical activity. Here, we report on the safety and efficacy of XMT-1536 in pts with platinum-resistant ovarian cancer in the expansion portion of the phase I study. Methods: The expansion study is enrolling pts with platinum-resistant high grade serous ovarian, fallopian tube, or primary peritoneal cancer with up to 3 prior lines of therapy and pts with 4 prior lines of therapy regardless of platinum status. Doses of 36 and 43 mg/m2 administered intravenously every 4 weeks (q4w) are being evaluated. Tumor tissue will be retrospectively evaluated for NaPi2b expression. Results: As of 01-May-2020, 27 pts with ovarian cancer have enrolled: median age was 70 years (range 55 to 85); median prior lines of therapy was 3 (range 1 to 5); >50% had received prior bevacizumab and/or a PARP inhibitor. Twelve pts were dosed at 36 mg/m2 and 15 pts were dosed at 43 mg/m2, the MTD determined in dose escalation. The most frequently (≥20%) reported treatment-related adverse events were fatigue, nausea, vomiting, pyrexia, decreased appetite, diarrhea, and transient increase in AST. As of 01-May-2020, 20 pts were evaluable for response assessment. Treatment with XMT-1536 yielded 2 complete and 5 partial responses with an objective response rate of 35% and disease control rate of 80%, with a favorable trend toward response in tumors with higher NaPi2b expression. Data on safety, response, duration of response, and correlation of response with NaPi2b expression will be presented. At the time of presentation data will be updated with a data cut off of August 2020 and include additional pts and longer follow up for currently enrolled pts. Conclusions: XMT-1536 treatment at 36 and 43 mg/m2 q4w has shown a favorable safety profile and antitumor activity in ovarian cancer. These data support further clinical development of XMT-1536. Clinical trial identification: NCT03319628.

Hematology/Oncology
Mazieres J, Rittmeyer A, **Gadgeel SM**, Hida T, Gandara D, Cortinovis D, Barlesi F, Yu W, Matheny C, Ballinger M, and Park K. 4-year survival in randomised phase II (POPLAR) and phase III (OAK) studies of atezolizumab (atezo) vs docetaxel (doc) in pre-treated NSCLC. *Annals of Oncology* 2020; 31:S821-S822. Conference Abstract.

Background: Atezo (anti–PD-L1) showed overall survival (OS) benefit over doc in the phase II (POPLAR; N=287) and phase III (OAK; N=1225) studies in patients (pts) with advanced NSCLC. 4-year survival analysis from both studies is reported for the first time. Methods: In both studies, pts were randomised 1:1 to receive atezo (1200 mg) or doc (75 mg/m2) IV Q3W; PD-L1 expression was assessed by the Ventana SP142 assay on tumour cells (TC) and tumour-infiltrating immune cells (IC); landmark OS was estimated by the Kaplan-Meier method. Results: The minimum follow-

up was 53 (POPLAR) and 45 (OAK) mo − an additional 17 and 19 mo follow-up, respectively, from prior reports. 4-year survival rates with atezo vs doc were 14.8% vs 8.1% and 15.5% vs 8.7% in POPLAR and OAK, respectively. The long-term OS benefit of atezo vs doc was seen across histology and PD-L1 expression subgroups. Of pts in the atezo arms who lived ≥4 years in POPLAR (N=15) and OAK (N=43), 40% and 23% were in the PD-L1–high (TC3 or IC3) subgroup, 33% and 37% were in the PD-L1–negative (TC0 and IC0) subgroup, and 87% and 88% had non-squamous histology, respectively. Among 4-year survivors in the doc arms, 2/4 (50%) and 17/26 (65%) received subsequent immunotherapy in POPLAR and OAK, respectively, vs 3/15 (20%) and 10/43 (23%) in the atezo arms. Fewer Grade 3-4 treatment (tx)-related adverse events (AEs) and AEs leading to tx withdrawal occurred in the atezo vs doc arms in both studies. Conclusions: 4-year OS rates favoured atezo vs doc regardless of histology and PD-L1 expression in both studies, despite a high rate of subsequent immunotherapy in the doc arm. The PD-L1–high subgroups continued to derive the greatest OS benefit with atezo vs doc; however, the PD-L1–negative subgroups also sustained an improved long-term OS benefit with atezo vs doc. Most pts in the doc arms received subsequent immunotherapy. Atezo tx was well tolerated, and safety was consistent with prior reports. [Formula presented] Clinical trial identification: NCT01903993 (POPLAR), NCT02008227 (OAK).

