University of Toledo
College of Medicine & Life Sciences
Department of Medicine
Annual Research Symposium

September 30, 2021

Volume 1

COLLEGE OF MEDICINE
AND LIFE SCIENCES

THE UNIVERSITY OF TOLEDO

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Message from the Chair

It is my great pleasure to welcome you to the Inaugural Department of Medicine Annual Research Symposium. Our program includes welcoming remarks from the Dean of the College of Medicine and Life Sciences, Dr. Christopher J. Cooper, from the President of the University of Toledo, Dr. Gregory Postel, and from Dr. Rujun Gong, Professor and Vice Chair of Medicine. This will be followed by a keynote address presented by Dr. Jeffrey S. Ross**,** who is an internationally renowned investigator, *Medical Director, Foundation Medicine, Inc. Cambridge, MA and the Jones-Rohner Endowed Professor of Pathology & Urology Upstate Medical University in Syracuse, NY.* The symposium will conclude with an abstract and poster session highlighting ongoing research projects by trainees and investigators working in the Department of Medicine. This year approximately 180 abstracts and posters have been submitted, representing every division in the Department of Medicine and covering a wide range of topics such as case reports, quality and outcome studies, metanalyses, clinical translational and laboratory science. The submissions have also been judged by a panel of investigators, with prizes awarded to the highest-rated abstracts in several categories. I am particularly grateful to Drs. Cooper, Postel, Gong, and Ross for joining us, and to all of our faculty and trainees for their interest and active support of the symposium.

Our mission at University of Toledo is to provide University-quality care to our patients, to train the next generation of physicians and investigators, and to conduct research to increase our knowledge of human biology, health and illness, and medical therapeutics. Faculty and trainees in the Department of Medicine are actively engaged in all of these endeavors; however, the research that we do may sometimes be siloed and not well known across divisional and departmental lines. One important purpose of this meeting is to increase awareness of the depth and strength of our research portfolio, and to recognize and honor many highly-successful and productive trainees and investigators within the Department of Medicine. I hope that this and subsequent meetings will call attention to the importance of our research mission and promote collaboration across programs, divisions, and departments, to energize our students and faculty engaged in research, and ultimately to facilitate its growth and overall success.

Thank you for your interest, enjoy the symposium, and please use this abstract book to identify areas of new and overlapping interest and to develop common goals and new collaborations.

Sincerely,

Lance D. Dworkin, M.D.
Mercy Professor of Education & Chair
Department of Medicine
University of Toledo College of Medicine & Life Sciences
Academic Chief of Medicine, ProMedica

Keynote Speaker

Jeffrey S. Ross, M.D.

Medical Director, Foundation Medicine Cambridge, Massachusetts
Jones-Rohner Endowed Professor of Pathology, Oncology and Urology Upstate Medical University Syracuse, New York

Jeffrey Ross, M.D. is a leader in the field of molecular diagnostics, having received a number of academic awards, been awarded three patents and authored more than 600 peer-reviewed scientific articles and abstracts, four textbooks and numerous book chapters in the fields of pathology, molecular diagnostics, oncology and translational cancer research.

Dr. Ross is the Cyrus Strong Merrill Professor and Chair of the Department of Pathology and Laboratory Medicine at Albany Medical College, where he directs an extramurally-funded research laboratory in molecular pathology. Between 1999 and 2004, Dr. Ross served as Scientific Fellow and Head of Molecular Pathology at Millennium Pharmaceuticals before co-founding Syfr, Inc. an RFID Specimen Management and IHC/ISH/FISH autostainer company. Prior to that Dr. Ross served as Medical Director for Managed Care for Roche Biomedical Laboratories and Laboratory Corporation of America.

Since 2000, Dr. Ross has been a member of the NIH Clinical Oncology Study Section. He serves on the editorial boards and reviewer lists of numerous scientific journals and is Associate Editor for Basic Science of the American Journal of Clinical Pathology. He has served in multiple leadership positions for the American Society of Clinical Pathologists, the College of American Pathologists, the International Academy of Pathology, the Association of Pathology Chairs and the American Society of Clinical Oncology.

He is a graduate of Oberlin College, Oberlin, Ohio and The State University of New York at Buffalo School of Medicine in Buffalo, New York. He served as an intern resident and fellow in Anatomic and Clinical Pathology at the Massachusetts General Hospital in Boston, Massachusetts.

Schedule of Events

1ST ANNUAL DEPARTMENT OF MEDICINE RESEARCH SYMPOSIUM

Thursday, September 30, 2021

Collier Building (100-A)

WELCOME & INTRODUCTIONS

4:00pm	Dr. Lance Dworkin Chair, Department of Medicine
4:05	Dr. Gregory Postel President, University of Toledo
4:10	Dr. Christopher Cooper Dean, College of Medicine and Life Sciences
4:15	Dr. Rujun Gong Vice Chair for Research, Department of Medicine

KEYNOTE SPEAKER

4:20	Dr. Jeffrey S. Ross Jones-Rohner Endowed Professor of Pathology & Urology Upstate Medical University, Syracuse, NY Medical Director Foundation Medicine, Inc., Cambridge, MA

Interprofessional Immersive Simulation Center (lobby)

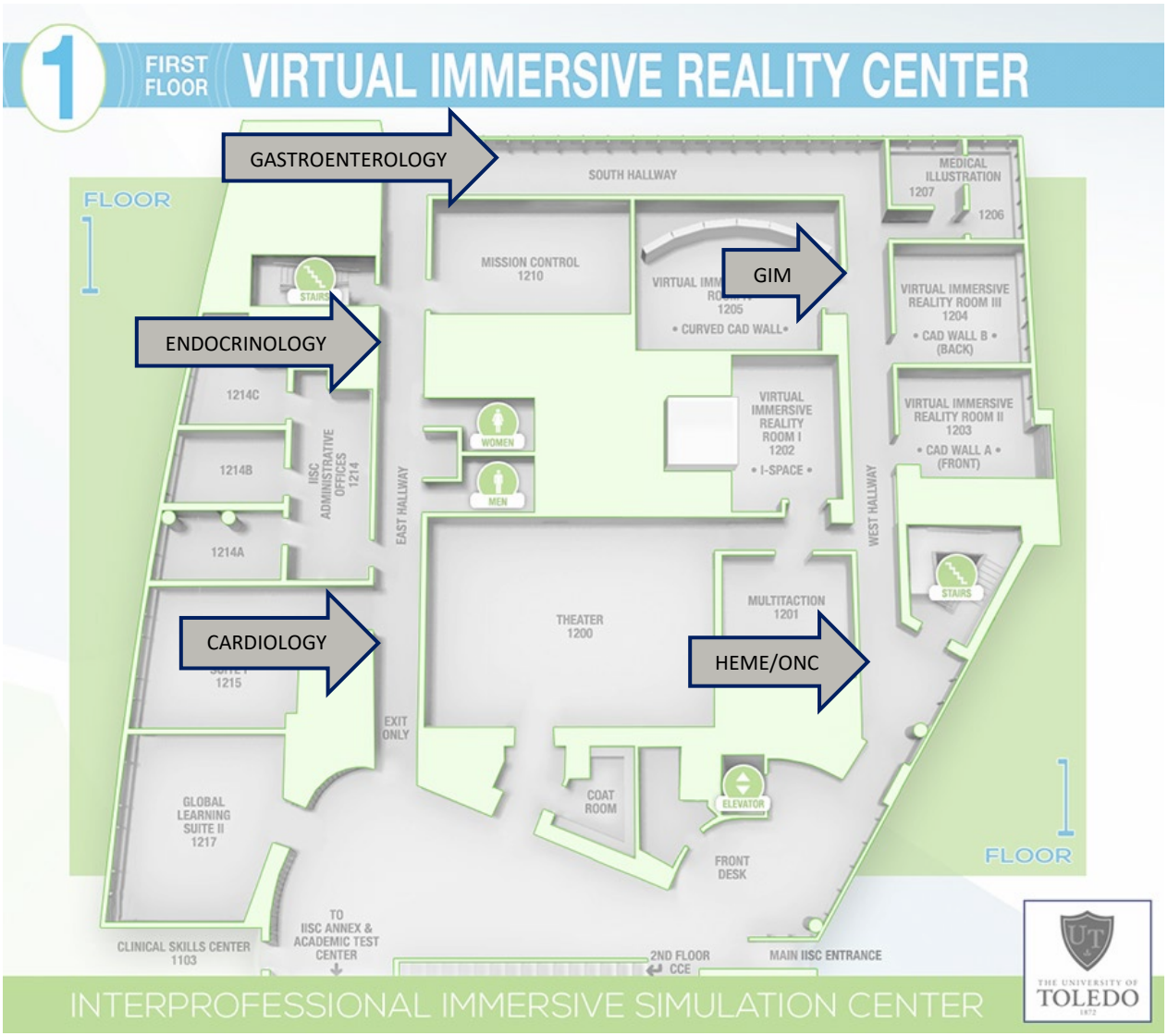
RECEPTION

5:30	Poster Session
6:30	Awards

Floor Plan / Abstract Locator

Immersive Interprofessional Simulation Center (IISC)

Posters are arranged by division and are displayed on floors one and two of the IISC. The map below identifies the location of posters by division.



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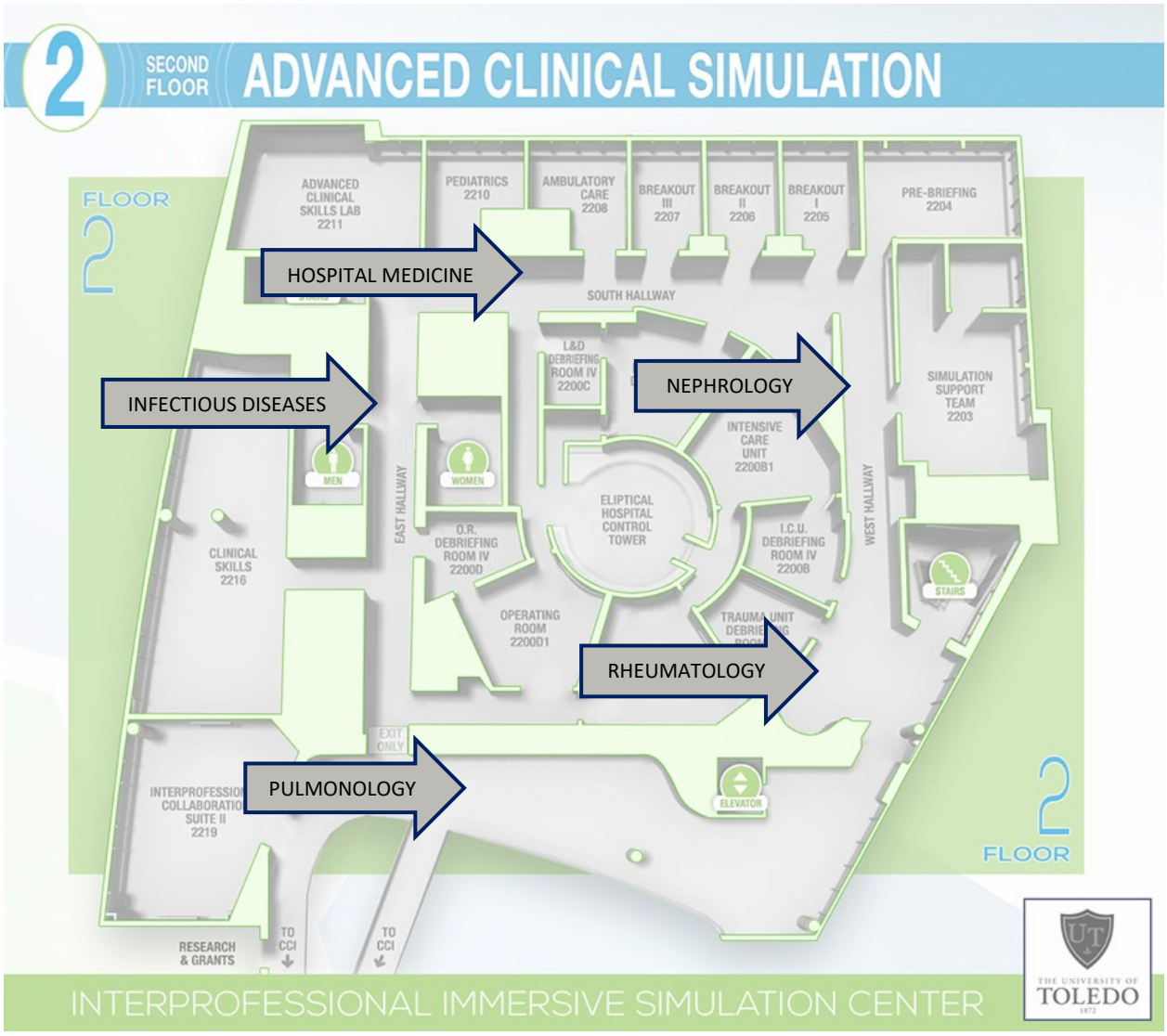

Abstracts

First Floor:

- Cardiology
- Endocrinology
- Gastroenterology
- General Internal Medicine (GIM)
- Hematology/Oncology

Second Floor:

- Hospital Medicine
- Infectious Diseases
- Nephrology
- Pulmonology
- Rheumatology

Categories of Presenters:

- Clinical Fellow (CF)
- Faculty (F)
- Graduate Student (GS)
- Medical Student (MS)
- Research Fellow (RF)
- Resident (R)
- Staff (S)

CARDIOLOGY

Azizullah Beran (R)

Low-dose Aspirin and Mortality in Patients with Coronavirus Disease 2019: A Meta-Analysis

Azizullah Beran, Mohammed Mhanna, Wasef Sayeh, Omar Sajdeya, Waleed Abdulsattar, Omar Srour, Hazem Ayesh, Fnu Zafrullah, Ehab Eltahawy

Introduction: Exaggerated inflammation and hypercoagulability are the hallmarks of moderate to severe coronavirus disease 2019 (COVID-19). Several studies have investigated the use of low-dose aspirin in COVID-19 due to its anti-inflammatory and anti-thrombotic effects. However, the data regarding its impact on mortality in COVID-19 is still conflicting. This meta-analysis aimed to evaluate the effect of aspirin use on mortality among COVID-19 patients.
Methods: We performed a comprehensive literature search of PubMed, Embase, Web of Science, WHO COVID, LitCOVID, and Cochrane databases from inception through May 30, 2021, for all published studies that evaluated the influence of low-dose aspirin usage on mortality among COVID-19 patients. The primary outcome of interest was the mortality rate. Pooled risk ratio (RR) and 95% confidence intervals (CIs) were obtained by the Mantel-Haenszel method within a random-effect model.
Results: A total of nine observational studies involving 16123 patients with COVID-19 (7115 patients in the aspirin group and 8258 in the control group) were included. The mean age was 65.9±12.3 years, and males represented 94% of patients. There was no statistically significant difference between the two groups (RR 0.87, CI 95% 0.53-1.42, P = 0.57, I^2 = 93%). A leave-one-out sensitivity analysis showed consistent results. Although there was a visible asymmetry in the funnel plot, Egger's regression analysis did not demonstrate statistically significant publication bias (P = 0.32).
Conclusions: Our meta-analysis demonstrated that low-dose aspirin was not associated with reduced mortality in patients with COVID-19. However, randomized controlled studies are needed to validate our findings.

Joshua Breidenbach (GS)

Aerosolized Harmful Algal Bloom Toxin Microcystin-LR Induces Type 1 Inflammation of the Airways

Joshua D. Breidenbach, MS; Thomas M. Blomquist, MD PhD; Andrew Kleinhenz; Apurva Lad, MS; Robin C. Su, PhD; Benjamin W. French; James C. Willey MD; Jeffrey R. Hammersley, MD; Amira Gohara, MD; R. Mark Wooten, PhD; Erin Crawford, MS; Nikolai Modyanov, PhD; Deepak Malhotra, MD PhD; Steven T. Haller, PhD; David J. Kennedy, PhD

Introduction: Harmful algal blooms are on the rise and pose serious health concerns due to the release of cyanotoxins. Microcystin-LR (MC-LR) is one of the most frequently produced cyanotoxins and has recently been detected in aerosols generated from bloom-containing water. However, the human health effects of MC-LR aerosols on pulmonary health remain unknown. Literature suggests that MC-LR exposure has a pro-inflammatory influence on the airways. The objective of this study was to determine the extent of the pro-inflammatory effects of MC-LR on the airways to elucidate the implications of risk in healthy and potentially vulnerable human populations.
Methods: An *in vitro* 3D primary human airway model was exposed to environmentally relevant concentrations of aerosolized MC-LR. Additionally, mouse exposures to aerosolized MC-LR at a concentration chosen to mimic the *in vitro* study in which C57BL/6J mice (prone to Type 1 inflammation) and BALB/c mice (prone to Type 2 inflammation) were compared.
Results: Gene and protein abundance in both the *in vitro* human 3D primary airway and in vivo mouse models demonstrated significant increases in cytokines associated with granulocytic inflammation (CXCL1, GM-CSF, CCL3, CCL2, all $p<0.05$), thus suggesting a general inflammatory response. Importantly, this response was observed in the C57BL/6J but not the BALB/c mice, suggesting a specificity for Th1 and Th17 driven Type 1 inflammation.
Conclusions: The results of this study suggest aerosolized MC-LR induces Th1/Th17 pulmonary inflammation and warrants further investigation into the potential impact of exposure in at-risk human populations with pre-existing Type 1 inflammatory pulmonary conditions.

Joshua Breidenbach (GS)

GeneToList.com: A web application to assist with gene identifiers for the non-bioinformatics-savvy scientist

Joshua D. Breidenbach, E. Francis Begue III, Steven T. Haller, David J. Kennedy

Introduction: The increasing incorporation of omics technology into clinical and translational medicine presents challenges to end users of the large and complex datasets that are generated by these methods. A particular challenge in genomics is that the nomenclature for genes is not uniform between large genomic databases or between commonly used

genetic analysis tools. While some efforts have been made to allow for the conversion of gene identifiers, these usually require advanced knowledge of programming languages. We aimed to ease the burden of these workflows for non-bioinformatics-savvy scientists.
Methods: A web application was built in Python using the Plotly Dash package, which provides a Python framework for building web applications and relies on common javascript web frameworks Flask, Plotly.js, and React.js. Gene information for 34,000+ taxa were collected from the National Center for Biotechnology and Information (NCBI).
Results: This web application assists in 2 separate tasks. The first, is the conversion of gene identifiers between formats, such as ensemble ID's and official gene symbols recognized by NCBI. The second, is matching gene identifiers against a database and suggesting matches, allowing for the curation of a list of genes with officially recognized uniform identifiers. The resulting web application is available at the website GeneToList.com.
Conclusions: The result of these efforts is a publicly available and free to use web application to assist biologists and biomedical scientists in navigating gene data. This is meant to aid in the uniformity of a list of genes before being used for any following analysis.

Cameron Burmeister (R)

Efficacy and Safety of Direct Oral Anticoagulants Versus Vitamin K Antagonists in the Treatment of Left Ventricular Thrombus: A Systematic Review and Meta-analysis

Cameron Burmeister, MD, Azizullah Beran, MD, Mohammed Mhanna, MD, Sami Ghazaleh, MD, Jeremy C. Tomcho, MD, Aadil Maqsood, MD, Omar Sajdeya, MD, and Ragheb Assaly, MD

Introduction: Current recommendations support vitamin K antagonists (VKAs) for LVT treatment. Limited data exist regarding direct oral anticoagulants (DOACs) in LVT treatment. This meta-analysis investigates the efficacy and safety of DOACs versus VKAs for LVT.
Methods: Comprehensive literature search using PubMed, Embase, and Cochrane Library databases through November 2020 was performed for studies that evaluated the efficacy and safety of DOACs versus VKAs in LVT. Primary outcomes were LVT resolution, overall thromboembolic events, and thromboembolic stroke. Secondary outcomes were major bleeding and all-cause mortality. Pooled risk ratio (RR) and 95% confidence intervals (CIs) were obtained by Mantel–Haenszel method within a random-effects model. Heterogeneity was assessed by I2 statistic.
Results: Eleven studies including 2153 LVT patients on anticoagulation (570 DOACs vs. 1583 VKAs) were included. LVT resolution was significantly higher in DOACs compared with VKAs [RR: 1.18 (95% CI: 1.04–1.35); P 5 0.01, I2 5 25%]. However, no significant difference existed between DOACs and VKAs regarding overall thromboembolic events [RR: 1.10 (95% CI: 0.75–1.62); P 5 0.61, I2 5 0%] and thromboembolic stroke [RR: 0.63 (95% CI: 0.39–1.02); P 5 0.06, I2 5 0%]. Major bleeding [RR: 1.00 (95% CI: 0.66–1.51); P 5 0.99, I2 5 4%] and all-cause mortality [RR: 0.84 (95% CI: 0.50–1.43); P 5 0.53, I2 5 0%] were similar between groups.
Conclusions: DOACs may be more efficacious in achieving LVT resolution compared with VKAs. However, no significant difference existed between the two groups in thromboembolic events, major bleeding, and all-cause mortality.