Hematology/Oncology
Oh DY, Arkenau T, Lee KW, Alsina M, Marti FM, Chung IJ, Saif W, **Wang D**, O'Dwyer P, Chau I, Lee MA, Chong E, Hilger-Rolfe J, Cole G, and Kim SY. Phase Ib/II study of ibrutinib (ibr) in combination with cetuximab (cetux) in patients (pts) with previously treated metastatic colorectal cancer (mCRC). *Annals of Oncology* 2020; 31:S428. Conference Abstract.

Background: Third- or later-line treatments for mCRC have low response rates (1–37%) and limited PFS (1.4–5.6 mo) and OS (6.1–14.0 mo) (Arnold Ann Oncol 2018). Ibr is a once-daily Bruton's tyrosine kinase (BTK) inhibitor approved for the treatment of various B-cell malignancies. Ibr also inhibits other kinases, including ETK, ITK, and EGFR tyrosine kinase (Wang Clin Cancer Res 2018; Dubovsky Blood 2013; Gao J Natl Cancer Inst 2014), and may provide complementary activity with cetux. Dual targeting of EGFR may improve OS in mCRC (Weickhardt J Clin Oncol 2012). This cohort of the phase Ib/II study (NCT02599324) evaluated efficacy and safety of ibr + cetux in pts with mCRC. Methods: Eligible pts had KRAS or NRAS wild type mCRC previously treated with 2–4 regimens and were cetux-naive. Pts received oral ibr once daily at 560 mg (starting dose) or 840 mg (recommended phase II dose) plus IV cetux (400 mg/m2 initial dose then 250 mg/m2 weekly) in 21-d cycles until unacceptable toxicity or progression. Efficacy (overall response rate [ORR], PFS, duration of response [DOR], disease control rate [DCR], and OS) and safety are reported. Results: 58 pts received ibr + cetux (ibr 560 mg, n=8; ibr 840 mg, n=50). Median age was 62 y; 38%, 40%, and 22% of pts had received 2, 3, and 4 prior regimens for mCRC, respectively. Median follow-up was 20.9 mo. ORR was 16% (Table). Median PFS was 4.8 mo (range 3.9–5.6). Median treatment duration was 3.2 mo for ibr and 3.0 mo for cetux. Grade ≥3 adverse events (AEs) occurred in 41 pts (71%); the only grade ≥3 AE occurring in ≥10% of pts was dermatitis acneiform (15 pts [26%]). Two pts (3%) had AEs leading to death; neither were related to study drug. Two pts (3%) had major hemorrhage and 53 pts (91%) had rash of any grade (grade ≥3 in 17 pts [29%]). Conclusions: Ibr + cetux was moderately active in heavily pretreated, refractory, cetux-naive pts with mCRC. There were no new safety signals and the safety profile was consistent with those of the individual drugs. [Formula presented] Clinical trial identification: NCT02599324.

Hematology/Oncology
Omlin AG, Graff JN, Hoimes CJ, Tagawa ST, **Hwang C**, Kilari D, Ten Tije AJ, McDermott R, Vaishampayan UN, Elliott T, Gerritsen WR, Wu H, Kim J, Schloss C, de Bono JS, and Antonarakis ES. KEYNOTE-199 phase II study of pembrolizumab plus enzalutamide for enzalutamide-resistant metastatic castration-resistant prostate cancer (mCRPC): Cohorts (C) 4 and 5 update. *Annals of Oncology* 2020; 31:S514-S515. Conference Abstract.

Background: We present results including time to cytotoxic chemotherapy and time to new anticancer therapy from the multicohort phase 2 study KEYNOTE-199 (NCT02787005) in chemotherapy-naive patients (pts) with mCRPC treated with pembrolizumab (pembro) + enzalutamide (enza) after progression on enza and who had RECIST-measurable (C4) or bone-predominant nonmeasurable (C5) disease. Methods: Pts with or without prior abiraterone were eligible if they developed resistance to enza following prior response. Pts continued on enza and received pembro 200 mg IV Q3W for up to 2 y or until progression, toxicity, or withdrawal. End points: ORR per RECIST v1.1 (C4) by blinded independent central review (primary), DOR (C4), DCR, rPFS per PCWG3-modified RECIST, OS, time to cytotoxic chemotherapy, time to new anticancer therapy, and safety. Results: 126 pts (C4, 81; C5, 45) were treated. Median (range) PSA was 31 ng/mL (0.4-1667) in C4 and 19 ng/mL (1-1750) in C5. Median (range) time from enrollment to data cut off was 15 mo (7-21) in C4 and 19 mo (7-21) in C5. In C4, ORR (95% CI) was 12% (6-22; 2 CRs, 8 PRs) and median (range) DOR was 6.3 mo (2.5+ to 13.4); 4 responders (73% by Kaplan-Meier estimation) had a response ≥6 mo. Efficacy analyses are displayed in the table. Grade ≥3 treatment-related AEs occurred in 26% of pts in C4 and 24% in C5. Two pts in C4 died of immune-related AEs (Miller Fisher syndrome and myasthenia gravis). Incidence of any grade/grade 3-4 rash (regardless of treatment relatedness) was higher than previously reported for individual agents (33%/6%) but manageable with standard of care treatments. [Formula presented]

Conclusions: Pembro + enza after enza resistance had manageable safety and showed antitumor activity for RECIST-measurable and bone-predominant mCRPC. This combination is being evaluated in the ongoing KEYNOTE-641 phase III trial (NCT03834493). Clinical trial identification: NCT02787005.

Hematology/Oncology
Ou SI, Solomon B, Shaw A, **Gadgeel SM**, Besse B, Soo RA, Abbattista A, Thurm H, Toffalorio F, Wiltshire RJ, and Bearz A. Lorlatinib in patients with ALK+ NSCLC treated beyond initial disease progression. *Annals of Oncology* 2020; 31:S842. Conference Abstract.

Background: The third-generation tyrosine kinase inhibitor (TKI) lorlatinib showed overall and intracranial anti-tumor activity in patients with ALK+ NSCLC in the ongoing phase 2 trial NCT01970865. Efficacy was noted in treatment-naïve patients and following progression on previous ALK inhibitor therapy. This retrospective analysis investigated the potential clinical benefit of continuing lorlatinib beyond progressive disease (LBPD) in patients with ALK+ NSCLC. Methods: Patients with advanced ALK+ NSCLC were permitted to remain on study treatment after RECIST-defined disease progression if they continued to experience clinical benefit as per investigator judgment. Herein, continuation was defined as >3 weeks lorlatinib treatment after PD documentation by investigators. Patients were excluded if best overall response to initial lorlatinib was PD or indeterminate. Only patients who received prior crizotinib ± chemotherapy (Group A) or ≥1 second-generation ALK TKI ± chemotherapy (Group B) were included. Characteristics at baseline/progression, efficacy outcomes during lorlatinib treatment, and overall survival (OS) in LBPD and non-LBPD patients were assessed. Results: In total, 102 patients were included in the analysis (Table). In Group A, 21/28 patients (75.0%) continued LBPD with a median post-PD treatment duration (TD) of 11.8 months and overall TD of 32.4 months. In Group B, 56/74 patients (75.7%) continued LBPD with a median post-PD TD of 5.7 months and overall TD of 16.4 months. Median OS in Group B LBPD and non-LBPD patients was 26.5 months (95% CI: 18.7–35.5) and 14.7 months (95% CI: 9.3–38.5), respectively. Median OS in Group A LBPD was not reached (NR) and in non-LBPD was 24.4 months (95% CI: 12.1–NR) [Formula presented]. Conclusions: Majority of patients continued LBPD. Median OS was longer in LBPD vs non-LBPD groups. Further evaluations to better assess the clinical benefit of continuing treatment with lorlatinib beyond RECIST-determined progression are warranted. Clinical trial identification: NCT01970865.

Hematology/Oncology
Siu LL, **Wang D**, Hilton J, Geva R, Rasco D, Abraham AK, Markensohn JF, Suttner L, Siddiqi S, Altura RA, and Maurice-Dror C. Initial results of a phase I study of MK-4830, a first-in-class anti–immunoglobulin-like transcript 4 (ILT4) myeloid-specific antibody in patients (pts) with advanced solid tumours. *Annals of Oncology* 2020; 31:S462. Conference Abstract.