Jacob Connolly (MS)

Circulating PON Lactonase Activity Predicts Major Adverse Cardiac Events in Subjects with Atherosclerotic Renal Artery Disease

Jacob Connolly (Undergraduate Student), Chrysan J. Mohammed Ph.D., Zhen Sun, M.S., Pamela S. Brewster, M.S., Tyler J. Reid M.S., Prabhatchandra Dube Ph.D., Christopher J. Cooper M.D., Lance D. Dworkin M.D., Deepak Malhotra M.D., Ph.D., Steven T. Haller Ph.D., David J. Kennedy Ph.D.

Introduction: Decreased paraoxonase (PON) plasma lactonase activity is associated with increased oxidant stress and cardiovascular risk in settings such as coronary artery disease as well as some etiologies of chronic kidney disease (CKD). However, whether PON lactonase activity predicts outcomes in atherosclerotic renal artery stenosis (ARAS) is unknown. We sought to determine the prognostic value of PON lactonase activity in ARAS subjects.
Methods/Results: PON lactonase activity was measured in plasma of ARAS participants and either systolic hypertension while taking ≥2 antihypertensive drugs or CKD (n=718) enrolled in the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial as well as a cohort of apparently healthy, normotensive non-ARAS subjects (n=33). ARAS participants were prospectively followed for incident major adverse cardiac events over a median follow-up period of 43 months. PON lactonase activity in ARAS participants was significantly lower vs non-ARAS participants [P<0.001]. Participants were dichotomized based on the baseline plasma levels of PON lactonase activity, into high (> median) or low (≤ median) groups and were used to predict incident MACE at 3 years. Participants with lower PON

lactonase activity had increased MACE at 3 years [p<0.05]. Lower PON lactonase activity (hazard ratio 1.26, 95% CI 1.0 to 1.53, p=0.016) was a predictor of MACE even after adjusting for traditional risk factors and medication use (adjusted hazard ratio 1.22, 95% CI 1.01 to 1.50, p=0.04).
Conclusions: In ARAS, decreased PON lactonase activity predicts higher risk of incident long-term adverse cardiovascular events in multivariate models adjusting for established clinical and biochemical risk factors.

Prabhatchandra Dube (RF)

Paraoxanase 1 deletion leads to increased cardiac remodeling and cardiac fibrosis in a Dahl salt-sensitive rat model of chronic kidney disease

Prabhatchandra Dube, Fatimah K. Khalaf, Chrysan J. Mohammed, Armelle DeRiso, Dhanushya Battepati, Tiana Sarsour, Iman Tassavvor, Andrew L. Kleinhenz, Steven T. Haller, Eric E. Morgan, David J. Kennedy

Introduction: Paraoxanases (*Pon*) are hydrolytic enzymes with lactonase activity. Pon-1 synthesis occurs in liver and circulates bound to high-density lipoproteins (HDL), contributing to HDL's antioxidant, anti-inflammatory and anti-atherogenic properties. Decreased circulating Pon-1 activity is associated with increased oxidant stress and adverse clinical outcomes in the setting of chronic kidney disease (CKD). Whether decreased *Pon-1* is mechanistically linked to adverse cardiovascular outcomes in CKD, however, remains unclear. We tested the hypothesis that *Pon-1* is cardioprotective in a Dahl salt-sensitive model of hypertensive renal disease.
Methods/Results: Ten week old, age-matched male and female SS-Wild type and SS-Pon-1 knockout rats were fed 8% high salt for up to 12 weeks to initiate the salt-sensitive hypertensive renal disease. SS-*Pon1* KO rats had negligible circulating PON activity when compared to SS as measured by a fluorometric lactonase activity assay. Early mortality was observed in male SS-*Pon1* KO rats, while no mortality was observed in female SS-*Pon1* KO rats or in either male or female SS rats. Echocardiography in SS-*Pon1* KO male rats demonstrated an increased relative wall thickness, fractional shortening, mean velocity of circumferential fiber shortening and cardiac index vs age matched SS rats. Histological examination of heart sections of SS-*Pon1* KO male rats showed a significant increase in fibrosis and heart-weight-to-body-weight ratio compared to the age matched SS rats.
Conclusion: Our findings suggest that loss of PON-1 in salt-sensitive hypertensive rats leads to a cardiac phenotype consistent with compensated heart failure including increased left ventricular function and hypertrophy with increased cardiac fibrosis and mortality.

Prabhatchandra Dube (RF)

Renin-Angiotensin Metabolite Profiling via LC-MS/MS Reveals Sex Dependent Differences Induced by High-Salt Diet in Dahl-S Rats

Prabhatchandra Dube Ph.D., Chrysan J. Mohammed PhD., Fatimah K. Khalaf Ph.D., Shungang Zhang Ph.D., Dhilhani Faleel M.S., Sophia Soehnlen, Jacob Connolly, Andrew Kleinhenz B.S., Oliver Domenig Ph.D., Lance D. Dworkin M.D., Deepak Malhotra M.D., Ph.D, Steven T. Haller Ph.D., David J. Kennedy, Ph.D.

Introduction: Understanding how sex influences the pathophysiology of cardiovascular and renal disease may enhance precision medicine approaches that account for sex differences in these diseases. The renin-angiotensin-aldosterone system (RAAS) plays a central role in the development and progression of cardiovascular and renal disease. In addition to the classic RAAS pathway, an alternative RAAS pathway produces angiotensins that can counteract classical RAAS hormones. We hypothesized that RAAS profiling in a high-salt fed Dahl-S rat model would reveal significant sex differences in both classic and alternative RAAS pathways.
Methods/Results: Ten-week-old male and female Dahl-S rats were fed either 0.2% salt normal chow (SS-NC), or 8% high-salt diet (SS-HS) for eight weeks. Equilibrium RAAS profiling via LC-MS/MS was performed in plasma samples. In response to high-salt diet, both male and female SS-HS rats had significant reductions vs. SS-NC in plasma aldosterone, Ang II, Ang IV and plasma renin activity, although the magnitude of reduction was generally greater in males vs. females. Alternatively, only male SS-HS rats had significant reductions vs. SS-NC in plasma Ang I, Ang III, as well RAAS metabolites of the alternative RAS axis, Ang [1-5] and Ang [1-7] vs. SS-NC. Comparing female vs. male SS-HS rats, females had significantly increased levels of angiotensins of the classic RAS pathway, such as Ang I, Ang II, Ang III and Ang IV after high-salt diet.
Conclusion: High-salt diet induces significant sex-dependent differences in RAAS pathways of Dahl-S rats and may provide important insight into cardiovascular and renal injury seen in this model.

Ahmed Elzanaty (CF)

Coronary Computed Tomography Angiography Vs Standard of Care for evaluation of NSTE-ACS; A systematic Review and Meta-analysis

Ahmed Elzanaty, Eman Elsheikh, Mahmoud Khalil, Ahmed Maraey, Salik Nazir, Mohamed Mhanna, Azizullah Beran

Background: Non-ST elevation acute coronary syndrome (NSTE-ACS) is one of the common cardiac emergencies that pose a diagnostic challenge, especially in the absence of EKG changes or elevation in cardiac markers. Coronary computed tomography angiography (CT) has an established role in the evaluation of stable chest pain with ESC giving it class I recommendation. The role of CCTA in the management of NSTE-ACS is less clear.
Purpose: To evaluate the hypothesis of CT efficacy in identifying and managing patients with NSTE-ACS in comparison to the standard of care (SOC).
Methods: We searched MEDLINE, EMBASE, and Cochrane Central for randomized controlled trials (RCT) that compared initial CT utilization vs SOC in patients presenting with acute chest pain with suspected or confirmed NSTE-ACS. SOC arm included initial evaluation and triaging by treating physician including but not limited to clinical observation, serial cardiac markers, stress testing, and invasive coronary angiography (ICA). Studies with follow-up data of ≥ 1 month were included. Outcomes evaluated were incidence of rehospitalization/ER visits post index visit, referral to ICA, and presence of significant lesion during ICA requiring revascularization.
Results: A total of 6,862 patients (3,663 in the CT arm and 3,199 in the SOC) were analyzed from 13 RCTs. No statistically significant difference was noted between two intervention arms with regards to repeat hospital visits [Odds ratio (OR): 1.02; 95% CI: 0.85 – 1.24; P=0.82; I^2=0%], and referral to ICA (OR: 1.32: 95% CI: 0.95 – 1.83; P=0.10; I^2=66). CT was however more likely to uncover significant lesions requiring revascularization compared to SOC arm (OR: 1.77; 95% CI:1.32-2.37; P=0.0001; I^2=23%].
Conclusion: Our meta-analysis showed that in patients with suspected NSTE-ACS, CT is associated with similar rates of ICA referral and re-admissions albeit being more likely to uncover hemodynamically significant lesions that require revascularization. These findings are consistent with the finding of the recently published VERDICT trial that showed comparable efficacy between coronary CT and ICA[1-16].

Ahmed Elzanaty (CF)

Meta-analysis of The Efficacy and Safety of P2Y12 Inhibitor After Short Course of 3 Months or Less of DAPT In Patients Undergoing PCI

Ahmed Elzanaty MD, Salik Nazir MD, Mohamed Awad MD, Ehab A Eltahawy MD, MPH

Background: Current guidelines recommend dual antiplatelet therapy (DAPT) following stent placement for at least 6-12 months. However, with the advent of newer generation stents, the optimal duration of DAPT to balance bleeding and thrombotic risks has been under debate. Recent studies investigated the utility of short course of DAPT followed by P2Y12 inhibitors with promising but under-powered results to some of the outcomes.
Methods: We conducted a search of MEDLINE, EMBASE and Cochrane Central. Studies of patients undergoing percutaneous coronary intervention (PCI) with a minimum follow up of 12 months, that were randomized to short (≤ 3 months) vs standard DAPT (≥12 months) were included. Major adverse cardiovascular events (MACE [a composite of cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke]), stent thrombosis and major bleeding were main outcomes. Study-specific odds ratios and corresponding 95 % confidence intervals were calculated and combined using random-effects model.
Results: A total of 20,706 patients (10,344 in short DAPT group and 10,362 in standard DAPT group) were analysed from four studies. Non-statistically significant difference was observed for MACE (odds ratio [OR] = 0.95, 95 % CI: 0.81-1.08, P= 0.92, I2 =0%) myocardial infarction or stent thrombosis. However, statistically significant major bleeding reduction was noted in the short DAPT regimen albeit with increased heterogeneity.
Conclusion: In patients undergoing PCI, a short course of DAPT followed by P2Y12 inhibitors was non-inferior to current standard treatment at 12 months with respect to MACE and thrombotic events with a statistically significant reduction in major bleeding events.

Konrad Katterle (MS)

Impact of baseline heart failure and heart failure subtype on brain natriuretic peptide levels in patients with acute pulmonary embolism

Konrad Katterle BS, Matthew Niedoba BS, Vanessa Pasadyn BA, Ayla Cash MPH , Pamela Brewster MA, Alexandria Mann, Rajesh Gupta MD, The University of Toledo College of Medicine and Life Sciences Department of Medicine

Introduction: Among patients with acute pulmonary embolism (PE), elevated levels of brain natriuretic peptide (BNP) correlate with right ventricular dysfunction and increased morbidity and mortality. It is unclear whether standard BNP cut-offs should be used for PE risk stratification among patients with heart failure (HF), who may have elevated BNP at baseline.
Methods: One hundred and eighty-three patients diagnosed with acute PE between 2010 and 2015 at the University of Toledo Medical Center were identified. Patients were categorized as: no HF, heart failure with reduced ejection fraction (HFrEF), or heart failure with preserved ejection fraction (HFpEF). No HF was defined as having no prior history of HF and an EF ≥ 50%. HFrEF was defined as history of HF and an EF < 50%. HFpEF was defined as history of HF and an EF ≥ 50%.
Results: One hundred and forty-two patients were classified as no HF (median BNP 112 pg/mL), while 41 were classified as HF (median BNP 422 pg/mL) ($p<0.0001$).
Conclusion: Patients with HFrEF in this study have significantly higher median BNP compared to patients with HFpEF or no HF. These results suggest that risk stratification for PE using current BNP cut-off guidelines may not be optimal for patients with HFrEF.

Lauren Gerard Koch (F)

Rat Models of Low and High Intrinsic Exercise Capacity Provide Translational Relevance to the Study of Complex Diseases and Aging

Samantha J. McKee and Lauren Gerard Koch

Exercise capacity is a more powerful predictor of mortality than other risk factors including hypertension, smoking and diabetes. Poor performance on treadmill running- or extended walking tests are often prognostic for future health declines. To test this strong association between exercise capacity and survivability, we developed rat models of Low-Capacity Runners (LCR) and High-Capacity Runners (HCR) by two-way selective breeding for intrinsic exercise capacity based on a treadmill exercise test like those done in the clinic. Currently at generation 46 of selection, the difference in exercise capacity between LCR and HCR rats is >12-fold and the differential in lifespan is between 6 to 8 months. Consistent with the human literature, we find numerous disease risks segregate in LCR rats including cardiovascular disease, metabolic syndrome, obesity, fatty liver disease, increased susceptibility to cancer, and Alzheimer's disease. In contrast, HCR rats display attributes associated with vitality such as higher maximal oxygen consumption, leanness, higher level of physical activity, and resistance to the ill-effects of high fat diets. This multi-generational selection experiment is powerful because it provides a divergent animal model system that more closely mimics the genetic and phenotypic diversity within human populations and simultaneously tests the *Energy Transfer Hypothesis (ETH): Variation in capacity for energy transfer (i.e., exercise capacity, mitochondrial health) is the central mechanistic determinant of the divide between health and disease*. Our exercise rat models provide a translational approach that is different from mainstream concepts for understanding the ostensibly "intractable" nature of complex disease and aging.

Apurva Lad (GS)

Antioxidant Therapy Restores Hepatic Phase I & II Metabolic Enzymes Altered by Exposure to Microcystin-LR in a Murine Model of Diet-induced Non-alcoholic Fatty Liver Disease

Apurva Lad MS (Graduate Student), Jonathan Hunyadi BS, Joshua D. Breidenbach MS, Jacob Connolly UG, Fatimah K. Khalaf MBchB, PhD, Prabhatchandra Dube PhD, Shungang Zhang PhD, Andrew L. Kleinhenz BS, David Baliu-Rodriguez PhD, Dragan Isailovic PhD, Terry Hinds PhD, Deepak Malhotra MD PhD, Steven T. Haller PhD, David J. Kennedy PhD

Introduction: We have shown that exposure to the environmental liver toxin Microcystin-LR (MC-LR) in the setting of pre-existing Non-alcoholic Fatty Liver Disease (NAFLD) induces significant hepatotoxicity and oxidative stress. Therefore, we hypothesized if targeted antioxidant therapy would improve MC-LR metabolism and reduce hepatic injury.
Methods: Six-week-old C57Bl/6J mice fed with choline-deficient high fat diet with 0.1% methionine to induce NAFLD were gavaged with 100 µg/kg MC-LR/24 hrs for 15 days. Antioxidants included augmentation of the glutathione detoxification pathway with N-acetylcysteine (NAC) given at 40 mM in drinking water; and interruption of specific Src kinase-mediated oxidant signaling pathways with a novel peptide (pNaKtide) at 25 mg/kg injected intraperitonially once a week.
Results: Histologic analysis revealed significant increase in hepatic inflammation with MC-LR exposure which was attenuated in both antioxidant treatment groups. 8-OHDG levels in urine and protein carbonylation in liver, both markers of oxidative stress, were significantly downregulated upon antioxidant treatment after MC-LR exposure. Analysis of key

drug transporters as well as Phase I & II enzymes using quantitative PCR revealed that exposure to MC-LR significantly upregulated expression of the drug transporter Abcb1a; Cyp3a11, Phase I enzyme belonging to the Cytochrome P450 family whereas Phase II enzymes, Pkm (Pyruvate kinase, muscle), Pklr (Pyruvate kinase, liver, and RBC) and Gad1 (Glutamic acid decarboxylase) were significantly downregulated. Antioxidant therapy with both pNaKtide and NAC significantly attenuated these changes and restored microcystin detoxification.
Conclusion: These results suggest that NAFLD significantly alters the metabolism of MC-LR, and this can be reversed with targeted antioxidant treatment.

Nikolai Modyanov (F)
A trial-specific BetaM protein is a novel transcriptional regulator of cardiac hypertrophic response and myogenesis
Nikolai Modyanov, PhD (Faculty), Nisar Ahmad PhD, Xiaoming Fan MD, PhD, Prabhatchandra Dube PhD, Shungang Zhang PhD, Esha Kashaboina, Eshita Kashaboina, Nikolay Pestov PhD, Abdullah Nasif MD, Rajesh Gupta MD, Saqib Masroor MD, David J. Kennedy PhD, Steven T. Haller PhD

Background: The ability to appropriately repair or regenerate functional cardiac tissue is the major force determining adverse outcomes after cardiac injury. We previously discovered the Na,K-ATPase BetaM-subunit into a muscle specific transcriptional regulator. We hypothesized that BetaM is a novel transcriptional regulator of genes involved in cardiac repair.
Methods/Results: RT-PCR analysis demonstrated that cardiac BetaM is expressed exclusively in intact rat atrial myocytes. Using luciferase reporter assays, we demonstrated that expression of exogenous BetaM in C2C12 cells up-regulates cardiac transcription factors such as myocyte enhancer factor-2 (Mef2, 2X), Nkx2.5 (6X) and atrial natriuretic factor (ANF, 2X). BetaM also up-regulated endogenous MyoD mRNA and protein. Furthermore, luciferase reporter assays showed that BetaM up-regulates the MyoD reporter activity (3X) in a dose dependent manner. The interaction of BetaM with the MyoD promoter *in vivo* was analyzed by ChIP assays using chromatin from rat neonatal skeletal muscle and electrophoretic mobility shift assays and demonstrated that BetaM-containing transcriptional complexes are bound to specific E-box and CArG elements of the distal regulatory region of the MyoD promoter. To characterize BetaM function *in vivo,* transcriptome analysis was performed in newborn Atp1b4 KO and WT myocytes and revealed strong changes in expression of components of the calcium-dependent Calcineurin – Nfat signaling cascade involved in maladaptive cardiac hypertrophy.
Conclusion: Our studies reveal that BetaM regulates the activity of essential cardiac hypertrophic response genes and master regulators of myogenesis indicating that BetaM is a novel member of a small group of atrial-specific proteins that regulate cardiac repair.

Matthew Niedoba (MS)
Impact of baseline heart failure on RV:LV diameter ratio in patients with acute pulmonary embolism
Matthew Niedoba BS, Vanessa Pasadyn BA, Konrad Katterle BS, Ayla Cash MPH, Pamela Brewster MA, Alexandria Mann, Rajesh Gupta MD

Introduction: Among patients with acute pulmonary embolism (PE), an elevated right ventricular to left ventricular diameter (RV:LV) ratio is associated with increased morbidity and mortality. It is unclear whether standard RV:LV cut-off values should be used for PE risk stratification among patients with heart failure (HF), who may have abnormal baseline RV:LV values
Methods: 171 patients diagnosed with acute PE between 2010 and 2015 at the University of Toledo Medical Center were included in this study. Patients were categorized as: no HF, heart failure with reduced ejection fraction (HFrEF), and heart failure with preserved ejection fraction (HFpEF). No HF was defined as having no prior history of HF and an ejection fraction (EF) $\geq$ 50%. HFrEF was defined as history of HF and an EF $<$ 50%. HFpEF was defined as history of HF and an EF $\geq$ 50%.
Results: 142 patients were categorized as no HF, 13 were categorized as HFrEF, and 16 were categorized as HFpEF. Mean LV diameter among patients with HFrEF was significantly higher [52.2 mm] compared to no HF [38.1 mm] and HFpEF [42.1 mm] (p=0.0240).
Conclusion: Patients with HFrEF in this study had significantly higher mean LV diameter and lower RV:LV ratio compared to patients with HFpEF or no HF. These results suggest that risk stratification using current RV:LV ratio guidelines may underestimate PE risk among patients with HFrEF.

Vanessa Pasadyn (MS)

Trends in pulmonary embolism mortality rates by age group in the United States, 1999-2019

Vanessa Pasadyn BA, Ayla Cash MPH, Abdul Mannan Khan Minhas MD, Salik Nazir MD, Robert W. Ariss BS, Rajesh Gupta MD

Introduction: Acute pulmonary embolism (PE) is a major cause of mortality in the United States. Recent reports indicate that PE-related mortality rates have increased among individuals 25-64 and 65-79 years old and plateaued among individuals ≥80 years old. A narrowly focused and clinically meaningful age group analysis is necessary.
Methods: Death certificate data from the Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research database were examined to determine all-cause PE mortality trends from 1999 to 2019 among adults 25-39, 40-54, 55-69, 70-84, and ≥85 years old. The crude death rates for individual years were calculated by dividing the number of PE-related deaths by the corresponding population. Annual percentage change (APC) was calculated to determine trends.
Results: PE-related mortality rates increased among those 25-39, 40-54, and 55-69. APC was highest for individuals 25-39 years old, whose death rate increased from 1.8 to 2.0 (APC 0.7 [95% confidence interval (CI) 0.2 to 1.1]) between 1999 and 2014 and continued to increase from 2.0 to 2.4 (APC 4.1 [95% CI 1.8 to 6.5]) between 2014 and 2019. Recent death rates decreased or plateaued among individuals older than 70.
Conclusions: Despite significant improvements in PE risk stratification and clinical management, recent PE related mortality rates increased significantly among those younger than 69 years old. The APC in mortality was highest among those 25-39 years old. Among individuals older than 70 years old, recent death rates decreased or plateaued.