Background: MK-4830 is a novel, first-in-class human IgG4 monoclonal antibody targeting the myeloid-specific ILT4 receptor. MK-4830 catalyzes reprogramming of tumour-associated macrophages, relieving myelosuppression and enhancing T cell function. We present data from the first-in-human phase I dose escalation study (NCT03564691) of MK-4830 and MK-4830 + pembrolizumab (pembro). Methods: Pts with advanced solid tumours received MK-4830 IV Q3W at escalating doses alone and with pembro. Primary end points were safety and tolerability. PK was a secondary end point; exploratory objectives included ORR per RECIST v1.1, evaluation of receptor occupancy (RO), and immune correlates of response in blood and tumour. Results: Among 84 pts, 50 received MK-4830 monotherapy; 34 received MK-4830 + pembro. Median age was 62 years; 50% previously received ≥3 lines of therapy. No dose-limiting toxicities were observed; maximum-tolerated dose was not reached. Any-grade AEs were consistent with those common to pembro. Treatment-related AEs were reported in 52% of pts; most were grade 1/2. MK-4830 steady-state serum PK at Ctrough was achieved at the highest dose levels, at which almost all pts had ≥95% blood RO. Preliminary efficacy data show 11 objective responses, with 2 complete responses and 9 partial responses; 1 response was observed in a patient receiving MK-4830 monotherapy. All responses occurred in heavily pretreated pts, 5 of whom had not had a response to prior anti–PD-1 therapy. Responses were durable; some pts received >1 year of treatment. Pre- and on-treatment (n=15) biopsies enabled a preliminary assessment of correlation between RO and immune cell subsets before and during treatment. Conclusions: This first-in-class MK-4830 antibody targeting ILT4 given as monotherapy and in combination with pembro was well tolerated and showed dose-related evidence of target engagement. Durable responses were observed with both MK-4830 alone and with MK-4830 + pembro in heavily pretreated pts, 5 of whom progressed on prior anti–PD-1 therapies. These initial data support the further development of MK-4830 + pembro for pts with advanced solid tumors. Clinical trial identification: NCT03564691.

Neurosurgery
Park P, **Chang V**, Schwalb JM, **Nerenz D**, **Schultz LR**, Easton RW, Kashlan O, Oppenlander ME, and Aleem I. 145. The impact of Michigan's new opioid prescribing laws on spine surgery patients: analysis of the Michigan Spine Surgery Improvement Collaborative (MSSIC). *Spine Journal* 2020; 20(9):S71-S72. Conference Abstract.

BACKGROUND CONTEXT: In response to the opioid abuse epidemic, the state of Michigan passed new legislation designed to limit use of narcotics. Specific requirements included patient education with attestation, prescription system query, 7-day supply limit for acute pain, and a bona fide prescriber-patient relationship. The major aspects of these opioid laws were effective beginning July 1, 2018. PURPOSE: To evaluate the impact of these new restrictive laws on preoperative narcotic use, short-term outcomes, and readmission rates after spinal surgery. STUDY DESIGN/SETTING: Patient data from 1 year prior to and 1 year after initiation of the new opioid laws were queried from the Michigan Spine Surgery Improvement Collaborative (MSSIC) database, a spine-specific registry. PATIENT SAMPLE: Michigan Spine Surgery Improvement Collaborative (MSSIC) Registry. OUTCOME MEASURES: Patient-Reported Outcomes Measurement Information System (PROMIS) short form Physical Function (PF) 4a. METHODS: The MSSIC registry prospectively enrolls patients undergoing surgery for degenerative spine disease. Prior to and after implementation of the major elements of the new laws, 12,325 and 11,988 patients, respectively, were treated. Chi-square and t-tests were used to examine differences between pre and postopioid law implementation. RESULTS: Pre- and postopioid law patients had generally similar demographic and surgical characteristics. Notably, after passage of the opioid laws, the number of patients taking daily narcotics preoperatively decreased from 3,783 (48.7%) to 2,698 (39.7%), P <.0001. At 3 months postoperatively, there were no differences in PROMIS PF (41.5 vs 41.8, P =.0789), minimum clinically important difference (56.0% vs 58.0%, P =.060), numeric rating scale (NRS) of back pain (3.5 vs 3.4, P =.1745, NRS of leg pain (2.7 vs 2.7, P =.6909), satisfaction (83.8% vs 84.0%, P =.763), or 90-day readmission rate (6.7% vs 6.4%, P =.3688) between groups. Although there was no difference in readmission rates, pain as a reason for readmission was marginally more common (1.05% vs 1.48%, P =.0032). CONCLUSIONS: There was a meaningful decrease in preoperative narcotic use, but notably there was no apparent negative impact on postoperative recovery, patient satisfaction, or short-term outcomes after spinal surgery despite more restrictive opioid prescribing. Although the readmission rate did not significantly increase, pain as a reason for readmission was marginally more frequently observed.

Public Health Sciences

Park P, **Chang V**, Schwalb JM, **Nerenz D**, **Schultz LR**, Easton RW, Kashlan O, Oppenlander ME, and Aleem I. 145. The impact of Michigan's new opioid prescribing laws on spine surgery patients: analysis of the Michigan Spine Surgery Improvement Collaborative (MSSIC). *Spine Journal* 2020; 20(9):S71-S72. Conference Abstract.