Neha Patel (R)

Efficacy and safety of hypertonic saline plus furosemide in patients with acute decompensated heart failure: A systematic review and meta-analysis

Neha Patel, Mitra Patel, Ahmed Elzanaty, Sapan Bhuta, Cameron Burmeister, Jeremy Tomcho, Sami Ghazaleh

Background: Treatment of acute decompensated heart failure (ADHF) involves aggressive diuresis, and salt restriction is thought to aid in the efficacy of diuresis. However, salt restriction may have an antidiuretic effect due to reduction in glomerular filtration rate. Data suggests there may be a role for hypertonic saline solution (HSS) with furosemide in ADHF.
Methods: We performed a literature search using PubMed, Embase, and Cochrane Library from inception through November 2020 to investigate the efficacy and safety of HSS in ADHF. The primary outcomes were weight loss, brain natriuretic peptide (BNP), and length of stay (LOS). Secondary outcomes were post-intervention creatinine and change in creatinine.
Results: 8 studies (7 randomized controlled trials, 1 observational study) involving 2365 patients were included in the meta-analysis. Compared to placebo, the HSS group had significantly increased weight loss (MD 0.95; 95% CI 0.3, 1.59; P = 0.004), decreased BNP (MD -31.44; 95% CI -41.14, 21.74; P = <0.001), and decreased LOS (MD -2.37; 95% CI -3.31, -1.44; P <0.001). Due to increased heterogeneity in analysis of post-intervention creatinine and creatinine change, it is difficult to make any conclusions regarding these outcomes [Figure 1].
Conclusion: Our meta-analysis demonstrates that compared to furosemide alone, furosemide plus HSS led to improved clinical endpoints, such as weight loss, BNP, and LOS. Further trials are needed to confirm our findings and assess renal safety profiles.

Neha Patel (R)

Efficacy and safety of direct oral anticoagulants versus vitamin K antagonists in patients with atrial fibrillation and bioprosthetic valves - A systematic review and meta-analysis

Neha Patel, Ahmed Elzanaty, Mitra Patel, Eman Elsheikh

Introduction: Patients with atrial fibrillation (AF) and bioprosthetic valves (BPV) require long-term anticoagulation and current recommendations support the use of vitamin K antagonists (VKA). There is limited data regarding the use of direct oral anticoagulants (DOAC) in patients with AF and BPV.
Methods: We performed a literature search using PubMed, Embase, and Cochrane Library from inception through November 2020 to investigate the efficacy and safety of DOAC compared to VKA in patients with AF and BPV. The primary outcomes were MACE (MI, stroke, and CV death) and composite of stroke and systemic embolic event (SEE). Secondary outcomes were all-cause mortality and major bleeding (BARC 3-5, TIMI major).

Results: 5 studies (4 randomized controlled trials, 1 observational study) involving 1755 patients were included in the meta-analysis. Compared to VKA, the DOAC group had significantly lower rate of composite stroke and SEE (risk ratio (RR) 0.47; 95% confidence interval (CI) 0.24, 0.92; P = 0.03) and major bleeding (RR 0.57; CI 0.35, 0.93; P = 0.02). However, no significant difference existed between DOAC and VKA in terms of MACE (RR 0.6; CI 0.35,1.05; P = 0.07) or all-cause mortality (RR 0.93; CI 0.56, 1.54; P = 0.77) [Figure 1].
Conclusion: DOAC are more effective compared to VKA at preventing stroke and SEE, as well as major bleeding in patients with AF and BPV; however, there was no significant difference in MACE or all-cause mortality. Further trials with large sample sizes are needed to confirm our findings.

Rohit Vyas (CF)

Rapid Development and Exacerbation of Pulmonary Hypertension and Right Ventricular Failure after COVID-19 Viral Pneumonia – A Case Series

Rohit Vyas, MD; Chandramohan Meenakshisundaram, MD; FNU Zafrullah, MD; George Moukarbel, MD: Samer Khouri, MD

Introduction: With rising numbers of COVID-19 patients, the focus is on long-term outcomes. Here we present two patients who developed rapid-onset RV failure after COVID-19.
Case 1: This is a 73-year-old man with history of coronary disease. He reported atypical chest discomfort and took nitroglycerin. Severely hypotensive upon presentation. Initial echo showed reduced RV systolic function and severely elevated right-sided pressures (Figure 1B and C); previous echo was normal (Figure A). He had two hospitalizations in the last eight months for COVID-19. Prior to that he had excellent functional status.
Right heart catheterization was showed pre-capillary pulmonary hypertension and acute cor pulmonale. V/Q scan was unremarkable. High-resolution CT suggested honeycombing (Figure 1D). He was started on epoprostenol with improvement of pulmonary pressures.
Case 2: This is a 63-year-old lady with history of systemic sclerosis. She had been hospitalized for COVID-19 four months previously. Prior to that she was well-maintained on tadalafil and ambrisentan but presented with worsening exertional dyspnea. Echo showed reduced RV function and severely elevated pulmonary pressures (Figure 2B and C); previous echo showed normal RV function (Figure 2A). Chest CT showed worsening interstitial lung disease (Figure 2D). V/Q scan was normal.
RHC confirmed pre-capillary pulmonary hypertension. She was started on epoprostenol and discharged on home infusion. Now doing well and able to perform most daily activities.
Discussion: These cases show that COVID-19 may provoke PAH and worsen pre-existing PAH. Further large-scale studies are needed to elucidate the pathophysiology of this phenomenon.

Rohit Vyas (CF)

Impact of Pulmonary Artery Catheter Guided Management in Cardiogenic Shock: A Systematic Review and Meta-Analysis

Rohit Vyas, MD; Mohammed Mhanna, MD; Salik Nazir, MD; Zachary Holtazapple, BS; FNU Zafrullah, MD; Chandramohan Meenakshisundaram, MD; Samer Khouri, MD; Ehab Eltahawy, MD

Introduction: The utility of pulmonary artery catheters (PAC) in treatment of cardiogenic shock (CS) is unclear. In this meta-analysis, we aimed to evaluate the impact of PAC-guided treatment on survival in patients with CS.
Method: We performed a comprehensive literature search of multiple databases for studies that evaluated the clinical utility of PAC-guided management versus standard of care for CS. The primary outcome of interest was short-term mortality. Secondary outcomes were use of mechanical circulatory support (MCS) and inotropes. Pooled relative risk and corresponding 95% confidence intervals were calculated and combined using random effects model meta-analysis.
Results: A total of 8 studies including 2,139,811 patients with CS (187,857 managed with PAC-guided therapy vs. 1,951,954 managed with standard of care) were included in the final analysis. There was significant difference in the short-term mortality favoring PAC-guided management (RR:0.84; 95% CI:0.76-0.93; P<0.00001). Standard of care guided management was associated with higher risk for MCS and inotrope usage (RR:1.30; 95% CI:1.15-1.46; *P*<0.0001) and (RR:1.18; 95% CI:1.09-1.29; *P*<0.001) respectively.
Conclusions: Our meta-analysis demonstrated that PAC-guided therapy for patients with CS was associated with lower short-term mortality and lower probability to use MCS and inotropes. Further randomized clinical trials are needed to evaluate the utility of PAC as an adjunct tool in the management of CS.

ENDOCRINOLOGY

Alexa Jaume (GS) and Nicole Weis (GS)

Autonomic innervation of lymph nodes in autoimmune disease

Alexa Jaume, Nicole Weis and David Giovannucci

Introduction: Sjogren's syndrome (SS) is an autoimmune disease characterized by dry mouth and dry eyes. Understanding of SS is limited and lack targeted, effective therapies. Recent work suggests local, bi-directional neuro-immune circuits direct lymph nodes (LNs) to modulate tissue inflammation.
Methods: We used a mouse model of SS, lymphocyte and neural markers and confocal microscopy to probe the innervation of salivary and tear gland LNs and identify neuron types in the superior cervical ganglia (SCG) that projects to these tissues.
Results: Autonomic nerve fibers in LNs were visualized and there was a marked expansion of T and B cells observed in autoimmune animals. Surprisingly we observed that a subpopulation of SCG neurons were cholinergic.
Conclusions: Preliminary results establish rationale for further experiments to determine the anatomical relationship between sympathetic nerves and LNs, and whether sympathetic input is altered in autoimmune disease. This study may identify targets for new SS therapies.

Abed Kanzy (F)

Development of LADA post SARS-COV-2 mRNA vaccination

Kanzy, Abed; Madkhali, Mohammed; Imam, Shahnawaz; Jaume, Juan

Introduction: Latent autoimmune diabetes of adults (LADA) is a rare form of diabetes among elderly. This report presents the first case of new onset LADA in a patient with a history of noninsulin dependent diabetes post-SARS-CoV-2 mRNA vaccination.
Methods: Case report and critical literature review.
Results: 74 y/o with controlled diabetes solely on metformin for six years prior to vaccination with Pfizer/BNT162b2 mRNA vaccine, developed severe thrombocytopenia two week-post vaccination, leading to hospitalization. Patient was treated with IVIG and steroids for presumed ITP. Because patient's blood glucose levels remained elevated after discharge from the hospital, serum anti-GAD65 antibodies were ordered. Progressively rising antibody titers confirmed LADA and insulin therapy was initiated.
Conclusion: Immune exacerbation post-mRNA vaccination may result in autoimmunity. Screening for T1D/LADA and other autoimmune diseases may be needed post mRNA vaccination among those prone to autoimmunity especially now that mRNA vaccination for adolescents and children has bee cleared by regulatory agencies worldwide.

Matthew McCracken (MS)

Primary intrathyroidal adenocarcinoma ex pleomorphic adenoma: a case report

Matthew McCracken, MS; Stephanie Cole, MD

Carcinoma ex pleomorphic adenoma (CXPA) is a rare and aggressive malignancy arising from a benign pleomorphic adenoma. We present what is, to the best of our knowledge, the first case of a primary intrathyroidal carcinoma ex pleomorphic adenoma in an elderly male patient presenting with a thyroid nodule. The differential diagnosis for this lesion is broad and the thyroid nodule should be evaluated promptly with ultrasound and fine needle aspiration (FNA) biopsy based on appropriate criteria as described in the 2015 ATA guidelines for adult patients with thyroid nodules. Given this unique presentation, we discuss treatment and anatomic considerations for surgical resection. This diagnosis should be considered in the evaluation of thyroid nodules with more aggressive features. Available treatments include surgical resection with or without adjuvant radiation therapy, primary radiation therapy, and chemotherapy.

Azra Niaz (CF)

Clinical dilemmas of adrenal incidentaloma: Is change in HFU clinically significant?

Azra Niaz, MD, John Y Jun, MD, Sophia Ali, MD, Juan C Juame, MD.

Introduction: There has been a recent increase in the incidence of adrenal incidentaloma (AI), defined as an adrenal mass that's unintentionally discovered on imaging obtained for an indication other than suspected adrenal pathology, mainly because of increased availability and improved quality of imaging modalities. Differentiation based on malignant vs

benign and secretory vs non-secretory becomes the most important question on finding such mass. Another important question is long term follow up of these AI. We present a case that highlights the importance of follow up due to the potential of AI to increase in size and density over 3 year.

Case: A 58-year-old male with a history of ESRD secondary to hypertension, controlled hypertension, CAD s/p CABG was seen for a right 1.9 cm AI (found in 11/2016 on noncontrast CT abdomen), with low attenuation of approximately 10 Hounsfield units (HU). He was asymptomatic, normal vitals, and an unremarkable physical exam. Hormonal work up was negative for hyperaldosteronism and Cushing syndrome. About 1 year later, repeat CT abdomen reported an unchanged right, 2.0 x 1.7 cm adrenal mass, 22 HU. Hormonal work-up was not completed and patient was lost to follow up. Two years later, repeat CT abdomen reported increase size of AI to 2.7 cm and increase in attenuation of 24 HU precontract which increased to 55 HU on the immediate postcontrast exam and 55 HU on 13-minute delayed images. Hormonal work up was negative for Cushing syndrome and hyperaldosteronism. Plasma metanephrine was 0.50 with elevated plasma normetanephrine of 3.85. In light of being a renal transplant patient and due to increase in size, change in HU, and significantly elevated normetanephrine levels patient was referred for right adrenalectomy.
Discussion: Change in adrenal mass size is known to be a significant predictor of malignant potential. An unenhanced attenuation value <10 HU is characteristic of a lipid-rich adenoma, can predict benign adrenal adenoma with 98% specificity, and has a very low likelihood of a pheochromocytoma. European Society of Endocrinology recommends if the AI is homogenous, < 4 cm, with a density ≤ 10 UH, no imaging follow up is recommended and biochemical testing for ruling out pheochromocytoma is indicated in adrenal tumors with an unenhanced attenuation value >10 HU. However, the AACE/AAES guidelines recommends AI ≥ 1 cm and less than 4 cm, repeat imaging with noncontrast CT should be performed at 3–6 months and annually for 1-2 years and if the mass grows or becomes hormonally active then adrenalectomy should be performed. There are no prospective studies of the optimal frequency and duration of follow up for AI. Considering the increasing incidence of AI, further studies on the clinical significance of change in HU, such as risk of developing pheochromocytoma, along with standardized international guidelines would be helpful for clinicians in managing patients with AI.

Diane Wei (MS)

Assessing monogenic diabetes knowledge of an endocrinology group in medium-sized hospital

Diane Wei & Louis Philipson, MD PhD

Maturity onset diabetes of the young (MODY) is a heterogeneous group of autosomal dominantly inherited disorders (more broadly referred to as monogenic diabetes) which are characterized primarily by dysfunction of beta cells and insulin secretion. MODY makes up 2 - 5% of all cases of diabetes diagnosed under 35 and the most common mutations are within the GCK, HNF4A, and HNF1A genes. Typical features of MODY include childhood or adolescence onset of diabetes (usually before 25 - 35 years of age), low to normal BMI, significant family history of diabetes, and hyperglycemia with a lack of pancreatic autoantibodies (GAD65, IA-2A, ZnT8). We explore the knowledge and understanding of monogenic diabetes within an endocrinology group at a medium-sized hospital to better elucidate the potential needs of similar institutions. Through an anonymous questionnaire, we found that 87.5% had never made a diagnosis of monogenic diabetes, but 7 out of the 8 providers had encountered a patient with diabetes in the last two weeks that they could not categorize as Type 1 or Type 2 diabetes. The providers also identified barriers to genetic testing for monogenic diabetes including difficulty knowing where to send the genetic test request, what gene(s) to test for, and insurance coverage. Though 60% of the physicians had not considered monogenic diabetes as part of their differential, it is clear they have encountered patients who might meet criteria. Those who had considered monogenic diabetes encountered internal barriers that may have hindered the progress of their care. These results suggest that there is a need for additional monogenic diabetes education and development of a better genetic testing protocol within the institution.

Rukia Yosuf (MS)

Associations between physical activity and risk factors for type II diabetes in prediabetic adults

Rukia Isabel Yosuf (Medical Student), Maciej Buchowski, MD

Background: Diabetes is a national healthcare crisis related to both macrovascular and microvascular complications. Objectives: We hypothesized that higher levels of physical activity are associated with lower total and visceral fat mass, lower systolic blood pressure, and increased insulin sensitivity. Methods: Participant inclusion criteria: 21-50 years old, BMI ≥ 30 kg/m2, hemoglobin A1C 5.7-6.4, fasting glucose 100-125 mg/dL, and HOMA IR ≥ 2.5. Exclusion criteria: history of diabetes, hypertension, HIV, renal disease, hearing loss, alcoholic intake over four drinks daily, use of organic

nitrates or PDE5 inhibitors, and decreased cardiac function. Total physical activity was measured using accelerometers, body composition using DXA, and insulin resistance via fsIVGTT. Clinical and biochemical cardiometabolic risk factors, blood pressure and heart rate obtained using a calibrated sphygmomanometer. Anthropometric measures, fasting glucose, insulin, lipid profile, C-reactive protein, and BMP analyzed using standard procedures.
Results: We found correlations between levels of physical activity in a heterogenous group of prediabetic adults. Patients with more physical activity had a higher degree of insulin sensitivity, lower blood pressure, total visceral adipose tissue, and overall lower total mass. Total physical activity levels showed small, but significant correlations with systolic blood pressure, visceral fat, lean mass and insulin sensitivity. After normalizing for race, age, and gender using multiple regression, these associations were no longer significant considering our small sample size.
Conclusion: More research into prediabetes will decrease the population of diabetics overall. In the future we could increase sample size and conduct cross sectional and longitudinal studies in various populations with prediabetes.

GASTROENTEROLOGY

Yasir Al-Abboodi (CF)
Aggressive approach saves lives in people admitted for both upper gi bleeding and acute coronary syndrome
Yasir Al-Abboodi MD. MPH; Ahmed Al Chalabi MD; Ali Nawras MD, FACP FACG; Thomas Sodeman MD FACP

Introduction: We occasionally encounter patients with upper gastrointestinal bleed (UGIB) who also coronary syndrome (ACS) during a given admission. In this study we tried to give a better insight about this target population demography and what's the best approach in terms of treatment options and its relationship with the inpatient mortality .
Methods: We did retrospective analysis using the National Inpatient Data base (NIS) of 2014 to examine the mortality difference among people who were admitted for UGIB and ACS and received different interventions including no interventions, endoscopy (Colonoscopy/Endoscopy), Left heart Cath, or combination of left heart Cath and endoscopy. All diagnosis and procedures were captured using the ICD9 codes.
Results: 2830 ACS and UGIB related admissions were extracted from the data. Mean age is 68 yr. 62% (1750) male and 38% (1075) female. 73% (2070) white;14% (400) black; 7.1% (200) Hispanic;65(2.3%) Asian;25(0.9%) Native; %Others 2.5%. 195 out of the 2830 died. Of the 195 dead,130(66.7%) received no interventions,50(25.6%) received scopes only,10(5.1%) received left hearth catheterization only and 5 (2.6%) received both scopes and left hearth cath. Considering no intervention as a reference, the likelihood of surviving were 3.3, 3.1, and 1.5 among combined therapy, Left heart Cath only and scopes only respectively(P<0.005,Cl 95% 1.3-2.5).
Conclusion: Combined approach of endoscopy(colonoscopy/EGD) and left hearth catheterization for people with (UGIB and ACS) related admission have 3 times more likelihood to survive compared to patients who received no intervention.

Yasir Al-Abboodi (CF)
Evaluation of Relationship between Inflammatory Bowel Disease and Acute Coronary Syndrome
Yasir Al-Abboodi, Ahmed Al-Chalaby; Abdallah Kobeissy

Background: There is a debate if patients with history of inflammatory bowel disease (IBD) have higher risk of having acute coronary syndromes (ACS)
Method: Retrospective analysis for the national inpatient sample data base (NIS). All diagnoses including IBD, ACS, Hypertension (HTN), Diabetes mellites (DM), Smoking, obesity, Alcohol abuse were identified using International Statistical Classification of Diseases and Related Health Problems (ICD9). A binary logistical multifactorial analysis was used to calculate the Odd ratio. T test was used to examine the means. SPSS software version 24. Is used for analysis.
Result: 57984 admissions with history of inflammatory bowel disease (IBD) were identified using ICD9 codes. Of those, 7894 had Ulcerative colitis (UC.), 40628 with). 414(.7%) has acute coronary syndromes related admissions. Mean age of patients is 50+/-. 25209(43.5%) male, 32762(56.5%) female. 47144(81.3%) White, 5889(10.2%) Black, Hispanic 2941(5.1%),523(0.9%) Asians, 1251(2.2%) others. Mean length of stay for patient who had ACS related admissions and has history of IBD is 5.4 days vs. 4.4 days for people without history of IBD(P=0.08). Patient who with history of IBD is less likely to have ACS(P<000, OR:.73, CI:.0.669-.0812), Smoking,(P<0.05,OR:1.569, CI:1.540-1.600), HTN(P<.005,OR:2.732, CI:2.689-2.777),DM(P<0.005,OR:1.468,C1:0.428-1.508),Alcohol abuse(.P<0.05, OR:0585, .CI:0.56-.611). There is no inpatient mortality difference between ACS related admission with history of IBD vs no history of IBD(P=.535, OR:0.643,CI:1.60-2.588).

Conclusion: People with inflammatory bowel disease does not have a higher risk for acute coronary syndrome. There is no mortality difference between ACS related admission with or without history of inflammatory bowel disease. ACS related admission with history of inflammatory bowel disease has a longer length of stay but not statistically significant.