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Surgery

Bendix S, **Rteil A**, **Potti C**, **Chamogeorgakis T**, **Lace B**, **Woodward A**, and **Kabbani L**. Mycotic Aneurysm After Metallic Foreign Body Ingestion. *Journal of Vascular Surgery* 2020; 72(3):e304-e305. Conference Abstract.

Objective: The esophagus is a frequent foreign body impaction site. We present a case of foreign body ingestion complicated by erosion into the aorta, causing a mycotic aneurysm. Methods: We introduce the case of a 60-year-old man with abdominal pain, nausea, fatigue, and fevers. Blood cultures grew out gram-positive cocci. A computed tomography (CT) scan revealed a distal thoracic aortic saccular aneurysm, with a 2.8-cm linear metallic body penetrating the inferior border of the aneurysm, and intraluminal thrombus formation (Fig, A). CT of the abdomen

revealed portal vein thrombosis and splenic and hepatic abscesses. Esophagogastroduodenoscopy was unremarkable. Results: The patient was started on the appropriate antibiotic therapy. He was then taken to the operating room for an open thoracoabdominal aortic aneurysm repair with an interposition cryopreserved graft, with an intercostal muscle flap (Fig, B). A metal bristle was removed (Fig, C). He had an uneventful postoperative course and was discharged home on postoperative day 17. Follow-up CT angiography showed resolution of the infection and satisfactory repair (Fig, D). Postoperative esophagram showed no esophageal injury. Conclusions: We describe a case of a bristle from a metallic barbecue brush that was ingested. This penetrated the esophagus, causing a mycotic aneurysm with septic embolization to the spleen and liver. Our successful treatment approach involved open aortic repair with an interposition cryopreserved graft and an intercostal muscle flap. [Formula presented].

Surgery
Lin JC, **Ranasinghe B**, **Patel A**, and **Rogers CG**. Robot-assisted laparoscopic placement of extravascular stent for nutcracker syndrome. *Journal of Vascular Surgery Cases and Innovative Techniques* 2020; 6(3):346-347. Conference Abstract.

A 20-year-old man complained of debilitating left flank pain for 6 months with an episode of gross hematuria. Computed tomography showed compression of the left renal vein between the aorta and superior mesenteric artery with an aortomesenteric angle of 25 degrees. Venography showed a gradient of 3 mm Hg across the compression and 94.4% luminal compression of the left renal vein. After discussion of all surgical and endovascular options, robot-assisted laparoscopic placement of an extravascular cuff around the left renal vein was performed using the da Vinci X Surgical System (Intuitive Surgical, Sunnyvale, Calif). The patient did well with full resolution of the left flank pain.

Urology
Lin JC, **Ranasinghe B**, **Patel A**, and **Rogers CG**. Robot-assisted laparoscopic placement of extravascular stent for nutcracker syndrome. *Journal of Vascular Surgery Cases and Innovative Techniques* 2020; 6(3):346-347. Conference Abstract.

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Books and Book Chapters

Nursing
Fadhilah A, **Gabbar A**, and Bokhari AA. "Microsporidium". StatPearls. Treasure Island (FL), StatPearls Publishing Copyright © 2020, StatPearls Publishing LLC. PMID: 30725851. Full Text

Microsporidia are an unusually large group of unique, eukaryotic, obligate, intracellular parasites that biologists have studied for more than 150 years. Microsporidia are well-adapted pathogens and important agricultural parasites that infect honeybees, silkworms, and other insects. The organism is also a parasite for fish, rodents, rabbits, primates, and humans. This article reviews Microsporidia with emphases on the latest biological discoveries.

Pharmacy
Azzouz A, and Preuss CV. "Linezolid". StatPearls. Treasure Island (FL), StatPearls Publishing Copyright © 2020, StatPearls Publishing LLC. PMID: 30969615. Full Text

Linezolid is a synthetic oxazolidinone antimicrobial drug. It is indicated for gram-positive infections and approved for the treatment of bacterial pneumonia, skin and skin structure infections, and vancomycin-resistant enterococcal (VRE) infections, including infections complicated by bacteremia. Linezolid does not have approval for the treatment of gram-negative infections, catheter-related bloodstream infections, or catheter site infections.

Surgery
Altshuler P, **Nahirniak P**, and Welle NJ. "Saphenous Vein Grafts". StatPearls. Treasure Island (FL), StatPearls Publishing Copyright © 2020, StatPearls Publishing LLC. PMID: 30725720. Full Text

Coronary artery disease (CAD) is a highly prevalent and initial consensus disease afflicting many. Recently, the 2016 Heart Disease and Stroke Statistics update of the American Heart Association (AHA) reported a disease prevalence of 15.5 million persons among those 20 years and older in the USA. The treatment of CAD ranges from medical

management and lifestyle modification to invasive coronary revascularization. Coronary revascularization was first performed in 1960 by Dr. Robert H. Goetz who performed a right internal mammary artery (RIMA) anastomosis to the right coronary artery, and in 1967 Dr. René Favaloro first described the use of an autologous reversed greater saphenous vein (GSV) graft as a bypass graft. An easily accessible and reliable conduit with a significant length, the GSV continued to be the conduit of choice until 1986 when data revealed the left internal mammary artery (LIMA) as a superior vessel to revascularize the left anterior descending artery (LAD) territory of the myocardium. The LIMA graft showed a significant increase in graft patency and patient survival as compared to GSV and thus became the initial consensus vessel of choice for CABG. While the LIMA is currently used to revascularize LAD territory and in certain circumstances can be anastomosed to multiple vessels in sequential bypassing, it is not always a viable graft, and there is frequently a need for additional vessel harvest to revascularize other diseased segments. As coronary artery bypass grafting continues to evolve, saphenous vein grafts have remained as important conduits during revascularization of multi-vessel coronary artery disease or single vessel disease in which the LIMA has been rendered unusable.

Surgery
Le CK, **Nahirniak P**, Anand S, and Cooper W. "Volvulus". StatPearls. Treasure Island (FL), StatPearls Publishing Copyright © 2020, StatPearls Publishing LLC.2020. PMID: 28722866. Full Text

Volvulus occurs when a loop of intestine twists around itself and the mesentery that supplies it, causing a bowel obstruction. Symptoms include abdominal distension, pain, vomiting, constipation, and bloody stools. The onset of symptoms may be insidious or sudden. The mesentery becomes so tightly twisted that blood supply is cut off, resulting in bowel ischemia. Pain may be significant and fever may develop. Risk factors for volvulus include intestinal malrotation, Hirschsprung disease, an enlarged colon, pregnancy, and abdominal adhesions. A higher incidence of volvulus is also noticed among hospitalized patients with neuropsychiatric disorders such as Parkinson's disease, multiple sclerosis, etc. High fiber diet, chronic constipation with chronic use of laxatives and/or enema, and associated myopathy like Duchene muscular dystrophy, etc. are also associated with an increased risk of sigmoid volvulus. In adults, the sigmoid colon and cecum are the most commonly affected. On the contrary, splenic flexure is least prone to volvulus. In children, the small intestine and stomach are more commonly involved. Diagnosis is mainly clinical, however, characteristic radiological findings on plain radiograph, ultrasound, and upper GI series help in differentiating from other differentials. The present article will cover volvulus in adults with specific differences from midgut volvulus in children. However, a detailed discussion of malrotation and midgut volvulus is beyond the scope of this article. Sigmoidoscopy or a barium enema can be attempted as an initial treatment for sigmoid volvulus. However, due to the high risk of recurrence, bowel resection with anastomosis within two days is generally recommended. If the bowel is severely twisted or the blood supply is cut off, emergent surgery is required. In a cecal volvulus, part of the bowel is usually removed. If the cecum is still healthy, it may be returned and sutured in place. However, conservative treatment in both cases is associated with high rates of recurrence.

Surgery
Le CK, **Nahirniak P**, and Qaja E. "Cecal Volvulus". StatPearls. Treasure Island (FL), StatPearls Publishing Copyright © 2020, StatPearls Publishing LLC. PMID: 29262030. Full Text

Volvulus occurs when portions of the bowel get entangled upon a mesenteric axis, which can cause impairment of the blood supply or can result in complete or partial obstruction of the bowel lumen. This condition usually affects the colon. Colonic volvulus is a rare occurrence in the United States, attributing to approximately 4% of causes of large bowel obstruction, followed by cancer and diverticulitis. Of note, there are certain regions of the world where colonic volvulus happens more frequently. In areas of the Middle East, India, South America, Africa, and Russia, colonic volvulus attributes for approximately 50% of all accounts of colonic obstruction. The regional areas listed above have been coined the "volvulus belt." Sigmoid volvulus occurs more frequently compared to cecal volvulus.

Surgery
Manna B, **Nahirniak P**, and Morrison CA. "Wound Debridement". StatPearls. Treasure Island (FL), StatPearls Publishing. Copyright © 2020, StatPearls Publishing LLC. PMID: 29939659. Full Text

The concept of preparing the wound bed to promote reepithelialization of chronic wounds has been applied to wound management for more than a decade. The 4 general steps to follow for better preparation are compassed in the acronym DIME. D: Debridement of nonviable tissue within the Wound. . I: Management of Inflammation and Infection. M: Moisture control. E: Environmental and Epithelialization assessment. The DIME approach to chronic wound management is a global concept approach from which a more detailed pathway can be initiated to bring about wound resolution. The primary goal of debridement is to remove all the devitalized tissue from the wound bed to promote wound healing. Debridement is also used for removal of biofilm, bioburden along with senescent cells, and it is suggested to be performed at each encounter.