Muhammad Aziz (CF)

Efficacy of Endocuff Vision compared to first-generation Endocuff in adenoma detection rate and polyp detection rate in high-definition colonoscopy: A systematic review and network meta-analysis

Muhammad Aziz, Hossein Haghbin, Manesh Kumar Gangwani, Sachit Sharma, Yusuf Nawras, Zubair Khan, Saurabh Chandan, Babu P Mohan, Wade Lee-Smith, Ali Nawras

Background and Study Aims: Recently, the newer Endocuff Vision (ECV) has been evaluated for improving colonoscopy outcome metrics such as adenoma detection rate (ADR) and polyp detection rate (PDR). Due to lack of direct comparative studies between ECV and original Endocuff (ECU), we performed a systematic review and network meta-analysis to evaluate these outcomes.
Methods: The following databases were searched: PubMed, Embase, Cochrane, and Web of Sciences to include randomized controlled trials (RCTs) comparing ECV or ECU colonoscopy to high-definition (HD) colonoscopy. Direct as well as network meta-analyses comparing ADR and PDR were performed using a random effects model. Relative-risk (RR) with 95 % confidence interval (CI) was calculated.
Results: A total of 12 RCTs with 8638 patients were included in the final analysis. On direct meta-analysis, ECV did not demonstrate statistically improved ADR compared to HD colonoscopy (RR: 1.12, 95 % CI 0.99-1.27). A clinically and statistically improved PDR was noted for ECV compared to HD (RR: 1.15, 95 % CI 1.03-1.28) and ECU compared to HD (RR: 1.26, 95 % CI 1.09-1.46) as well as improved ADR (RR: 1.22, 95 % CI 1.05-1.43) was observed for ECU colonoscopy when compared to HD colonoscopy. These results were also consistent on network meta-analysis. Lower overall complication rates (RR: 0.14, 95 % CI 0.02-0.84) and particularly lacerations/erosions (RR: 0.11, 95 % CI 0.02-0.70) were noted with ECV compared to ECU colonoscopy.
Conclusions: Although safe, the newer ECV did not significantly improve ADR compared to ECU and HD colonoscopy. Further device modification is needed to increase the overall ADR and PDR.

Muhammad Aziz (CF)

Lactated Ringer's vs normal saline for acute pancreatitis: An updated systematic review and meta-analysis

Muhammad Aziz, Zohaib Ahmed, Simcha Weissman, Sami Ghazaleh, Azizullah Beran, Faisal Kamal, Wade Lee-Smith, Ragheb Assaly, Ali Nawras, Stephen J.Pandol, Stephanie McDonough, Douglas G.Adler

Introduction: Recent studies have evaluated and compared the efficacy of normal saline (NS) and lactated Ringer's (LR) in reducing the severity of acute pancreatitis (AP) and improving outcomes such as length of stay, the occurrence of the systemic inflammatory response syndrome (SIRS), ICU admission and mortality. We performed an updated systematic review and meta-analysis of the available studies to assess the impact of these fluids on outcomes secondary to AP.
Methods: We systematically searched the following databases: PubMed/Medline, Embase, Cochrane, and Web of Science through February 8th, 2021 to include randomized controlled trials (RCTs) and cohort studies. Random effects model using DerSimonian-Laird approach was employed and risk ratios (RR) and mean difference (MD) with 95% confidence interval (CI) were calculated for binary and continuous outcomes, respectively.
Results: 6 studies (4 RCTs and 2 cohort studies) with 549 (230 in LR and 319 in NS) were included. The overall mortality (RR: 0.73, CI: 0.31–1.69) and SIRS at 24 h (RR: 0.69, CI: 0.32–1.51) was not significantly different. The overall ICU admission was lower in LR group compared to NS group (RR: 0.43, CI: 0.22–0.84). Subgroup analysis of RCTs demonstrated lower length of hospital stay for LR group compared to NS group (MD: 0.77 days, CI: 1.44 –0.09 days).
Conclusion: Our study demonstrated that LR improved outcomes (ICU admission and length of stay) in patients with AP compared to NS. There was no difference in rate of SIRS development and mortality between LR and NS treatments.

Azizullah Beran (R)

Efficacy and safety of underwater versus conventional endoscopic mucosal resection for colorectal polyps: A systematic review and meta-analysis

Azizullah Beran, Sami Ghazaleh, Mohammed Mhanna, Hazem Ayesh, Saif-Eddin Malhas, Justin Chuang, Yasir Al-Alabboodi, Muhammad Aziz, Ali Nawras

Introduction: Endoscopic mucosal resection (EMR) is a commonly used endoscopic technique for removing colorectal polyps. Underwater EMR (UEMR) has recently been introduced as a potential alternative for conventional EMR (CEMR). However, its clinical outcomes compared to CEMR remains uncertain. Therefore, we conducted this meta-analysis to evaluate the efficacy and safety outcomes of UEMR compared to CEMR in the removal of colorectal polyps.
Methods: We performed a comprehensive literature search using MEDLINE and EMBASE databases through January 2021 for all published studies. The outcomes were en bloc resection, residual/recurrent polyps on follow-up, piecemeal resection, complete macroscopic resection, complete histological resection, and overall adverse events (intraprocedural and post-procedural bleeding and perforation). Pooled odds ratios (OR) with 95% confidence intervals (CI) were calculated using the random-effects model.
Results: Thirteen studies involving 2046 patients with 2517 polyps were included (1213 in UEMR, 1304 in CEMR). UEMR showed significantly better rates of en bloc resection (OR 1.51, 95% CI 1.01-2.18, P=0.03), residual/recurrent polyps on follow-up (OR 0.35, 95% CI 0.20-0.62, P=0.0003), piecemeal resection (OR 0.68, 95% CI 0.49-0.94, P=0.02), complete macroscopic resection (OR 12.56, 95% CI 4.88-32.33, P<0.00001). There was no significant difference in complete histological resection (OR 1.11, 95% CI 0.63-1.98, P=0.71), and overall adverse events (OR 0.92, 95% CI 0.52-1.62, P=0.76) between the two groups.
Conclusions: Compared to Conventional EMR, Underwater EMR demonstrated better rates of en bloc resection and complete macroscopic resection with lower risks of piecemeal resection and residual/recurrent polyps.

Azizullah Beran (R)

Efficacy and safety of over-the-scope-clip system in the management of non-variceal upper gastrointestinal bleeding: A systematic review and meta-analysis

Azizullah Beran, Sami Ghazaleh, Wasef Sayeh, Ziad Abuhelwa, Dipen Patel, Amna Iqbal, Sehrish Malik, Yasir Al-Alabboodi, Jordan Burlen, Ali Nawras

Introduction: Rebleeding and subsequent morbidity and mortality is a major disadvantage of conventional endoscopic therapeutic modalities for non-variceal Upper gastrointestinal bleeding (NV UGIB). Endoscopic hemostasis using the over-the-scope-clip (OTSC) system is a promising therapeutic modality for NV UGIB. In this meta-analysis, we aimed to evaluate the safety and efficacy of the OTSC system for the management of NV UGIB.
Method: We performed a comprehensive literature search, using PubMed and Embase databases through April 2021, for all published studies. The primary outcomes were technical and clinical success rates. The secondary outcomes were post-procedure re-bleeding and complications. All meta-analyses were conducted using a random-effects model.
Results: A total of 22 studies including 921 patients with 930 NV UGIB lesions were included. The most common etiology was peptic ulcer (77.95%), the rest were Mallory-Weiss lesion (5.51%), dieulafoy lesion (5.37%), post-endoscopic procedures (4.83%), anastomosis (4.43%), tumor (1.47%), and others (0.4%). The pooled technical success was achieved in 912 lesions [98.8%; 95% confidence interval (CI) 98.1-99.5%], and the pooled clinical success was achieved in 811 lesions (88.6%, 95% CI 84.8-92.3%). Eighteen studies (807 patients) reported the incidence of re-bleeding in 87 patients (9.2%, 95% CI 5.6-12.8%). The complications related to OTSC system procedure were reported only in 3 patients (0.3%).
Conclusions: The OTSC system seems to be an effective therapeutic option for NV UGIB, offering high technical and clinical success. However, further trials are needed to evaluate the effectiveness of the OTSC system for NV UGIB.

Azizullah Beran (R)

Efficacy and safety of lusutrombopag for patients with chronic liver disease and thrombocytopenia undergoing invasive procedures: A systematic review and meta-analysis

Azizullah Beran, Sami Ghazaleh, Mohammed Mhanna, Omar Srour, Justin Chuang, Jordan Burlen, Yasir Al-Abboodi, Ali Nawras, Ragheb Assaly

Introduction: Lusutrombopag (LUSU) has been recently approved by FDA to reduce the bleeding risk and the need for platelet transfusion for patients with thrombocytopenia and CLD before invasive procedures.
Methods: We performed a comprehensive literature search using multiple databases through April 2021, for all the studies that compared patients with thrombocytopenia (<50×10^9/L) and LCD who received LUSU versus placebo (PBO) prior to invasive procedures. The primary outcome was the proportion of patients who avoided pre-procedure platelet transfusion. The secondary outcomes were bleeding-related adverse events, thrombosis-related adverse events, and treatment-emergent adverse events. All statistical analysis was performed using the Review Manager software. Pooled odds ratios (OR) with 95% confidence intervals (CI) were calculated using the random-effects model.

Results: Three randomized controlled studies involving 372 patients (59.1% males, mean age 63.55, 202 patients in LUSU and 170 patients in PBO) were included. The proportion of patients who avoided platelet transfusion was significantly higher in LUSU compared to PBO (OR 12.58, 95% CI 3.34-47.43, P=0.0002). Bleeding-related adverse events were significantly lower in LUSU compared to PBO (OR 0.41, 95% CI 0.21-0.81, P=0.01) (Figure 2). There was no significant difference between LUSU and PBO in the rate of treatment-emergent adverse events (TEAEs), including thrombosis-related adverse events (OR 0.89, 95% CI 0.53-1.50, P=0.67).
Conclusions: Our meta-analysis shows that lusutrombopag is safe and effective in reducing the need for pre-procedure platelet transfusion and bleeding risk in patients with thrombocytopenia and chronic liver disease. However, further studies are needed to confirm our findings.

Azizullah Beran (R)
Hepatitis B virus reactivation in the setting of acute Epstein-Barr Virus infection: A case report
Azizullah Beran, Jack Sample, Jamie M. Stewart, Wasef Sayeh;, Jordan Burlen, Ali Nawras

Introduction: Hepatitis B virus (HBV) reactivation is not uncommon condition. HBV reactivation has been reported after immunosuppressive therapy especially with rituximab. There are several viral infections can trigger HBV reactivation, including hepatitis C virus (HCV) and human immunodeficiency virus (HIV) infections. However, there is no reported case of HBV reactivation triggered by Epstein-Barr virus (EBV) infection in the literature. To date, we report the first case of reactivation of HBV secondary to acute Epstein-Barr virus (EBV) infection.
Case presentation: A 47-year-old Caucasian male with a remote history of resolved acute Hepatitis B virus infection, who presented to our hospital with severe acute hepatitis which manifested as epigastric pain, jaundice, dark urine, light-colored stools, hyperbilirubinemia, and transaminitis in the 1000s. Ultimately, the patient was diagnosed with reactivation of HBV triggered by acute EBV infection. After several days of supportive treatment, his hepatic function normalized. He was discharged with scheduled follow-up at a hepatology clinic.
Conclusions: To our knowledge, this is the first case of HBV reactivation in the setting of acute EBV infection reported in the literature. In conclusion, EBV infection should be considered in the differential diagnosis of cases with HBV reactivation, particularly when common etiologies are excluded.

Azizullah Beran (R)
Predictors of fecal microbiota transplant failure in clostridioides difficile infection: An updated meta-analysis
Azizullah Beran, Sami Ghazaleh, Mohammed Mhanna, Omar Srour, Hazem Ayesh, Wade Lee-Smith, Mohammad Aziz, Sachit Sharma

Introduction: Fecal Microbiota Transplantation (FMT) is an effective treatment for recurrent/refractory Clostridioides Difficile (CDI) with a 10-20% risk of recurrence after a single FMT. In this meta-analysis, we aimed to evaluate the predictors of FMT failure.
Methods: A comprehensive search of MEDLINE, Embase, Cochrane, and Web of Science databases through July 2021 was performed. All studies that evaluated risk factors associated with FMT failure in a multivariate model were included. We calculated pooled odds ratios (OR) with 95% confidence intervals (CI) for risk factors reported in ≥ 3 studies using random-effects model.
Results: Twenty studies, involving 4327 patients (63.6% females) with recurrent/refractory CDI who underwent FMT, were included. FMT failed in 705 patients (16.3%) with 2-3 months of follow-up in most studies. A total of 12 different risk factors were reported in a multivariate model in ≥ 3 studies. Meta-analysis showed that advanced age, severe CDI, inflammatory bowel disease (IBD), peri-FMT use of non-CDI antibiotics, prior CDI-related hospitalizations, inpatient status, and poor quality of bowel preparation were significant predictors of FMT failure. Charlson comorbidity index, female gender, immunosuppressed status, patient-directed donor, and number of CDI recurrences were not associated with FMT failure.
Conclusions: Advanced age, severe CDI, concurrent IBD, peri-FMT use of non-CDI antibiotics, poor quality of bowel preparation, prior CDI-related hospitalizations, and inpatient FMT were associated with FMT failure. Our results may help develop a risk stratification model to predict FMT failure in CDI patients.

David Farrow (R)
Osler-Weber-Rendu Syndrome: A rare presentation of isolated variceal bleeding
David Farrow, Jordan Burlen, Benjamin Hart, Yaseen Alastal, Ali Nawras

Introduction: Hereditary hemorrhagic telangiectasia (HHT) is a hereditary condition and rare cause of portal hypertension. We present a case of HHT presenting as isolated variceal bleeding treated with transjugular intrahepatic portosystemic shunt (TIPS) procedure followed by high output heart failure.
Case Presentation: Patient is a 60-year-old female with no history of GI bleeding, cirrhosis, or alcohol use who was transferred from outside hospital for management of grade 3 esophageal varices found on EGD and CTA suggesting arterioportal fistula. On arrival, exam showed splenomegaly and abdominal distension; vital signs were stable. EGD demonstrated gastroesophageal varices with fresh blood from mucosal oozing in the gastric fundus. Interventional radiology (IR) was consulted who successfully placed TIPS shunt. The patient was discharged in stable condition.
Ten days later, patient re-presented to the ED for shortness of breath and lower extremity edema and was treated for heart failure exacerbation. Subsequently the patient had melena; patient was vitally stable with benign physical exam.. Hepatic arteriogram showed multiple peripheral hepatic artery to portal vein malformations. The largest malformation was treated with coiling and embolization. Outpatient treatment of the remaining fistulas was planned to maintain hepatic integrity. Upon careful review, the patient had a personal and family history of chronic epistaxis and family history of death from non-alcoholic cirrhosis. HHT was confirmed by the Curacao criteria.
Conclusion: HHT is an important differential diagnosis for patients with portal hypertension without history of cirrhosis or other obvious cause. Close inspection of family history should be performed to evaluate for HHT.

Sami Ghazaleh (R)
Efficacy and safety of peppermint oil in irritable bowel syndrome: A systematic review and meta-analysis of randomized controlled trials
Ghazaleh S, Beran A, Sharma S, Aziz M, Burlen J, Nawras A

Background: Irritable bowel syndrome (IBS) is a common functional disorder of the gastrointestinal tract characterized by abdominal pain and altered bowel habits in the absence of an organic disease. Initial management involves dietary modification and physical activity. Adjunctive pharmacologic therapy includes laxatives, antidiarrheal agents, and antispasmodic agents. A few studies have investigated the antispasmodic effects of peppermint oil, but its efficacy in IBS remains unclear.
Patients and Methods: We conducted a systematic review and meta-analysis the efficacy and safety of peppermint oil in IBS. We performed a comprehensive search in the databases of PubMed and Embase, through October 22, 2020. Our outcomes were: global improvement in IBS symptoms, improvement in abdominal pain, and occurrence of adverse events. The random-effects model was used to calculate the risk ratios (RR) and confidence intervals (CI).
Results: Seven randomized controlled trials involving 678 patients were included in the meta-analysis. Peppermint oil was superior to placebo in terms of global improvement in IBS symptoms (RR 2.13, 95% CI 1.68 – 2.69, $p < 0.00001$, $I^2 = 0\%$) and improvement in abdominal pain (RR 1.72, 95% CI 1.39 – 2.11, $p < 0.00001$, $I^2 = 0\%$). Adverse events were similar between patients who received peppermint oil or placebo (RR 1.17, 95% CI 0.76 – 1.79, $p = 0.48$, $I^2 = 0\%$).
Conclusions: Our meta-analysis demonstrated that peppermint oil was more effective than placebo in achieving improvement in global symptoms and abdominal pain in IBS. It was also not associated with more adverse effects compared with placebo.

Sami Ghazaleh (R)
Polyethylene glycol versus lactulose for the treatment of overt hepatic encephalopathy: A systematic review and meta-analysis
Ghazaleh S, Beran A, Khader Y, Burlen J, Aziz M, Nawras A

Introduction: Overt hepatic encephalopathy is a common complication of decompensated liver cirrhosis that require hospitalization. The standard therapy for hepatic encephalopathy involves the use of lactulose with or without rifaximin. Recent studies have investigated the role of polyethylene glycol (PEG) as an alternative treatment option, but its efficacy remains unclear because of paucity of studies.
Methods: We conducted a systematic review and meta-analysis that compared the efficacy of PEG with lactulose in patients hospitalized with overt hepatic encephalopathy. We performed a comprehensive search in the databases of PubMed and Embase through October 3, 2020. Outcomes were improvement of hepatic encephalopathy scoring algorithm (HESA) score by one (or more) grades and length of hospital stay. The random-effects model was used to calculate the risk ratios (RR), mean differences (MD), and confidence intervals (CI).
Results: Four studies, three randomized controlled trials and one prospective cohort, involving 279 patients were included in the meta-analysis. Improvement in HESA score by one (or more) grades was significantly higher in patients who

received PEG compared with patients who received lactulose (RR 1.38, 95% CI 1.16 – 1.64, p = 0.0003, I^2 = 14%). Length of hospital stay was significantly shorter in patients who received PEG compared with patients who received lactulose (MD -1.31 days, 95% CI -2.17 – -0.44, p = 0.003, I^2 = 74%).
Conclusions: Our meta-analysis demonstrated that PEG achieved higher rates of improvement in HESA score and shorter length of hospital stay when compared with lactulose.

Amna Iqbal (R)
Hepatomegaly in a young adult - Look for Mauriac syndrome
Amna Iqbal, MD; Ajit Ramagudu, MD; Stephanie Shea, MD; Wasef Sayeh, MD; Mona Hassan, MD

Introduction: Acute transaminitis in a young adult is a diagnostic challenge and has a broad differential. We describe a case of a young adult with history of diabetes mellitus presenting with elevated liver enzymes and was diagnosed with hepatic glycogenosis as a part of Mauriac syndrome.
Case Presentation: A 19-year-old male with past medical history of Type 1 diabetes mellitus diagnosed at age 2 and growth hormone deficiency with prior growth hormone replacement was admitted to the hospital with chief complaint of nausea, vomiting and abdominal pain for two days. Patient reported 7/10 intensity, non radiating, generalized abdominal pain for two days. He had mild diffuse abdominal tenderness and mild hepatomegaly on examination. Lab work was significant for blood glucose 239, AST 125, ALT 86, alkaline phosphatase 141. Patient was admitted for diabetic ketoacidosis and stated he had multiple admissions in the past for the same. A1c on presentation was 13%. Repeat lab studies showed AST 1121, ALT 404, alkaline phosphatase 158. CT abdomen and pelvis showed hepatomegaly, no discrete hepatic mass or ductal dilatation. Ultrasound abdomen revealed borderline size liver measuring 25 cm. Hepatitis panel, autoimmune panel, acetaminophen level, alpha -1 antitrypsin, serum ceruloplasmin, serum CPK, iron studies, TSH, tissue transglutaminase and anti-smooth muscle antibody were all unremarkable. There was no evidence of alcohol use. LFTs started trending down after two days with better glycemic control. Liver biopsy was performed which revealed diffusely swollen hepatocytes consistent with hepatic glycogenosis, scant portal and foci of lobular inflammation.
Discussion: Hepatic glycogenosis is a rare and overlooked manifestation of uncontrolled type 1 diabetes mellitus. Patients present with elevated transaminases and hepatomegaly. AST/ALT elevation >1 or a mixed pattern of hepatocellular injury is present. Patients have repeated admissions for DKA with A1c elevation > 10%. Median age of presentation is 18-45 though cases in younger and older people have also been identified. Liver biopsy reveals diffusely swollen hepatocytes filled with glycogen that stain deep purple with PAS (Figure 1 C) and disappear after treatment with diastase (Figure 1 D). These changes occur due to reversible accumulation of glycogen within hepatocytes as a result of excessive hyperglycemia and insulin treatment. Hepatic glycogenosis is reversible with glycemic control. Hepatic glycogenosis is often a part of Mauriac syndrome characterized by uncontrolled type 1 diabetes mellitus, growth retardation, hepatomegaly often with elevated liver enzymes and cushingoid features. It is imperative to recognize hepatic glycogenosis as a consequence of uncontrolled diabetes mellitus to avoid unnecessary testing.

Amna Iqbal (R)
Management of perforated esophageal diverticulum with endoscopic Over the Scope Clip (OTSC)
Amna Iqbal, MD; Khushbu R Patel; Jordan Burlen, MD; Naveena Luke; Sami Ghazaleh, MD; Azizullah Beran, MD; Justin Chuang, MD; Saif-Eddin Malhas , MD; Ziad Abuhelwa, MD; Wasef Sayeh, MD; Dipen Patel, MD; Sehrish Malik, MD; Christian Nehme, MD; Ali Nawras, MD

Introduction: Esophageal perforation is a medical emergency making early detection and management a key to survival and improved prognosis. We are presenting a case of a patient who developed esophageal perforation and fistula which was treated successfully by over the scope clip (OTSC) closure.
Case Description: An 82-year-old male presented to the emergency department with chief complaint of abdominal pain and shortness of breath. He had a laparoscopic esophageal diverticulectomy with heller myotomy and fundoplication performed for epiphrenic esophageal diverticulum and achalasia 15 days prior to presentation. CT scan chest demonstrated fluid and gas in the inferior mediastinum region of the prior diverticular resection and right-sided empyema. An EGD performed showed no perforation in the esophagus but approximately 7 cm above the squamocolumnar line, an area of healing tissue was identified. An esophageal stent was placed with the distal extent just above the GE junction, tube thoracostomy was also performed. Patient continued to have increased output from chest tube, repeat imaging demonstrated persistent leak and migration of the stent proximally. The stent was removed, CT chest next day showed free leak of contrast into the right pleural space and mediastinum consistent with perforation and leak along the right distal esophageal wall. A repeat EGD was performed demonstrating a small fistula at 38 cm from the incisors at the GE junction

with whitish necrotic tissue seen flowing through the fistula tract into esophageal lumen during suctioning. The fistula tract with the surrounding tissue was suctioned into the cap and the OTSC clip was deployed successfully over the fistula. Complete closure of the fistula was achieved and no further drainage was seen after deploying the clip. A fully covered 23 mm by 105 mm self expandable metallic stent was then placed across the site of the fistula.
Discussion: Esophageal perforation is a medical emergency. Various treatment options are available. The emerging safer trend for esophageal perforation is employing endoscopic modalities including through-the-scope clips (TTS), self-expandable metal stents (SEMS), suturing , over-the-scope clips (OTSC) and self-expandable plastic metal stents (PSEMS). TTS and OTSC are excellent interventional strategies for repair of esophageal perforation and leaks as they are associated with less morbidity and mortality compared to surgical intervention. They have made the closure of esophageal leaks profoundly easier.

Amna Iqbal (R)
Spontaneous gastric perforation - A case of nasogastric tube complication
Amna Iqbal, MD; Jordan Burlen, MD; Muhammad Aziz, MD; Ali Nawras, MD

Introduction: Acute abdominal pain and distension in a patient requires immediate assessment and treatment. A nasogastric tube (NG) placement is the first step taken to evaluate and treat acute surgical abdomen. Very rarely, this benign intervention could itself be a cause of acute surgical abdomen. Here we present a case of a 72-year-old female who developed gastric perforation due to NG tube which was placed first for ileus and then later on for enteral nutrition. The patient subsequently was found to have a gastric perforation due to NG tube.
Case Presentation: A 72-year-old female with no significant past medical history presented to the hospital with shortness of breath for 2 days. Patient was found to have bilateral pulmonary emboli and atrial fibrillation. During hospital stay, patient developed brown colored vomiting, surgical history was only significant for cholecystectomy and two C-sections. X-ray abdomen showed dilated loops of small and large bowel representing ileus. NG tube and rectal tube was placed which resolved the ileus after which NG tube was removed. Later in the hospital stay, patient developed hypoxic respiratory failure and was intubated. NG tube was placed again for enteral nutrition. Sixteen days after NG tube placement, patient developed fever, leukocytosis, tachycardia and complained of diffuse abdominal pain. CT abdomen and pelvis showed free air with free fluid in the peritoneum concerning for perforated viscus. Patient was taken to the operating room and exploratory laparotomy was performed. During surgery, upon exploration, NG tube tip was found causing a perforation of approximately 0.5 cm at the posterior gastric fundus. Primary repair with sutures was done and omental flap was placed on top of repair.
Discussion: The most common indication for placement of a nasogastric tube is to decompress the stomach in the setting of bowel obstruction. Nasogastric tube insertion is considered a fairly benign intervention but there can be several complications related to it including aspiration, electrolyte abnormalities, tube dislodgement and esophageal perforation during placement being the most common. In patients with acute abdominal distension or peritonitis, it is vital to quickly assess the cause of acute abdomen. For a patient with no risk factors for peptic ulcer disease, gastritis, NSAIDs use or a previous history of peptic ulcer disease, though rare, a nasogastric tube previously inserted for any indication should be considered as the cause of viscus perforation.

Sehrish Malik (R)
Mortality associated with endoscopic intervention of atrioesophageal fistula post atrial fibrillation radiofrequency ablation
Sehrish Malik, MD; M. Ali, MD; S. Ghazaleh, MD; D. Patel, MD; C. Nehme; A. Beran; J. Burlen; A. Nawras, MD

Introduction: Atrioesophageal fistula (AEF) is an extremely rare yet dreadful complication of radiofrequency ablation of refractory atrial fibrillation with high mortality rates if not diagnosed early & promptly treated. Due to its usual presentation of GI bleeding, endoscopic evaluation with air insufflation leads to worsening outcomes; we present a similar case which resulted in mortality of a patient post EGD evaluation.
Case Description/Methods: A 77-year-old male with history of atrial fibrillation on Xarelto & recent radiofrequency ablation 2 weeks prior presented with 3 episodes of hematemesis and hypotension. Emergent bedside EGD showed large clots in the stomach but source of bleeding was not seen. He developed acute respiratory distress requiring intubation, transfused 3 units PRBC and 1 unit FFP. Urgent echo showed RV dilation with small pericardial effusion. Cardiac tamponade was ruled out but concerns for AEF was raised due to recent procedure. IR angiogram ruled out active bleeding. CT without contrast revealed small pericardial & pleural effusions. MRI head showed multifocal ischemic changes indicating embolic disease. Antibiotics were started for blood culture revealing streptococcus. EGD showed an

excavated lesion near mid esophagus measuring 10mm with massive active spurting blood suspected to be ruptured fistula/aneurysm. No intervention was done since patient had asystolic arrest during the procedure. Air and water insufflation endoscopic techniques were used. ROSC was obtained in 12 mins. Cardiothoracic surgery was involved & suggested placing Blakemore tube initially before taking the patient to OR, however patient continued to deteriorate and he passed away shortly.
Discussion: Common cause of death include cerebral air embolism, massive GI bleeding & septic shock. Studies have reported low mortality with emergent surgical intervention(33%) next to endoscopic intervention(65%) next to non intervention treatment(97%)(Fig1). Emergent endoscopic intervention with air insufflation causing air embolism is the most common risk factor for mortality.

Sehrish Malik (R)

Pre-pyloric Gastric ulcer leading to stenosed pylorus, obstruction of gastric outlet and pseudo-gastroparesis

Sehrish Malik, MD; M. Ali, MD; Y. Al-Abboodi; A. Nawras, MD

Introduction: Gastric outlet obstruction (GOO) is a syndrome manifested with combination of early satiety, abdominal pain, postprandial vomiting and weight loss. The usual etiology is either mechanical (benign or malignant) or motility related. Most common cause of benign obstruction is peptic ulcer disease. Here we discuss a case of pre-pyloric ulcer with significant stenosis that mimics gastroparesis causing acquired GOO.
Case Description/Methods: 58 year old female with history of migraines, anxiety and chronic pain presented with generalized weakness, epigastric pain and melanotic stools. She was taking 2 pills of aspirin and Advil every 3 hours for past 2 weeks for toothache. On evaluation, she was vitally stable but had hemoglobin of 5.5. CTA of abdomen pelvis noted abnormal duodenum with diffuse mural thickening and mildly prominent lymph nodes. She was transfused 2 units PRBC. EGD revealed linear antral ulcer occupying 2/3rd of pre-pyloric area measuring 4cm extending into pylorus with minimal oozing. Pylorus was severely narrowed and ulcerated; XP scope was then used which passed through the pylorus into the duodenal bulb which appeared to be severely ulcerated. Patient had follow-through study which showed suspected mild stenosis &/or edema in pylorus secondary to ulcerative dislocation; however no bowel obstruction was noted. Biopsy ruled out malignancy & H. pylori infection and was consistent with chemical gastropathy. Gastrin level was also normal. Patient was transitioned to full liquids due to inability to tolerate solid foods. EGD 4 weeks later while on pantoprazole showed partial resolution of ulcerated lesions.
Discussion: Pre-pyloric ulcers are the most common form of PUD leading to GOO. Most common site is the pyloric channel or duodenal bulb which was the case in our patient. Acute ulcers usually cause inflammation and edema that leads to tissue deformation and obstruction especially with solid food particles getting lodged into the ulcer. Obstruction usually occurs in 2% of cases and is the least common complication contributing to gastroparesis like symptoms.

Anas Renno (CF)

Antireflux valve metal stent vs. conventional self expandable metal stent in distal malignant biliary obstruction: A systemic review and meta-analysis

Anas Renno, M.D., Yousef Abdel-Aziz, M.D., Tamer Ahmed, M.D., Yaseen Alastal, M.D., Javaid Toseef, M.D., Yasir Al-Abboodi, Ahmad Zuhaib, Ali Nawras M.D FACG

Background: In patients with distal malignant biliary obstruction (MBO), endoscopic biliary drainage using the conventional self-expandable metal stent (SEMS) is the gold standard method for palliative treatment. However, there are limited data on the role of the antireflux valve metal stent (ARVMS). The aim of this study was to compare the safety and efficacy of ARVMS and SEMS in distal MBO patients.
Methods: We searched PubMed, Ovid, Embase and the Cochrane Library from inception until April 2019 for relevant randomized controlled trials (RCTs). The selected studies provided data regarding technical and clinical success rates, adverse events and stent dysfunction. Data were meta-analyzed using RevMan software.
Results: Three RCTs were selected, enrolling 293 patients (147 ARVMS and 146 SEMS). The rates of technical success were 95.23% and 99.31% for ARVMS and SEMS groups, respectively [odds ratio (OR) 0.13; 95%CI: 0.01-1.06, p=0.06]. The clinical success rates were 91.57% and 89.36% for ARVMS and SEMS groups, respectively (OR: 1.30; 95%CI: 0.48-3.51, p=0.61). There was no significant difference between ARVMS and SEMS groups in terms of adverse events (OR: 0.61; 95%CI: 0.35-1.05, p=0.07) or stent dysfunction (OR: 0.77; 95%CI: 0.31-1.95, p=0.58), while stent occlusion was significantly lower in the ARVMS group (OR: 0.44; 95%CI: 0.26-0.76, p=0.003).

Conclusion: Our study showed that ARVMS and SEMS technical and clinical success rates were similar. Adverse events were comparable between the two arms; however, ARVMS was associated with lower risk of stent occlusion. Larger RCTs are required to verify the benefit of ARVMS in distal MBO patients.

Anas Renno (CF)

Diagnosis of intrapancreatic accessory spleen by endoscopic ultrasound-guided fine-needle aspiration mimicking a pancreatic neoplasm: A case report and review of literature

Anas Renno, M.D., Michael Hill, M.D., Yousef Abdel-Aziz, M.D., Hany Meawad, M.D., Ahmad Zuhaib, M.D., Ali Nawras, M.D. FACG

Accessory spleen (AS) is a benign condition where ectopic spleen tissue can be found elsewhere in the abdomen and pelvis, with approximately 20% of cases located at or in the tail of the pancreas. When discovered on imaging, it can be mistaken for conditions that do require surgical removal, including neuroendocrine tumor, and so accurate diagnosis of AS can prevent unnecessary surgery. Endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) is a commonly performed diagnostic modality that can lead to a confirmatory diagnosis of AS. We present a case of AS diagnosed at our institution by EUS-FNA and review the literature for all reported cases of AS that have been confirmed by EUS-FNA.

Wasef Sayeh (R)

Gastric stricture following post-laparoscopic sleeve gastrectomy gastric volvulus reduction and gastropexy treated with telescoping stent technique

Wasef Sayeh; MD, Azizullah Beran; MD, Sami Ghazaleh; MD, Dipen Patel; MD, MBA, Christian Nehmeh; MD1Sehrish Malik; MD, Justin Chaung; MD, Saif-Eddin Malhas; MD, Amna Iqbal; MD, Ziad Abuhelwa; MD, Waleed Khokher; MD, Dana Ghazaleh; MD, Ajit Ramadugu MD, Jordan Burlen; MD, Ali Nawras; MD

Introduction: Gastric volvulus has been reported after laparoscopic sleeve gastrectomy (LSG). Gastric sleeve stricture (GSS) complicates 0.7% - 4% of cases after LSG. Both complications were reported in the literature but never was a case of both volvulus and stricture reported, as far as we know.

Case Description/Methods: A 36-year-old lady presented with nausea, vomiting, oral intake intolerability after six weeks of undergoing LSG with para-esophageal hernia repair. Esophagogram showed tortuosity at the distal esophagus near the gastroesophageal junction (GEJ) but no esophageal stricture. The patient was taken to surgery, showing a gastric volvulus with extensive adhesions to the stomach. The adhesions were lysed, and volvulus was reduced, and gastropexy was done. After surgery, she tolerated the oral diet and was discharged home. Three weeks later, the patient was readmitted for dysphagia to liquids. EGD was done and showed two gastric strictures. A metallic stent was deployed successfully under fluoroscopic and endoscopic guidance. On the next day, she developed nausea and vomiting. Repeat EGD was done, which showed that the stent migrated proximally. Another self-expanding metallic stent was deployed with Its proximal end telescoping to the older stent to prevent migration. Three weeks later, repeat EGD was done, and interval improvement across strictures was noted.

Discussion: Gastric volvulus should be kept in mind when dealing with patients developing nausea and vomiting after bariatric surgery. Although endoscopic balloon dilation has been considered the preferred initial treatment for GSS, telescoping stenting can be used in select cases, such as in our case.

Sara Stanley (CF)

The impact of HCC locoregional therapy on peri-operative and post-transplant complications

Stanley S. DO, Caines A. MD, Mishra K. MD, Sturza S. MD, Abouljoud MS. MD, and Salgia RJ. MD

Introduction: Transplant candidacy in the setting of HCC is dependent on a patient meeting Milan criteria. For those who fall outside of Milan criteria, locoregional therapies (LRT) are used to decrease tumor burden as a bridge to liver transplant (LT). There is limited amount of data available regarding the effects of LRT on peri-operative LT outcomes.

Purpose: The aim of this study was to examine the effects of LRT for treatment of HCC on peri-operative transplant outcomes.

Methods:

- Retrospective chart review of patients who underwent LT from 2012 - 2018
- Patients with cirrhosis and HCC who were transplanted within the study period and received LRT for HCC prior to LT were compared to a control group of patients who did not receive LRT

Results:

- 160 LRT patients were compared to 200 controls

- Control group had significantly greater intra-operative transfusion requirements and longer hospital stays than LRT group
- No significant differences in the post-LT complications between the LRT and control groups
- On subgroup analysis there was no increase in complications based on type of LRT or number of LRT treatments received. However, the long-term post LT mortality rate was higher among those who received TARE compared to those who did not receive TARE (33% vs. 12%; p=0.015).

Conclusion: We found that LRT for HCC prior to LT did not lead to increased intra-operative transfusion requirements, longer post-LT hospital stay, higher post-LT complications, longer operative times, increased rates of return to the OR nor increased overall mortality when compared to patients who did not undergo LRT prior to LT.

Sara Stanley (CF)

Esophagogastroduodenoscopy with every endoscopic ultrasound - is it necessary?

Stanley, Sara DO; Abu Ghanimeh, Mouhanna K. MD; Abdulhamid, Ahmed MD; Zhang, Jinyu MD; Elbanna, Ahmed DO; Kumssa, Fitsum MD; Zuchelli, Tobias MD

Introduction: Endoscopic ultrasound (EUS) has been used increasingly as a safe and accurate diagnostic tool for a variety of gastrointestinal (GI) conditions. In 2015, the ASGE and ACG released standard quality indicators for endoscopic procedures. Performing an EUS for an "appropriate" indication and having adequate photos of structures of interest were among the key indicators with different grades for the clarity of benefit. There was no mention for the utility of pre-procedure esophagogastroduodenoscopy (EGD).

Purpose: To evaluate if EGD preceding EUS in asymptomatic patients changes management or patient outcomes.

Methods:

- Retrospective chart review of 1100 charts was performed.
- 158 patients were selected based on the criteria below.
- Inclusion criteria: Asymptomatic patients who underwent EGD prior to EUS over the last 4 years
- Exclusion criteria: Patients with gastrointestinal symptoms

Results:

- Mean age was 60.5 years. 63 patients were males.
- Most common indication for EUS was pancreatic followed by biliary (figure 1).
- Among 158 EGDs, 33 were normal, 125 had benign mucosal findings, 11 had Barrett's esophagus and 4 had GI malignancy. Overall, this led to change in management in 67% of patients (figure 2).
- There were no increased complications for EGD prior to EUS when compared to EUS alone.

Conclusion: Our study showed that performing an EGD prior to EUS in the absence of gastrointestinal symptoms is safe and changed management in 67% of asymptomatic individuals.

GENERAL INTERNAL MEDICINE (GIM)

Andrew Abrahamian (R)

Pathologically Confirmed Interstitial Nephritis: Suspected Doxycycline Induced

Andrew Abrahamian, MD (Resident); Cameron Burmeister, MD; Srini Hejeebu, DO

Introduction: This report describes a case of a patient presenting with diabetic ketoacidosis who experienced progressively worsening acute kidney injury after exposure to multiple nephrotoxic agents during hospital course. His presentation led to a relatively broad differential for acute kidney injury (AKI), which included contrast induced nephropathy, vancomycin-induced nephrotoxicity, and interstitial nephritis secondary to antibiotic use. Interstitial nephritis associated with doxycycline use is poorly described in the literature which delayed cessation of suspected offending agent.

Case Description: A 28-year-old male with past medical history of diabetes presented with diabetic ketoacidosis. On admission, patient underwent CT neck with contrast for evaluation of facial cellulitis and was placed on empiric antibiotic therapy (vancomycin, piperacillin-tazobactam and metronidazole). Patient was transitioned from intravenous antibiotics to oral doxycycline for MRSA positive cellulitis. Within 24 hours of starting doxycycline, the patient developed AKI (Cr 0.56 to 2.54 mg/dl, along with near threefold increase in blood urea nitrogen). Despite fluid resuscitation and oral prednisone, the patient's kidney function rapidly worsened. Doxycycline was discontinued, and 48 hours after the last dose, renal function began to steadily improve. Electron microscopy findings from renal biopsy exhibited severe acute interstitial nephritis likely from antibiotics.

Conclusion: Due to initial lack of characteristic interstitial nephritis findings, patient was originally believed to be experiencing acute tubular necrosis secondary to contrast nephropathy and vancomycin toxicity, which lead to a delay in determining the true etiology of the AKI; although rare, doxycycline-induced interstitial nephritis should be included in differential.

Ziad Abuhelwa (R)

Romiplostim for SARS-CoV-2 Vaccine Induced Immune Thrombocytopenia

Ziad Abuhelwa, Ying Ning, Waleed Abdulsattar, Sami Ghazaleh, Navkirat Kahlon, Ahmed Elsayed

Introduction: Millions of people in the United States have received SARS-CoV-2 vaccines under strict safety monitoring. Few adverse effects have been reported including thrombocytopenia.
Case presentation: A 65-year-old woman with a non-significant past medical history presented with epistaxis and extensive skin rash after she received her first dose of vaccine Moderna. Laboratory investigations showed hemoglobin 12.6 g/dL, white blood cells 8.4×10^9/L and platelet count 3×10^9/L. Coagulation profile and serum chemistry were unremarkable. Human immunodeficiency virus, hepatitis B virus and hepatitis C virus antibodies were non-reactive. Peripheral blood smear showed thrombocytopenia without blasts or morphologic abnormalities including schistocytes or spherocytes. She was started on intravenous (IV) dexamethasone and IV immunoglobulin with no response. Later, she was started on Rho(D) immunoglobulins for 2 doses and weekly romiplostim at a dose of 1 mcg/kg. Five days later, day 13 post vaccination, platelet count improved to 77×10^9/L with no further episodes of epistaxis (Figure 1).
Discussion/Conclusion: Immune Thrombocytopenia (ITP) is a rare autoimmune disorder characterized by increased platelet destruction and decreased platelet production. A small but growing number of cases of thrombocytopenia after administration of SARS-CoV-2 vaccine have been reported. Most cases presented with mucocutaneous bleeding and were treated as ITP and responded well to the standard treatment options. Rarely ITP after SARS-CoV-2 vaccine can have a lag of response to the standard treatment like dexamethasone and IVIG. Thrombopoietin receptor agonist agents may be useful in cases of refractory ITP related to SARS-CoV-2 vaccination.