Surgery
Valdes PJ, **Nahirniak P**, and Diaz MA. "Vein Graft Stenosis". StatPearls. Treasure Island (FL), StatPearls Publishing. Copyright © 2020, StatPearls Publishing LLC. PMID: 29763122. Full Text

The long-term patency and success of saphenous venous grafts in coronary artery bypass graft surgery (CABG) remains a challenge due to their accelerated atherosclerosis rates as well as multifactorial causes of graft failure. Venous graft bypass procedures have been practiced for over a century, and are not yet perfected. In 1906, Goyanes inserted the first autogenous vein graft into a human, using a popliteal vein as an interposition graft to bridge an arterial defect, following excision of a syphilitic popliteal aneurysm. By 1962, the development of selective coronary angiography allowed Sabiston to perform the first right coronary artery bypass procedure. The art of coronary artery bypass grafting was further developed and refined by Garret and Favaloro.

Surgery
Wernick B, **Nahirniak P**, and Stawicki SP. "Impaired Wound Healing". StatPearls. Treasure Island (FL), StatPearls Publishing. Copyright © 2020, StatPearls Publishing LLC.2020. PMID: 29489281. Full Text

In a way, history of wound care is the history of humankind. Well before any written historical record, chronic wounds of all shapes and sizes have plagued patients and created a significant burden on their caretakers. It has long been noticed that some patient factors are more likely to be associated with better wound healing . Likewise, certain wound types have been noted to be associated with a better prognosis than others. Until recently, there has been little scientific evidence regarding the risk factors and characteristics, both positive and negative, responsible for wound healing behaviors . This article will review factors that lead to poor wound healing and the latest advances in their care.

HFHS Publications on COVID-19

Administration
Miller J, **Fadel RA**, **Tang A**, **Perrotta G**, **Herc E**, **Soman S**, **Nair S**, **Hanna Z**, **Zervos MJ**, **Alangaden G**, **Brar I**, and **Suleyman G**. The Impact of Sociodemographic Factors, Comorbidities and Physiologic Response on 30-day Mortality in COVID-19 Patients in Metropolitan Detroit. *Clin Infect Dis* 2020; Epub ahead of print. PMID: 32945856. Full Text

Behavioral Health Services/Psychiatry
Gautam M, Kaur M, and **Mahr G**. COVID-19-Associated Psychiatric Symptoms in Health Care Workers: Viewpoint From Internal Medicine and Psychiatry Residents. *Psychosomatics* 2020; 61(5):579-581. PMID: 32439184. Full Text

Cardiology/Cardiovascular Research
Al-Darzi W, **Aurora L**, **Michaels A**, **Cowger J**, **Grafton G**, **Selektor Y**, **Tita C**, **Hannawi B**, **Lanfear D**, **Nemeh HW**, and **Williams CT**. Heart Transplant Recipients with Confirmed 2019 Novel Coronavirus Infection: The Detroit Experience. *Clin Transplant* 2020; e14091. Epub ahead of print. PMID: 32940925. Full Text

Dermatology
Lyons AB, and **Hamzavi IH**. Ultraviolet C Induced Skin Reaction from Ultraviolet Germicidal Irradiation of N95 Respirators During the COVID-19 Pandemic. *Photodermatol Photoimmunol Photomed* 2020; Epub ahead of print. PMID: 32974955. Full Text

Dermatology
Ozog DM, Sexton JZ, **Narla S**, Pretto-Kernahan CD, Mirabelli C, **Lim HW**, **Hamzavi IH**, **Tibbetts RJ**, and **Mi QS**. The Effect of Ultraviolet C Radiation Against Different N95 Respirators Inoculated with SARS-CoV-2. *Int J Infect Dis* 2020; Epub ahead of print. PMID: 32891736. Full Text

Diagnostic Radiology
Hadied MO, **Patel PY**, **Cormier P**, **Poyiadji N**, **Salman M**, **Klochko C**, **Nadig J**, **Song T**, **Peterson E**, and **Reeser N**. Interobserver and Intraobserver Variability in the CT Assessment of COVID-19 Based on RSNA Consensus Classification Categories. *Acad Radiol* 2020; Epub ahead of print. PMID: 32948442. Full Text