Ashu Acharya (R)

Assessment of central line duration to help reduce CLABSI rate by raising awareness among AICU staff and residents

Ashu Acharya MD, Cameron J Burmeister MD, Saffa Iftikhar MD, Aya Abugharbyeh MD, Wasef Sayeh MD, Yasmin Khader MD, Sarah Mustafa MD, Kanana Aburayyan MD, Michael Conley MD, William R Barnett MS, Erica Reynard MSN, RN, Ragheb Assaly MD

Introduction: Central line-associated bloodstream infections (CLABSIs) are a significant cause of morbidity, mortality, and expense in hospitals. Literature shows that utilizing a systematic team-based approach for proper line maintenance is effective in reducing CLABSI rates. Utilizing these principles, we set to improve CLABSI rate and central venous catheter (CVC) line duration in the resident-staffed intensive care unit (ICU).
Methods: We retrospectively collected baseline data from January 1, 2021 to April 20, 2021 regarding central line insertion site, line duration, and CLABSI rate. Then, we developed a structured knowledge pre-intervention survey to assess resident understanding surrounding CVC duration and CLABSI. CVC guidelines were developed and shared among nursing staff, residents, and ICU team members at an educational session. An audit tool was developed and implemented in tandem with modified interprofessional rounding practices to enforce CVC guidelines. Data was reanalyzed after four weeks to objectively determine the effect of our interventions on CVC duration and CLABSI rate. A post-intervention survey was conducted to qualitatively assess improvements in resident knowledge on CVC line duration and CLABSI.
Results: During the intervention period, our initiatives reduced CVC line duration by 33% and reduced CLABSI rate by 50%. In addition, there was increased compliance in CVC infection protocol, increased resident/ICU staff CLABSI knowledge, and improved rounding practices between ICU team members.
Conclusion: This project demonstrates how introducing a simple, systematic, team-based central line quality improvement initiative significantly reduced CVC line duration and CLABSI rates while improving resident and staff knowledge in a resident-staffed ICU setting.

Basil Akpunonu (F)

Bilateral Accessory (Aberrant) Renal Arteries Associated with Uncontrolled Hypertension Role of Renin-Angiotensin-Aldosterone Antagonist Drugs for Treatment to Goal

Basil Akpunonu, Jeannine Hummell, Brian Tasma, Chiamaka Mbaso, Joseph Akpunonu, Haitham Elsamaloty

Background: Accessory (aberrant) renal arteries (ARA) are extra vessels that supply the kidneys in addition to the usual single arteries. They can be seen in up to 30% of adults and typically arise from the abdominal aorta but can also originate from other abdominal pelvic arterial systems. Accessory vessels are usually longer and smaller than normal vessel and could lead to perfusion abnormalities that activate the Renin-Angiotensin-Aldosterone system. Accessory renal arteries can complicate various urological, abdominal surgery, interventional radiological, and transplantation procedures. The prevalence of ARA has been noted in patients with uncontrolled blood pressure, but the causative relationship has been a subject of interest and discussions.
Objective: What is the cause of persistent hypertension and hypokalemia in a 49-year-old-woman who had developed hypertension earlier in previous pregnancies?
Result: A plasma renin level was elevated and as part of the investigation of persistent hypokalemia, multi-detector computed tomographic angiography examination with axial slices was done with sagittal and coronal reconstruction as well as 3 dimension (3D) volume rendering. The examination showed duplicated renal arteries in both the right and left kidneys with small calibers. No surgical intervention was done. High doses of Losartan 100mg daily, Carvedilol 12.5 mg twice daily, and Spironolactone 50mg daily was required to get her blood pressure to goal.
Conclusion: Accessory renal arteries may contribute to or exacerbate maintenance and control of blood pressure and no vascular intervention is needed. Drugs affecting the Renin-Angiotensin-Aldosterone pathway may play a role in the treatment of patients with accessory (aberrant) renal arteries if hypertension is renin medicated.

Sarah Aldrich (F)
PROVIDE-2: Evaluation of pharmacist-driven diabetes management on patient outcomes in academic internal medicine clinics
Lauren Willard, PharmD Candidate; Emily Brassell, PharmD Candidate; Marilee Clemons, PharmD, BCACP; Sarah Aldrich, PharmD, BCACP; Basil Akpunonu, MD, FACP

Introduction: It is well documented that interdisciplinary chronic disease management improves health outcomes. As medication experts, pharmacists enhance effective diabetes care across all settings. PROVIDE-2 aims to evaluate the impact of pharmacist visits on comprehensive care in ambulatory patients with diabetes. PROVIDE-1, a pilot study, reviewed 100 patients meeting study criteria. Due to positive results from this preliminary analysis, additional patients were evaluated.
Methods: Through collaborative practice agreements, pharmacists provide education and medication management. Adult patients within the general internal medicine practice with a pharmacy consult for diabetes management between 8/16/18 and 2/13/20 were included. Retrospective, chart-review yields the following data points for analysis: HbA1c, time-to-goal, metformin optimization, immunizations, and cardioprotective and renoprotective medication initiation.
Results: Results show a statistically significant HbA1c absolute reduction of 1.62% (p=0.000*) and an average consult duration of 6.5 months. With extrapolation, a yearly HbA1c absolute reduction is estimated to be 2.98%. For antidiabetic medication optimization, statistical significance was found for metformin and GLP-1 agonists. Results showed a 19.05% increase in patients optimized on metformin by the last pharmacist interaction (p=0.000*). For GLP-1 initiation, a 23.81% increase was seen by the last pharmacist interaction (p=0.000*).
Conclusions: Overall, the results show that patients achieved improved glycemic control and optimization of guideline directed therapy when followed by a pharmacist for diabetes management. Our findings support pharmacist management of diabetes in the ambulatory setting and showcase the effectiveness of the University of Toledo General Internal Medicine clinics and their pharmacists with an HbA1c reduction greater than previous literature.

Hazem Ayesh (R)
Bronchial Carcinoid Associated Ectopic ACTH Syndrome: Diagnostic Challenge
Hazem Ayesh, MD,MPH; Odai Alhasanat, MD; Azizullah Beran, MD; Mohammed Mhanna, MD; Aadil Maqsood, MD

Introduction: Pulmonary carcinoid is an extremely rare tumor with an incidence of 0.22 – 0.66 per 100,000 person-years. Carcinoid tumors represent 1% of malignant pulmonary tumors. Carcinoid tumor is known to cause ectopic ACTH syndrome (EAS).
Methods: A 31-year-old female patient presented to the hospital with the complaint of recent weight gain, diarrhea, worsening acne, and darkening of the skin. Notable labs include low potassium at 2.9 mEq/L, normal Renin/aldosterone ratio, normal TSH, normal metanephrine and catecholamines levels. Low dose dexamethasone suppression test (LDDST) was performed and showed a nonsuppressed cortisol. LDDST results confirmed with 24-hours urinary cortisol level which was elevated at 337 mcg/24 hrs. ACTH level came back elevated at 86 units which supports a secondary etiology

of Cushing's syndrome. High dose dexamethasone suppression test (HDDST) showed suppression which consistent with Cushing's disease.
Results: Multiple cases in literature showed suppression of HDDST in EAS. Further workup revealed normal insulin-like growth factor-1(IGF-1), prolactin, FSH, and LH. These tests make Cushing's disease less likely on the differential. However, due to the patient's symptoms of intermittent diarrhea, 5-hydroxyindoleacetic acid (5-HIAA) level was ordered and came back significantly elevated. The patient was presumptively diagnosed with bronchial carcinoid-associated EAS. Biopsy revealed typical carcinoid.
Conclusions: Interestingly, the patient had incidental pituitary microadenoma but IGF-1, prolactin, FSH, LH unremarkable. Improvement of symptoms after lobectomy supports the diagnosis of EAS. HDDST is a helpful utility in differentiating Cushing's disease from other secondary causes of Cushing's syndrome, but it's suppressed in EAS caused by bronchial carcinoid.

Hazem Ayesh (R)
Management of Hypertriglyceridemia-induced pancreatitis in COVID-19 Patients
Hazem Ayesh, MD, MPH; Odai Hasan Alhasanat, MD

Introduction: Hypertriglyceridemia (HTG) is important cause of acute pancreatitis (AP) and represents about 1-14% of all patients with AP. Triglyceride (TGA) level >1000 mg/dl is highly associated with AP.
Methods: A 30-year-old African-American female patient presented to the emergency department with one-day history of severe upper abdominal pain, associated with nausea and vomiting. Physical examination revealed abdominal tenderness. Sodium low at 132, bicarbonate low at 20 [22-32 mmol/L], Glucose elevated at 257, lipase elevated at 143 U/L, triglycerides elevated at 27,732 mg/dL, Hemoglobin A1c elevated at 8.9%. COVID-19 was positive. CT abdomen/pelvis with contrast showed peripancreatic fluid and fat stranding, fatty liver infiltrate. Patient started on insulin infusion with dextrose 5%.
Results: AP is associated with high mortality especially when associated with HTG. Early aggressive management is associated with improved clinical outcomes. Plasmapheresis is effective in rapid reduction of TGA level but should be initiated within 24 – 48 hours after presentation. Establishing central access is challenging in COVID-19 patients given the high disease transmission risk. So patient was started on insulin infusion instead. Serum TGA level decreased by 70% in the first 24 hours and 92%. There's no episode of hypoglycemia during hospital stay. To help prevent future HTG-AP attacks, patient was started on icosapent ethyl 2 g twice daily and fenofibrate micronized 67 mg daily.
Conclusion: In summary, management of HTG-AP in COVID-19 patients is quite challenging. Lowering the risk of disease transmission and minimizing invasive procedures is important where insulin infusion become very helpful.

Hazem Ayesh (R)
Amiodarone-Induced Hypothyroidism Initially Presenting as Decompensated Heart Failure and Hyponatremia
Hazem Ayesh, MD, MPH, Cameron Burmeister, MD, MS, Azizullah Beran, MD, Basil Akpunonu, MD

Introduction: Amiodarone is an effective antiarrhythmic, but it is associated with altering thyroid function, ranging from thyrotoxicosis to hypothyroidism. In this study, we discuss amiodarone-induced hypothyroidism (AIH) presenting with hyponatremia and myxedema.
Methods: A 75-year-old Caucasian man with a history of ischemic heart disease with an ejection fraction of 55-60% was seen in the ED with complaints of worsening lower limb edema and shortness of breath. He was recently started on amiodarone nine months ago. Labs showed mildly low HB of 11.7, low Na of 125 mmol/L, elevated creatinine at 1.67 mg/dl. TSH was elevated at 93 uIU/mL and low free T4 at less than 0.25 ng/dL with a negative anti-TPO. A diagnosis of amiodarone-induced hypothyroidism was made, and the patient was started on increased on levothyroxine 25 mcg daily. Significant improvement was noted in mental status, sodium level, and volume status within three days.
Results: This case illustrates the need to constantly investigate the etiology of decompensated heart failure, especially when new medications with potential culprit side effects are noted or suspected. Amiodarone which is helpful in the management of atrial fibrillation has been known to cause thyroid dysfunction as hypo or hyperthyroidism. What is not widely known is that these endocrine dysfunctions can occur just a few weeks after therapy initiation.
Conclusions: We recommend that patients who started on amiodarone be monitored for thyroid dysfunction; especially when they present with deterioration in the cardiac function or show symptoms of endocrinopathy.

Hazem Ayesh (R)

A Case of Autoimmune Polyglandular Syndrome Type 3b Initially Presenting as Generalized Weakness in an Elderly Patient

Hazem Ayesh, MD, MPH, Cameron Burmeister, MD, MS, Ahmed Abdelrahman, MD, Azizullah Beran, MD, Pooja Suri, MD

Introduction: Autoimmune polyglandular syndrome (APS) is a multiorgan genetic autoimmune disease. APS-3B subtype is autoimmune thyroiditis with pernicious anemia. In this case, we will discuss an elderly female patient diagnosed with APS-3B.
Methods: A 69-year-old Caucasian female patient with a past medical history of autoimmune thyroiditis presented to ED with a two-month history of generalized weakness and nausea. Physical exam was positive for depigmented skin macules over the upper extremities. Lab results showed hemoglobin 8.2, high MCV at 121, WBC low at 1.9, LDH 1153[100 - 235 U/L], TSH low at 0.28, free T4 1.7 [0.61 - 1.60 ng/dL], Vitamin B12 level low at <50. Blood smear showed absolute neutropenia with flow cytometry unremarkable. Chest x-ray and urinalysis were negative. Immunofixation showed low IgM 44 [45 - 281 mg/dL], low IgG 619 [635 - 1,741 mg/dL]. Intrinsic factor antibodies (IF-Ab) were positive. Hematology reported that hemolytic anemia is less likely given Coombs test was negative. The combination of pernicious anemia, autoimmune thyroiditis, and vitiligo supported the diagnosis of autoimmune APS-3B. There was a normalization of vitamin B12 level and symptomatic improvement on a one-week follow-up.
Results: The patient was diagnosed with autoimmune thyroiditis in 2014 with positive anti-TPO antibodies and elevated TSH. Hypothyroidism causes macrocytic anemia, which may delay pernicious anemia diagnosis. Many studies reported that autoantibodies can be detected before developing symptoms of organ involvement.
Conclusions: APS-3B is a rare disorder. Diagnosis is difficult because hypothyroidism causes macrocytic anemia. Early detection of APS-3B may help to prevent complications.

Hazem Ayesh (R)

Hypopituitarism as the Initial Presentation of Pituitary Metastasis From Lung Cancer

Hazem Ayesh, MD, MPH, Cameron Burmeister, MD, MS, Ahmed Abdelrahman, MD, Azizullah Beran, MD

Introduction: The annual incidence of hypopituitarism 4.2 cases of 100,000. Causes include primary tumor, metastasis, and non-tumor causes such as radiation therapy, infiltrative lesions, infection, and traumatic brain injury. Metastatic pituitary tumors constitute about 7-9% of the cases, with lung and breast cancers are the most common primary tumors.
Methods: 48-year-old Caucasian female patient presented to ED with abdominal pain, diarrhea, fatigue, and headache. Labs showed glucose of 53 mg/dL, low free T4 0.52 ng/dL, low FSH 1.3 mIU/ml, low LH <0.2 mIU/ml, low ACTH 1.4 pg/mL, low morning cortisol 2.2 ug/dL, low DHEASO4 3ug/dL, low IGF-1 16 ng/ml. She was diagnosed with hypopituitarism and started on IV hydrocortisone and levothyroxine. MRI brain showed interval growth of pituitary lesion into the suprasellar cistern with a mass-effect on the optic chiasm measuring 2.4 X1.6X 1.9 cm with a lesion in the right cerebellar hemisphere. Vertebral MRI showed multiple metastatic lesions in spine. CT chest showed spiculated left upper lobe mass, and biopsy showed metastatic poorly differentiated epithelial malignancy lung origin.
Results: 2011 MRI brain showed a mildly enlarged pituitary gland. MRI brain two months before admission showed a pituitary gland diameter of 1.6 cm. She reported symptoms of nausea, vomiting, and weakness for more than one year ago. The fact that the patient had pituitary enlargement eight years ago likely delayed the diagnosis of pituitary metastasis.
Conclusions: Symptomatic patients with pituitary enlargement on brain imaging may benefit from a close follow-up and biochemical testing for early diagnosis and treatment.

Hazem Ayesh (R)

Acquired Hemophilia A in an Elderly Patient Complicated With Deep Venous Thrombosis: A Case Study

Hazem Ayesh, MD, MPH Cameron Burmeister, MD, MS Azizullah Beran, MD Waleed Abdulsattar, MD Mohammed Mhanna, MD Dr. Sandeep Kukreja, MD

Introduction: Acquired hemophilia A (AHA) is an autoimmune disorder associated with spontaneous production autoantibodies targeting internal factor VIII. The incidence of AHA is 1.3 to 1.5 cases per million population per year.
Methods: A 78-year-old Caucasian male patient with a past medical history significant for hypertension presented to the hospital with left lower extremity swelling. On physical examination, the patient had hematoma with ecchymosis over the scrotal area and inner thigh. Notable labs showed: low hemoglobin at 6.9, elevated aPTT at 70. Bilateral lower extremity venous doppler ultrasound showed left acute femoral deep vein thrombosis (DVT). CT angiogram of the lower extremities

showed thigh hematoma. Mixing study showed incomplete correction of aPTT. Factor VIII inhibitor level was elevated at 8.5 Bethesda units, and Factor VIII assay was low at 5% which is consistent with AHA. Patient was started on prednisone, cyclophosphamide, and recombinant factor VIII. On discharge, the patient's aPTT was 37, factor VIII level of 38%, inhibitor 6.4 BU.
Results: Management of AHA consists of replacement of consumed coagulation factors and elimination of the coagulation factor inhibitor. For replacement, Factor VIII or activated factor VII are utilized. Prednisone and cyclophosphamide are used to neutralize inhibitor activity. AHA should be considered in patients with an isolated elevation in aPTT, a normal INR and a high Factor VIII inhibitor levels.
Conclusions: Association with DVT is uncommon but provides a medical challenge. In the setting of both severe active bleeding and deep venous thrombosis, IVC filter could be utilized.

Hazem Ayesh (R)
Non-Suppressed Plasma Renin Activity in Primary Aldosteronism With Hypertensive Kidney Disease
Hazem Ayesh

Introduction: Renin aldosterone ratio (ARR) serves as a widely used screening test. Elevated ARR with suppressed plasma renin activity (PRA) is considered a positive screening test which should be followed by confirmatory testing. There are cases when PA is associated with non-suppressed PRA as in our case.
Methods: A 37-year-old African American female patient with a past medical history of chronic kidney disease stage 4 presented to the hospital with a complaint of severe headache for 2. Elevated blood pressure at 190/101 mmHg. Labs showed elevated creatinine at 4.84 [0.40 – 1.00 mg/dL] with normal potassium level. Unremarkable renal duplex ultrasound, unremarkable thyroid function test, normal free plasma metanephrine. Plasma aldosterone concentration (PAC) elevated at 64.1 [3.1 – 35.4 ng/dL] with normal PRA at 1.7 ng/mL/hr. Calculated ARR was elevated at 37.7 ng/dL per ng/mL/hour.
Results: There are reports in literature that PA is more common than initially thought and has adverse effects on cardiovascular and renal systems independent of hypertension. So early diagnosis and management are highly recommended. Multiple case studies reported non-suppressed PRA in patients with PA, especially when associated with hypertensive kidney disease and arteriosclerosis.
Conclusions: We suggest focusing on ARR as a reliable screening for PA and not solely depend on the fact that PA is associated with suppressed PRA, especially in these cases. Another important point is to consider lowering ARR cutoff for diagnosis of PA since PRA isn't completely suppressed in these cases.

Hazem Ayesh (R)
Pembrolizumab-induced thyroiditis
Hazem Ayesh, MD, MPH; Cameron Burmeister, MD MS; Jeremy C. Tomcho MD; Rawish Fatima MD; Srini K. Hejeebu DO FACP

Introduction: Pembrolizumab is a humanized monoclonal antibody that acts on T cell programmed death receptor-1 (PD-1) resulting in activation of T-cell mediated response and destruction of malignant cells. Administration of pembrolizumab is associated with immune-related adverse events (irAEs). Thyroid irAEs have a reported incidence of 3.2-10.1 % in patients receiving pembrolizumab. We present a case of pembrolizumab-induced thyroiditis in a patient with esophageal adenocarcinoma.
Methods: A 54-year-old Caucasian female with past medical history of hypothyroidism and stage IV poorly differentiated distal esophageal adenocarcinoma presented to the ED with generalized weakness and confusion. Physical exam was notable for cachexia and bilateral upper extremity resting tremor. Vital signs were BP 116/79, pulse 133. Labs showed TSH 0.01 [0.49-4.67], free T4 3.01 [0.61-1.60], thyroglobulin 229.1 [0-35 ng/ml], free T3 3.01 [2.50 - 3.90 pg/mL], cortisol 21.2 (normal. Thyroid ultrasound showed diffuse heterogeneous echotexture consistent with thyroiditis. Thyroid-stimulating hormone receptor (TSH-R), thyroid peroxidase (TPO), thyroglobulin, and thyroid-stimulating antibodies (TSI) were normal.
Results: The patient's elevated T4 with elevated thyroglobulin makes iatrogenic hyperthyroidism unlikely. Total T3:T4 ratio was >20 and free T3: free T4 ratio > 0.3, which is consistent with Graves' disease however, TSHR Ab was negative, and the thyroid ultrasound did not show hyperemia, instead supported destructive thyroiditis. The downtrend of T4 during hospital stay favors acute thyroiditis. Endocrinology attributed the hyperthyroidism to pembrolizumab-induced thyroiditis.
Conclusions: Pembrolizumab is known to have secondary side effects including thyroiditis. Active surveillance will help in the prevention, early detection, and treatment of future thyroid-related irAEs.

Hazem Ayesh (R)

Immune thrombocytopenia associated with COVID-19 successfully managed with Intravenous immunoglobulin and glucocorticoid

Hazem Ayesh, MD, MPH; Mohammed Mhanna, MD; Azizullah Beran, MD; Srini K. Hejeebu, DO
MD

Introduction: Immune thrombocytopenia (ITP) is an autoimmune disease characterized by low platelet counts of <100x 109/L. COVID-19 can result in acute respiratory distress syndrome and multiorgan failure. Thrombocytopenia is detected in 5–41.7% of COVID-19 patients. We'll discuss a case of COVID-19 associated ITP managed successfully with glucocorticoid and Intravenous immunoglobulin (IVIG).
Methods: A 76-year-old female patient presented with 5 days history of generalized skin rash. She also reported fatigue, mouth pain, visual disturbances, and arthralgia. Physical exam revealed multiple hemorrhagic blisters over the soft palate and diffuse bilateral non-blanchable petechial rash. Notable labs showed low platelets at 3 x 109/L, low hemoglobin at 7.6 g/dL, elevated INR at 1.4. COVID-19 was positive. She received 2 units of platelet and started on IVIG/dexamethasone. Hepatitis B, hepatitis C, and HIV were unremarkable. ANA antibodies were positive but anti-dsDNA antibodies were negative. Abdominal ultrasound was unremarkable.
Results: ITP is a diagnosis of exclusion. lab testing for other etiologies was unremarkable. The fact that the patient had anemia with low hemoglobin may be explained by the active bleeding. The reticulocyte index came back low at 1.02 which may indicate hypoproliferation which is common in acute bleeding (< 7 days). Given the low platelet level and active bleeding, 2 units of platelets were transfused. And IVIG/ dexamethasone given per American Society of Hematology (ASH) recommendations.
Conclusions: It's important to early recognize ITP diagnosis and differentiate it from COVID-19 associated thrombocytopenia, so we can provide a more targeted therapeutic plan to lower mortality.

William Barnett (F)

Utilization of autopsy findings for evaluating the accuracy of clinical diagnosis

William R. Barnett MS, Mohammad Saud Khan MD, Amira Gohara MD, Jacob Torrison MD, Christian Coletta MD, Ragheb Assaly

Introduction: Autopsy has long been recognized as an important tool for learning and quality improvement in clinical practice. Physicians often utilize autopsy findings for evaluating the accuracy of their clinical diagnosis, identifying any unsuspected conditions, and establishing a cause of death.
Methods: Autopsies were reviewed from January 2011 to May 2015. Kappa coefficients were used to measure agreement between clinical diagnosis and the cause of death at autopsy. Agreement between pre- and post-mortem deaths was defined as listing at least one pre-mortem diagnosis in the main final autopsy diagnosis. A Mann-Whitney U test was conducted to compare the median time to death among the agreement and non-agreement groups.
Results: 141 autopsies were reviewed, while 71 autopsy records were included in the final analysis based on availability of clinical information. Almost perfect agreement was found in cases of meningitis, endocarditis, stroke, and sepsis, while there was moderate agreement among cases of brain hemorrhage, myocardial infarction, and pulmonary embolism. In some cases, such as liver cirrhosis and ischemic bowel necrosis, there was no agreement found; however, these cases were not statistically significant. The median time to death was 8.5 days (IQR 4-17) in the agreement group, while it was 4 days (IQR 2-7) in the non-agreement group ($P = 0.004$).
Conclusions: The level of agreement between clinical and autopsy diagnosis varies from case-to-case, while the duration of stay may be a factor in reaching agreement. This study highlights the importance of autopsy as a potential learning experience for trainees.

William Barnett (F)

A single institution experience for the selection of internal medicine candidates via panel interview style

William R. Barnett MS, Yasir Illahi MD, Ghattas Alkhoury MD, Zubair Khan MD, Ragheb Assaly MD

Introduction: Residency programs have used various criteria to select candidates, but there is not a consensus of which factors define a well-rounded candidate. Equally, there is overreliance on some objective elements, such as test scores. The aim of the study was to evaluate a 3-member panel interview style in selecting internal medicine candidates using both objective and subjective criteria.

Methods: Our study cohort included 115 categorical candidates. ANOVA was used to assess if there was a difference in the mean subjective composite scores of the 3-member panel. Multiple linear regression was used to model the relationship between the scoring and the final rankings of the candidates.
Results: The ANOVA revealed there was not a difference in mean subjective scores between the 3-member panel, $F(2,114) = 1.37$, $p = 0.256$. Final rankings were regressed on quality of medical school, grades/awards, USMLE scores, scholarly activities, clinical science potential, and the subjective composite score, which was highly significant, $F(6,114) = 112.486$, $p < 0.001$. The quality of medical school, subjective composite scores, and USMLE scores demonstrated very significant effects on the final rankings. Furthermore, both scholarly activities and grades/awards were significant predictors. Lastly, clinical science potential was not a significant predictor of final ranking.
Conclusions: Our study emphasizes on having a more balanced assessment tool that considers both the objective and subjective aspects, as both contribute towards the final rank order list. Individually, members of the panel did not differ in their overall assessment of a candidate.

William Barnett (F)

Compliance and adherence to continuous positive airway pressure during the COVID-19 pandemic

William R. Barnett MS, Muthukumar Radhakrishnan MD, Andre Aguillon MD, Youngsook Yoon MD, Hazem Ayesh MD, Omar Assaly BA, Nicholas Griffin RPSGT, Ragheb Assaly MD

Introduction: Continuous positive airway pressure (CPAP) is currently the treatment of choice for patients with obstructive sleep apnea (OSA). Due to the 2019 novel coronavirus disease outbreak (COVID-19), it was suggested that inconveniences and other difficulties produced by the situation could have a negative impact on compliance and adherence to treatment.
Methods: 587 patients diagnosed with OSA and treated with CPAP participated in a telemonitoring program in the Toledo, Ohio area. The mean daily usage and the number of patients identified as low adherers, which was defined as a mean CPAP usage of less than 10 minutes, were compared before and at various times during the pandemic. The previous year (2019) and peak COVID-19 cases in the county were used to separate time periods in the analysis.
Results: Based on a repeated measures ANOVA, the mean daily usage differed significantly between time points, $F(2.774, 1625.733) = 3.164$, $p = 0.027$. Post-hoc analysis revealed CPAP usage slightly decreased early in the pandemic (6.22 vs. 6.06 hours). A Cochran's Q test determined a significant difference in the proportion of low adherers over time, $\chi^2(3) = 35.057$, $p = 0.000$. Based on post-hoc tests, low adherence differed significantly where there were more low adherers during peaks times when compared to the pre-pandemic period. In addition, there were significantly more low adherers in late 2020/early 2021 when compared to earlier in the pandemic.
Conclusions: While the mean daily usage was over 6 hours, low adherence steadily increased throughout the pandemic.

William Barnett (F)

Assessment of ventilator-associated events using the geometric distribution

William R. Barnett MD, Ragheb Assaly MD, Fadi Safi MD, Sadik Khuder PhD John Macko PharmD

Introduction: Hospital-acquired rare events, such as nosocomial infections and other low-occurring incidents in the clinical environment are difficult to monitor using traditional quality indicators. Using the Centers for Disease Control and Prevention definition of ventilator-associated events (VAE), we demonstrate an alternative method for assessment of rare events. The objective of our study was to focus on a method to differentiate between expected and unexpected events among the rarest-occurring VAE category: possible ventilator-associated pneumonia (PVAP).
Methods: Data were gathered from January 2014 - December 2015 by our Infection Prevention Department as part of its responsibility for daily VAE surveillance. The probability of an event was calculated using the geometric distribution. As a point of comparison, monthly PVAP rates were calculated using events/1000 ventilator days.
Results: Post-PVAP probability does not fluctuate greatly from month to month despite changes in the monthly PVAP rate. For example, in 2 consecutive months (May-July 2014), the PVAP rate increased from 2.1 - 6.4 events/1,000 ventilator days; however, the post-PVAP probabilities only changed from 0.04198 - 0.04617 by the end of July. Likewise, from September-December 2014, the monthly PVAP rate decreased from 5.5 - 2.9 events/1,000 ventilator days, but post-PVAP probabilities only changed from 0.04362 - 0.04247.
Conclusions: Our method is an appropriate alternative to monitor and evaluate PVAP. Our experience dictates that a month might go by without an event only to have ≥1 occurrences in subsequent months. This implies that lack of an event does not mean the problem has significantly improved or completely disappeared.

William Barnett (F)

Case-control study investigating parameters affecting ventilator-associated events in mechanically ventilated patients

William R. Barnett MD, Aahd Kubbara MD, Fadi Safi MD, Sadik Khuder PhD John Macko PharmD, Ragheb Assaly MD

Introduction: In 2013, the Centers for Disease Control and Prevention developed guidelines to categorize certain ventilated patients into 3 categories under 1 umbrella term: ventilator-associated events (VAEs). The first category is a ventilator-associated condition (VAC), followed by infection-related ventilator-associated complication (IVAC), and eventually possible ventilator-associated pneumonia (PVAP). The objective of this study was to explore the effect of a wide variety of factors on the development of VAEs.
Methods: 186 cases were matched 1:1 with controls based on age, sex, unit of intubation, use of vasopressors while intubated, and total ventilator days. Controls were randomly selected among patients who were mechanically ventilated for at least 3 days to meet the VAE definition. We considered only 2 groups for the analysis: VAC, in which patients reached only the first stage of the VAE spectrum, and IVAC-plus, which combined cases from both the IVAC and PVAP categories.
Results: Among VACs, patients intubated in the hospital ward, with a history of CAD or COPD, or on TPN were associated with higher hazards. Conversely, patients with CHF or administered morphine while intubated were associated with lower hazards. Among IVAC-plus, patients with COPD, tube-fed, or on TPN were associated with higher hazards. Conversely, patients with CHF or intubated in either the ICU or OR were associated with lower hazards.
Conclusions: This study invites further exploration of predictive models to improve risk assessments among mechanically ventilated patients, as well as further investigation regarding the new factors and their mechanisms in the evolution of VAEs.

William Barnett (F)

H-1B visa sponsorship and physician trainee retention: A single institution experience

William R. Barnett MS, Yousef Abdel-Aziz MD, Zubair Khan MD, Nezam Altorok MD, Ragheb Assaly MD

Introduction: In 2013, the Centers for Disease Control and Prevention developed guidelines to categorize certain ventilated patients into 3 categories under 1 umbrella term: ventilator-associated events (VAEs). The first category is a ventilator-associated condition (VAC), followed by infection-related ventilator-associated complication (IVAC), and eventually possible ventilator-associated pneumonia (PVAP). The objective of this study was to explore the effect of a wide variety of factors on the development of VAEs.
Methods: 186 cases were matched 1:1 with controls based on age, sex, unit of intubation, use of vasopressors while intubated, and total ventilator days. Controls were randomly selected among patients who were mechanically ventilated for at least 3 days to meet the VAE definition. We considered only 2 groups for the analysis: VAC, in which patients reached only the first stage of the VAE spectrum, and IVAC-plus, which combined cases from both the IVAC and PVAP categories.
Results: Among VACs, patients intubated in the hospital ward, with a history of CAD or COPD, or on TPN were associated with higher hazards. Conversely, patients with CHF or administered morphine while intubated were associated with lower hazards. Among IVAC-plus, patients with COPD, tube-fed, or on TPN were associated with higher hazards. Conversely, patients with CHF or intubated in either the ICU or OR were associated with lower hazards.
Conclusions: This study invites further exploration of predictive models to improve risk assessments among mechanically ventilated patients, as well as further investigation regarding the new factors and their mechanisms in the evolution of VAEs.

William Barnett (F)

Larger endotracheal tube size in women increase the risk for ventilator-associated events

William R Barnett MS, Prabath Herath Mudiyanselage DO, Hossein Haghbin MD, Momen Banifadel MD, Josephine Adunse MD, Fadi Safi MD, Ragheb Assaly MD

Introduction: Even though endotracheal tube (ETT) size selection is often the result of clinical judgement, factors such as age, gender, height, body mass index (BMI), and anticipated bronchoscopies are often considered before insertion. The objective of this study was to explore whether gender differences exist in ventilator-associated event (VAE) development based on larger ETT selection.

Methods: To determine the association between ETT size and VAEs, Pearson $\chi 2$ tests were conducted, and odds ratios (ORs) with 95% confidence intervals (CIs) were reported for each gender. We conducted a post hoc analysis using a t test or the Mann-Whitney U test where appropriate.
Results: Within both the male and female populations, the results of the $\chi 2$ tests indicated a statistically significant relationship between ETT and VAE development, $\chi 2 = 20.05$ (P = .000) and $\chi 2 = 10.17$ (P = .001), respectively. Among male patients, 64 of 160 VAEs and 104 of 160 controls were intubated with 8.0-mm ETTs (OR, 0.39; 95% CI, 0.22–0.58). Conversely, among female patients, 34 of 89 VAES and 15 of 89 controls were intubated with 8.0-mm ETTs (OR, 3.03; 95% CI, 1.44–6.62). We did not detect any statistical differences between female height and BMI between ETT size groups or within female patients intubated with 8.0-mm ETTs only.
Conclusions: We propose some potential mechanisms for higher rates of VAE development among female patients. More longitudinal folds in larger endotracheal cuffs, longer ETT tips in shorter airways, and frequent ETT repositioning are all possible factors with larger ETTs.

William Barnett (F)
Initial MEWS score to predict ICU admission or transfer of hospitalized patients with COVID-19: A retrospective study
William R. Barnett MS, Muthukumar Radhakrishnan MD, John Macko PharmD, Bryan T. Hinch MD, Nezam Altorok MD, and Ragheb Assaly MD

Introduction: Our academic medical center developed a modified early warning score (MEWS) system in 2015 and it was rolled out hospital-wide the following year. Since serious adverse events in hospitalized patients are often preceded by signs of clinical deterioration, we believed MEWS scores could be used to predict events, such as cardiopulmonary arrest. As the coronavirus pandemic continues, could MEWS provide any usefulness in predicting ICU level care among hospitalized COVID-19 patients?
Methods: Initial MEWS scores were considered either at admission or prior to ICU transfer. Sequential organ failure assessment (SOFA) scores were manually calculated and included as a point of comparison.
Results: According to the largest Youden's index, the optimal cutoff value for predicting ICU admission or transfer was a MEWS score of 5. The area under the curve of the receiver operating characteristic (AUC) was 0.935 (95% confidence interval [CI], 0.892–0.979). With regards to SOFA, the score was also 5 with an AUC of 0.924 (95% CI, 0.874−0.973). When the MEWS and SOFA optimal cutoff values are used as predictors of ICU admission or transfer, there is no difference in the two models as assessed by DeLong's test ($Z = -1.061$, p-value = 0.289).
Conclusions: Considering MEWS is a less burdensome scoring system, hospitals should consider adopting a method to calculate MEWS scores on admission with a plan to periodically monitor their patients for increasing scores.

William Barnett (F)
Does a starting positive end-expiratory pressure of 8 cmH2O decrease the probability of a ventilator-associated event?
William R Barnett MS, Aadil Maqsood MD, Nithin Kesireddy MD, Waleed Khokher MD, Zachary Holtzapple BS, Fadi Safi MD, Ragheb Assaly MD

Introduction: Ventilator-associated events (VAEs) are objective measures as defined by the Centers for Disease Control and Prevention (CDC). To reduce VAEs, some hospitals have started patients on higher baseline positive end-expiratory pressure (PEEP) to avoid triggering VAE criteria due to respiratory fluctuations.
Methods: At our institution, VAEs were gathered from January 2014 through December 2019. Using the CDC-defined classifications, VAEs were split into two groups to separate patients with hypoxemia only (VAC) and those with hypoxemia and evidence of inflammation or infection (IVAC-plus). We used the geometric distribution to calculate the daily event probability before and after the protocol implementation. A probability threshold was used to determine if the days between events was exceeded during the post-protocol period.
Results: A total of 306 VAEs were collected over the study period. Of those, 155 were VACs and 107 were IVAC-plus events during the pre-protocol period. After implementing the protocol, 24 VACs and 20 IVAC-plus events were reported. There was a non-significant decrease in daily event probabilities in both the VAC and IVAC-plus groups (0.083 vs. 0.068 and 0.057 vs. 0.039, respectively).
Conclusion: We concluded a starting PEEP of 8 cmH_2O is unlikely to be an effective intervention at reducing the probability of a VAE. Until specific guidelines by the CDC are established, hospitals should consider alternative methods to reduce VAEs.

William Barnett (F)

Detection of ventilator-associated events among adults using naïve Bayes classifier

William R. Barnett MS, Nithin Kesireddy MD, Aadil Maqsood MD, Waleed Khokher MD, Zachary Holtzapple BS, Fadi Safi MD, Ragheb Assaly MD

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Conclusion: We concluded a starting PEEP of 8 cmH_2O is unlikely to be an effective intervention at reducing the probability of a VAE. Until specific guidelines by the CDC are established, hospitals should consider alternative methods to reduce VAEs.

William Barnett (F)

Detection of COVID-19 patients requiring escalation to ICU status using a naïve Bayes classifier

William R Barnett MS, Aadil Maqsood MD, Zachary Holtzapple BS, Chad Jaenke BS, Fadi Safi MD, Ragheb Assaly MD

Background: The naïve Bayes classifier can consider different variables, such as age, gender, race/ethnicity, comorbidities, and initial laboratory values to determine the probability a patient may need to be admitted or transferred to an intensive care unit (ICU).
Methods: Patients with COVID-19 were identified from four area hospitals in Toledo, OH. After identifying significant variables, we began using standard procedures to construct a classifier. The dataset was split 7:3 to create samples for training and testing. To appraise the model's performance, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), area under the curve (AUC), and the Matthew's correlation coefficient (MCC) were calculated.
Results: A total of 574 COVID-19 patients were included in the study. There were 402 patients in the training sample and 172 patients in the testing sample. The naïve Bayes classifier demonstrated an overall accuracy result of 75.6% (95% CI; 68.5% – 81.8%) using 14 variables. The model was able to correctly classify 84.9% of ICU status patients (sensitivity), but only 54.7% of non-ICU status patients (specificity). The PPV and the NPV were 80.1% and 61.7%, respectively. The AUC was 0.717 (95% CI; 0.629 – 0.805) and the MCC was 0.410.
Conclusion: We present a classification model that potentially could be used alongside other tools to screen patients with COVID-19 early in their hospital course to identify those needing escalation to ICU level care.

Azizullah Beran (R)

Atypical Case of Gradenigo Syndrome in an Immunocompetent Elderly

Azizullah Beran, Jamie M. Stewart, Mohammed Mhanna, Omar Srour, Hazem Ayesh, Wasef Sayeh, Ammar Kayyali

Introduction: Gradenigo Syndrome (GS) (petrous apicitis) is a rare complication of chronic suppurative otitis media, especially in the post-antibiotic era. GS is described as a triad of otitis media/mastoiditis, facial/retro-orbital pain, and abducens palsy (diplopia). Herein, we describe the atypical presentation of GS in an immunocompetent elderly.
Case presentation: A 67-year-old male presented with a throbbing left ear pain for three months but worsened over two weeks. It was associated with left facial pain that worsened with chewing and left conductive hearing loss. He denied diplopia or facial weakness. Before hospitalization, he received multiple courses of antibiotics and underwent a myringotomy with no relief. Physical exam showed point tenderness of the left mastoid, but the extra-ocular movement was intact. CT scan of facial bones showed left-sided mastoiditis. MRI brain showed left mastoid effusion and petrous apicitis, involving the paths of the trigeminal, facial, vestibulocochlear, and abducens nerves, consistent with Gradenigo syndrome. The patient was started on broad-spectrum IV antibiotics. Left tympanoplasty with mastoidectomy with

ossicular chain reconstruction and atticotomy was performed. Intraoperative tissue cultures were negative. Extensive lab workup including immunoglobulins was unremarkable. The patient's facial and ear pain resolved, and he was discharged on doxycycline and amoxicillin/clavulanate for a total of four weeks.
Conclusions: The full triad of GS may not always be present, especially in the post-antibiotic era and in the elderly. Careful clinical and physical examination, including neuroimaging, is necessary to suspect and recognize Gradenigo syndrome.