Diagnostic Radiology
Zhang R, Tie X, **Qi Z**, **Bevins NB**, Zhang C, Griner D, **Song TK**, **Nadig JD**, Schiebler ML, Garrett JW, Li K, Reeder SB, and Chen GH. Diagnosis of COVID-19 Pneumonia Using Chest Radiography: Value of Artificial Intelligence. *Radiology* 2020; Epub ahead of print. PMID: 32969761. Full Text

Emergency Medicine
Miller J, **Fadel RA**, **Tang A**, **Perrotta G**, **Herc E**, **Soman S**, **Nair S**, **Hanna Z**, **Zervos MJ**, **Alangaden G**, **Brar I**, and **Suleyman G**. The Impact of Sociodemographic Factors, Comorbidities and Physiologic Response on 30-day Mortality in COVID-19 Patients in Metropolitan Detroit. *Clin Infect Dis* 2020; Epub ahead of print. PMID: 32945856. Full Text

Infectious Diseases
Gudipati S, **Zervos M**, and **Herc E**. Can the One Health Approach Save Us from the Emergence and Reemergence of Infectious Pathogens in the Era of Climate Change: Implications for Antimicrobial Resistance? *Antibiotics (Basel)* 2020; 9(9). PMID: 32937739. Full Text

Infectious Diseases
Miller J, **Fadel RA**, **Tang A**, **Perrotta G**, **Herc E**, **Soman S**, **Nair S**, **Hanna Z**, **Zervos MJ**, **Alangaden G**, **Brar I**, and **Suleyman G**. The Impact of Sociodemographic Factors, Comorbidities and Physiologic Response on 30-day Mortality in COVID-19 Patients in Metropolitan Detroit. *Clin Infect Dis* 2020; Epub ahead of print. PMID: 32945856. Full Text

Internal Medicine
Miller J, **Fadel RA**, **Tang A**, **Perrotta G**, **Herc E**, **Soman S**, **Nair S**, **Hanna Z**, **Zervos MJ**, **Alangaden G**, **Brar I**, and **Suleyman G**. The Impact of Sociodemographic Factors, Comorbidities and Physiologic Response on 30-day Mortality in COVID-19 Patients in Metropolitan Detroit. *Clin Infect Dis* 2020; Epub ahead of print. PMID: 32945856. Full Text

Nephrology
Miller J, **Fadel RA**, **Tang A**, **Perrotta G**, **Herc E**, **Soman S**, **Nair S**, **Hanna Z**, **Zervos MJ**, **Alangaden G**, **Brar I**, and **Suleyman G**. The Impact of Sociodemographic Factors, Comorbidities and Physiologic Response on 30-day Mortality in COVID-19 Patients in Metropolitan Detroit. *Clin Infect Dis* 2020; Epub ahead of print. PMID: 32945856. Full Text

Nephrology
Singh N, Tandukar S, Zibari G, Naseer MS, Amiri HS, and **Samaniego M**. Successful Simultaneous Pancreas and Kidney Transplant in a Patient Post-COVID-19 Infection. *Kidney Int* 2020; Epub ahead of print. PMID: 32946881. Full Text

Neurology
Syed MJ, Lisak RP, **Delly F**, and Zutshi D. Reply from the authors: Myasthenic crises in COVID-19. *J Neurol Sci* 2020; 417:117061. PMID: 32741591. Full Text

Pathology and Laboratory Medicine
Ozog DM, Sexton JZ, **Narla S**, Pretto-Kernahan CD, Mirabelli C, **Lim HW**, **Hamzavi IH**, **Tibbetts RJ**, and **Mi QS**. The Effect of Ultraviolet C Radiation Against Different N95 Respirators Inoculated with SARS-CoV-2. *Int J Infect Dis* 2020; Epub ahead of print. PMID: 32891736. Full Text

Public Health Sciences
Miller J, **Fadel RA**, **Tang A**, **Perrotta G**, **Herc E**, **Soman S**, **Nair S**, **Hanna Z**, **Zervos MJ**, **Alangaden G**, **Brar I**, and **Suleyman G**. The Impact of Sociodemographic Factors, Comorbidities and Physiologic Response on 30-day Mortality in COVID-19 Patients in Metropolitan Detroit. *Clin Infect Dis* 2020; Epub ahead of print. PMID: 32945856. Full Text

Surgery
Docimo S, Jr., Jacob B, **Seras K**, and Ghanem O. Closed Facebook groups and COVID-19: an evaluation of utilization prior to and during the pandemic. *Surg Endosc* 2020; Epub ahead of print. PMID: 32926250. Full Text