Azizullah Beran (R)

Effect of prone positioning on clinical outcomes of non-intubated patients with COVID-19: A systematic review and meta-analysis

Azizullah Beran, Mohammed Mhanna, Omar Srour, Hazem, Ayesh, Omar Sajdeya, Sami Ghazaleh, Asmaa S. Mhanna, Cameron Burmeister, Aadil Maqsood, Ragheb Assaly

Introduction: Prone positioning (PP) in awake patients has been recently proposed as an adjunctive treatment for non-intubated coronavirus disease 2019 (COVID-19) patients requiring oxygen therapy to reduce the risk of intubation. However, the magnitude of the effect of PP on clinical outcomes in these patients remains uncertain.
Methods: We performed a comprehensive literature search for all studies that compared PP versus control in non-intubated patients with COVID-19. The primary outcomes were the need for endotracheal intubation, in-hospital mortality, and need for ICU admission. The secondary outcomes were the length of hospital and ICU stay. Pooled risk ratio (RR) and mean difference (MD) with the corresponding 95% confidence intervals (CIs) were obtained by the Mantel-Haenszel method within a random-effect model.
Results: A total of eight studies involving 802 patients (297 patients received PP and 539 did not) were included with a mean age of 60.45±18.9 years, and males were 67.2%. The follow-up period ranged from 14 to 30 days. There was no significant difference between the two groups regarding the need for endotracheal intubation (RR 0.84, 95% CI 0.58-1.20, P = 0.34), in-hospital mortality (RR 0.67, 95% CI 0.37-1.21, P = 0.18), or need for ICU admission (RR 0.95, 95% CI 0.62-1.46, P = 0.82).
Conclusions: Prone positioning did not reduce the risk of endotracheal intubation, mortality, and ICU admission in non-intubated patients with COVID-19. However, more large-scale trials with a standardized protocol for prone positioning are needed to better evaluate its effectiveness in this select population.

Azizullah Beran (R)

Micronutrient supplements and mortality in patients with coronavirus disease 2019: A systematic review and meta-analysis

Azizullah Beran, Mohammed Mhanna, Omar Srour, Hazem, Ayesh, Waleed Khokher, Asmaa S. Mhanna, Yasmin Khader, Wasef Sayeh, Jamie M. Stewart, Ragheb Assaly

Introduction: Micronutrient supplements have been used in managing viral illnesses. However, the role of these micronutrients in reducing mortality in patients with Coronavirus disease 2019 (COVID-19) remains unclear. We conducted this meta-analysis to provide a quantitative assessment of the effect of these individual micronutrients on mortality in COVID-19.
Methods: A comprehensive literature search through April 24th, 2021, using multiple electronic databases was performed. All individual micronutrients reported by ≥3 studies and compared with standard-of-care (SOC) were included. The outcome was mortality. All statistical analyses were performed using the Review Manager. Pooled risk ratios (RR) and corresponding 95% confidence intervals (CI) were calculated using the random-effects model.
Results: A total of 14 studies involving 2269 patients with COVID-19 that investigated three individual micronutrient supplements: vitamin C, D, and zinc, were included. Four studies evaluated vitamin C in 290 patients (151 in vitamin C and 139 in SOC). Vitamin C had no significant effect on mortality (RR 0.60, 95% CI 0.27-1.36, P=0.22). Seven studies assessed the effect of vitamin D on mortality among 1405 patients (477 in vitamin D and 928 in SOC) and it didn't reduce the mortality (RR 0.94, 95% CI 0.46-1.94, P=0.87). Four studies including 574 patients assessed the effect of zinc on mortality (365 in zinc and 209 in SOC) and there was no significant reduction in mortality (RR 0.83, 95% CI 0.59-1.16, P=0.28).
Conclusions: Vitamin C, D, and zinc did not reduce mortality in COVID-19. Further research is needed to validate this.

Azizullah Beran (R)

Inhaled epoprostenol treatment for COVID-19: A systematic review and meta-analysis

Azizullah Beran, Mohammed Mhanna, Omar Srour, Hazem, Ayesh, Omar Sajdeya, Sami Ghazaleh, Asmaa S. Mhanna, Waleed Kokher, Ragheb Assaly

Introduction: Inhaled pulmonary vasodilators such as epoprostenol (iEPO) used as adjunctive therapies for the treatment of refractory hypoxemia in patients with acute respiratory distress syndrome (ARDS). Hypoxemia in COVID-19 patients is mainly caused by ventilation-perfusion mismatch, which might be improved by iEPO. However, the effects of iEPO therapy on the clinical outcomes of COVID-19 remain unclear. Therefore, we conducted this meta-analysis to evaluate the impact of iEPO on the oxygenation parameters in COVID-19 patients with refractory hypoxemia.
Methods: We performed a comprehensive literature search using multiple databases through April 24, 2021, to include all published studies. All statistical analyses were performed using the Review Manager software (RevMan 5.3). The weighted mean difference (MD) with corresponding 95% confidence intervals (CI) were calculated using the random-effects model. A P-value <0.05 was considered statistically significant. The primary outcome measure was the change in oxygenation parameter (PaO2/FiO2) pre and post pulmonary vasodilators.
Results: A total of three studies involving 140 patients with COVID-19 were included. Inhaled epoprostenol therapy showed a significant improvement in oxygenation: PaO2/FiO2 (MD: 13.39, 95% CI: 2.84-23.94, P=0.01).
Conclusions: Our meta-analysis showed that inhaled epoprostenol improved oxygenation in COVID-19 patients. Inhaled epoprostenol may play a role as rescue therapy in COVID-19 patients with refractory hypoxemia. However, clinical trials are needed to confirm our findings.

Azizullah Beran (R)

Large fungating facial mass as initial presentation of anaplastic large cell lymphoma

Azizullah Beran, Hanna M. Knauss, Alena Sidwell, Logan D. Glosser, Jamie M. Stewart, Waleed Abdulsattar, Basil Akpunonu

Introduction: Anaplastic large cell lymphoma (ALCL) is a rare form of non-Hodgkin lymphoma (NHL). Certain ALCL subtypes are rapidly aggressive, thus mandate a timely diagnosis to optimize treatment and deter progression. NHL classically presents with lymphadenopathy and constitutional symptoms. However, ALCL can present with nonspecific cutaneous manifestations with minimal or absent constitutional symptoms. The cutaneous involvement may resemble common dermatologic conditions, delaying diagnosis.
Case presentation: A 59-year-old female presented with a painful enlarging forehead lesion. The mass began as a small comedone and grew progressively over a month. CT scan of the facial bones showed a 5.4 x 1.8 x 3.4 cm mass overlying the frontal bone, multiple facial masses overlying the left zygomatic arch, bilateral masses at the angle of the mandible, and enlarged lymph nodes in the cervical chain bilaterally. CT of the soft neck tissue showed soft tissue masses involving the temporalis muscle, bilateral parotid glands, and necrotic lymphadenopathy at the angle of the right mandible. Laboratory tests revealed a white blood cell count of 26.5 x 10E9/L and a platelet count of 563 x 10E9/L. All infectious workup was negative. Chest CT showed a new 1.7 cm peripherally spiculated right lower lobe mass. Biopsy of both forehead lesion and right lower lobe lung nodule showed morphological and immunohistochemical findings consistent with ALK- ALCL.
Conclusions: This case highlights the importance of considering lymphoma when patients present with cutaneous lesions of the face.

Sapan Bhuta (R)

Efficacy and safety of fibrinolysis versus surgery for management of prosthetic valve thrombosis: A systematic review and meta-analysis

S. Bhuta, MD (resident); N.J. Patel, MD; O. Sajdeya, MD; M. Mhanna, MD; P. Shastri, DO; C. Burmeister, MD, MS; J.C. Tomcho, MD; M.M. Patel, MD; A.M. Elzanaty, MD; A. Beran, MD; S. Ghazaleh, MD

Introduction: Prosthetic valve thrombosis (PVT) is a rare and life-threatening condition. The efficacy and safety of fibrinolysis versus surgical management of PVT remains unclear due to a paucity of studies.
Methods: A comprehensive search of PubMed, Embase, and Cochrane Library from inception through November 4, 2020 was conducted. The primary outcome was complete success as defined by clinical improvement and hemodynamic normalization of valve function measured by fluoroscopy or echocardiography. The secondary outcomes were early mortality, major bleeding, thromboembolism, and recurrence.

Results: Twelve observational studies involving 1132 patients were included in the meta-analysis. The rate of complete success was significantly lower in patients who underwent fibrinolysis versus surgery (RR 0.81, 95% CI 0.72 – 0.91, p = 0.0005, I^2 = 64%). There was no significant difference in early mortality (RR 0.64, 95% CI 0.32 – 1.28, p = 0.21, I^2 = 48%). There was a significantly higher rate of major bleeding (RR 2.46, 95% CI 1.09 – 5.52, p = 0.03, I^2 = 0%), thromboembolism (RR 9.77, 95% CI 4.45 – 21.46, p < 0.00001, I^2 = 0%), and recurrence (RR 2.21, 95% CI 1.03 – 4.70, p = 0.04, I^2 = 65%) with fibrinolysis versus surgery.
Conclusion: Our meta-analysis demonstrated fibrinolysis compared to surgical management of PVT is associated with significantly lower rates of complete success in achieving hemodynamic resolution as well as higher rates of major bleeding, thromboembolism and recurrence. There was no significant difference in early mortality. Further studies with larger sample sizes are needed to confirm our findings.

Justin Chuang (R)

Association between vitamin D levels and hepatocellular carcinoma: A systemic review and meta-analysis of prospective studies

Justin Chuang MD, Azizullah Beran MD, Sami Ghazaleh, MD, Jordan Burlen, MD, Muhammad Aziz, MD, Mona Hassan MD

Introduction: Hepatocellular carcinoma (HCC) is one of the most common cancer-related deaths worldwide. An inverse relationship has been studied and reported between vitamin D levels and HCC. However, this association has been inconsistent and remains controversial. We performed an updated meta-analysis of all available data on the association between 25-OH-vitamin-D levels and HCC.
Methods: We performed a comprehensive literature search using the MEDLINE, EMBASE, Cochrane, and Web of Science databases from inception through November 2020. We included prospective studies investigating circulating 25-OH-vitamin-D levels and risk of liver cancer. All meta-analyses were conducted using a random-effect model. Pooled rates were reported as the multivariate-adjusted risk ratios (RR) with 95% Confidence Interval (CI). The quality assessment of the included studies was performed using the Newcastle-Ottawa scale.
Results: A total of 10 prospective studies (1241 liver cancer events and 20,968 patients over an average of 18.8 years of follow-up) met our inclusion criteria and were included in the final analysis. The pooled data analyzing the association of circulating vitamin D levels with liver cancer risk showed that higher circulating vitamin D levels were associated with a lower risk of liver cancer (Pooled RR: 0.706, 95% CI: 0.569, 0.876, P = 0.02.), as shown in Figure 1.
Discussion: Our study suggests that there may be an inverse relationship between vitamin D levels and the risk of liver cancer. High levels of serum vitamin D may have protective effects against liver cancer. However, further studies with larger sample sizes are warranted to confirm our findings.

Justin Chuang (R)

Association between appendectomy and the risk of colectomy in patients with clostridium difficile infection: A systematic review and meta-analysis

Justin Chuang MD, Azizullah Beran MD, Sami Ghazaleh, MD, Jordan Burlen, MD, Muhammad Aziz, MD, Ajit Ramadugu, MD, Ali Nawras, MD

Introduction: The appendix has been suggested as a vestigial organ resulting from an evolutionary remnant. Previous studies suggested a lack of health consequences after patients received an appendectomy. However, newer studies have suggested that the appendix may serve as a replenishment of the gut microbiota and protect against the risk of fulminant Clostridium Difficile infections (CDI) leading to colectomy in severe cases. We therefore evaluated the correlation between appendectomy and the risk of colectomy in patients with CDI.
Methods: We performed a comprehensive literature search of PubMed/MEDLINE, EMBASE, and Cochrane. We collected patients with CDI-induced colectomy with and without a history of appendectomy. The primary outcome of interest was the occurrence of CDI-induced colectomy in both groups. The random-effects model was used to calculate the risk ratios (RR) and confidence intervals (CI). AP-value < 0.05 was considered statistically significant. Heterogeneity was assessed using the Higgins I2 index.
Results: A total of three retrospective cohort studies, including 1424 patients, met our inclusion criteria. A total of thirty-nine patients with a history of appendectomy required colectomy, while sixty-five patients without a history of appendectomy required colectomy. No statistically significant difference was found between the two groups regarding the occurrence of CDI-induced colectomy (RR: 1.14, 95% CI 0.53-2.49, P = 0.73, I2 = 71%) (Figure 1).

Discussion: Appendectomy does not appear to increase the risk of colectomy in patients with Clostridium Difficile infections. However, further studies with larger sample sizes are warranted to characterize this association better and confirm our findings.

Justin Chuang (R)

A case report: Over-the-scope clip closure of an esophageal-pleural fistula secondary to an esophageal stent placement

Justin Chuang MD, Jordan Burlen, MD, Khushbu Patel MS4, Naveena Luke MS4, Ajit Ramadugu MD, Ali Nawras, MD

Introduction: Esophageal fistula is a pathological connection between the esophagus and another structure. The most common treatment for esophageal fistula is airway stenting. However, several case series have demonstrated the superiority of the OTSC (over-the-scope clip) system for fistula closure. We report a case requiring multiple stent /OTSC placements in esophageal-pleural fistula due to underlying malignancy.
Case Description/Methods: A 57-year-old male with a stage IV esophageal cancer with esophageal stent presented with three days of back pain and shortness of breath. A gastrografin was performed and showed a fistula at the proximal aspect of the pre-existing esophageal stent (Fig 1A). A self-expandable metallic stent (SEMS) was utilized to bridge the fistula to the pre- existing esophageal stent. An esophagram two days later revealed extravasation and continuous esophageal leak. OTSC clip was then deployed at the fistula. A SEMS was also implanted through the patient's pre-existing stent. Endoscopy showed persistent esophageal perforation (Fig 1B).
Initial OTSC and SEMS combination was removed. After removal, a second OTSC was placed over the fistula, allowing for complete suction of the fistula into the OTSC clip cap (Fig 1C). We followed this by deploying another SEMS through the pre-existing stent and clipped them together. The proximal end of this new stent fully covered the fistula, creating a complete seal.
Discussion: This case is notable in that successful pleural-esophageal fistula closure secondary to existing esophageal stent erosion was achieved by utilizing a properly positioned OTSC with a stent-within-stent combination management.

Justin Chuang (R)

A Case Report: Eosinophilic esophagitis after an Allegra D bolus

Justin Chuang MD, Jordan Burlen MD, Khushbu Patel MS4, Naveena Luke MS4, Ajit Ramadugu MD, Ali Nawras MD

Introduction: Eosinophilic esophagitis is an immune mediated disorder that may be related to exposure to additive chemicals in crops, air pollutants, or supplements found within livestock. Diagnosis of EoE requires eosinophilic infiltration greater than 15 eosinophils per high power field with endoscopic evidence of abnormal esophageal changes. Here, we discuss a presentation of food bolus impaction secondary to EoE after ingestion of a nasal decongestant and antihistamine pill.
Case Description/Methods: A 22-year-old presented to the emergency department with sudden onset respiratory distress, regurgitation of clear oral secretions, and globus sensation post ingestion of a fexofenadine-pseudoephedrine tablet. An esophagogastroduodenoscopy (EGD) was performed and revealed a fexofenadine-pseudoephedrine capsule at 23 cm from the incisors along with a superficial ulceration at the corresponding level in the esophagus (Fig. 1A). The foreign body was successfully removed using raptor forceps (Fig. 1B). Further visualization demonstrated trachealization of the esophagus and furrowing and severe narrowing (< 10mm) which raised suspicion for eosinophilic esophagitis (Fig. 1C). Proximal biopsy indicated 16 intraepithelial eosinophils per high-power field within the squamous epithelium. The patient was discharged on an 8-week course of proton pump inhibitors.
Discussion: Eosinophilic esophagitis is defined as an immune-mediated esophageal disease characterized histologically by eosinophil-predominant inflammation. Our patient was reported to have up to 16 eosinophil per HPF from the proximal esophageal biopsy which satisfies the requirements for an EoE diagnosis. Based on current literature review, there have been no other reported cases of symptomatic food bolus impaction secondary to eosinophilic esophagitis after ingestion of antihistamines.

Marilee Clemons (F)

Utilization of a proactive population health strategy to identify and manage patients with Type 2 Diabetes Mellitus (T2DM)

Marilee Clemons, PharmD, BCACP; Sarah Aldrich Renner, PharmD, BCACP; Basil Akpunonu, MD, MSC, FACP; Nicholas Horen, MD; Shahab Ud Din, MD

Introduction: Primary care reimbursement models have shifted from fee for service care to value-based reimbursement that incorporates clinical outcomes and provides payments based on measures of clinical quality. One approach used to improve quality is population health management which proactively identifies high-risk patients and aims to implement an intervention to improve the health of the population. Health plan quality metrics can be used to guide where organizations should focus on quality initiatives. The diabetes mellitus quality metric for University of Toledo General Internal Medicine (UTGIM) demonstrated a significant number of patients had an HgA1c > 9.0%. A population health management strategy was used to proactively identify these patients and ensure timely, diabetes-focused, follow up was completed.
Methods: Identification of patients started with a monthly electronic medical record (EMR) generated report of all patients with T2DM and A1c>9.0%. The report was sent to clinical pharmacists to review for accuracy. Once high-risk status confirmed, patients were scheduled with their primary care provider or pharmacist for diabetes specific follow-up. After the initial visit, patients were followed via in person or telehealth visits every one to four weeks until A1c goal met.
Results: After twelve months, UTGIM's diabetes quality metric (A1C < 9%) improved from 19.4% to 75.6% demonstrating that proactive identification and targeted follow-up improves diabetes control.
Conclusions: Utilizing population health strategies to identify high-risk patients can improve patient outcomes and reduce expenditures to the healthcare system.

Rawish Fatima (R)
Gastrointestinal malignancies in sarcoidosis
Rawish Fatima, Saffa Iftikhar, Ashu Acharya, Joan Gekonde, Yasmin Khader, Muhammad Aziz, Sachit Sharma, Nezam Altorok

Introduction: Systemic sclerosis is an autoimmune disease which causes fibrosis and loss of function of skin and internal organs secondary to fibroproliferative changes of microvasculature. It often involves organs like the lungs, skin, eyes, nose, muscles, heart, liver, spleen, bowel, kidney, testes, nerves, lymph nodes, joints, and brain. There has also been some evidence of sarcoidosis causing lymphoma.
Methods: We queried the 2017 Nationwide Inpatient Sample (NIS) database using ICD-10-CM diagnosis codes to identify all adult patients admitted with a diagnosis of sarcoidosis. We also identified various gastrointestinal disorders and malignancies using ICD-10 codes. Outcomes assessed was association between sarcoidosis and GI disorders and malignancies. A logistic regression was done to obtain Odds Ratio (OR) of the association. Statistical analysis was performed using STATA software
Results: We assessed association between sarcoidosis and GI disorders and malignancies. Total adult population was 30.4 million, total sarcoidosis population was 82,060 and total non-sarcoidosis population was 30,317,940. Our data showed that patients with sarcoidosis showed increased incidence of esophageal, colon and rectal cancers.
Conclusion: There are theories about sarcoidosis causing malignancy or vice versa. Activation of immune cells with the help of chemokines such as CCL 5 and CCL 2, T17 lymphocyte and IL 17-A exhibit proinflammatory response in Sarcoidosis. These alterations in immune response can lead to malignancy. There is a need of further studies to find the pathogenesis but implementing early detection methods for these carcinomas will be something that should be used to improve prognosis in patients with sarcoidosis.

Rawish Fatima (R)
Unusual cause of obstructive pneumonia, granulomatosis with Polyangiitis (GPA)
Rawish Fatima, Ashu Acharya, Yasmin Khader, Joan Gekonde, Saffa Iftikhar, Samah Musa, Nezam Altorok

Introduction: Granulomatosis with polyangiitis (GPA), previously known as Wegener's granulomatosis is a type of vasculitis that usually presents with triad of upper respiratory, pulmonary and renal involvement.
Case Presentation: We present a case of 28-year-old female who presented with intermittent sinus pain, cough, chest tightness, joint pain and body aches that had been ongoing for 2 months. CT chest on admission showed right middle and lower lobe pneumonia with partial occlusion, soft tissue prominence along the right mediastinum and hilum. CT chest on admission showed right middle and lower lobe pneumonia with partial occlusion, soft tissue prominence along the right mediastinum and hilum. Bronchoscopy showed severe inflammation of carina, severe inflammatory changes on the right main bronchus with complete occlusion of the right bronchus intermedius, partial occlusion of right upper lobe bronchus, mucous plugging of right lower and middle lobe and cobblestone appearance of left mainstem bronchus. She was diagnosed with granulomatosis with polyangiitis based on cobble stone appearance of bronchi, series of symptoms, lack

of improvement on antibiotics and significant improvement with steroids. Improvement of her symptoms was observed after starting steroids and methotrexate and she was discharged home with outpatient follow up.
Conclusion: GPA should therefore be considered as a differential in patients having any form of pulmonary involvement despite not having any pulmonary nodules and lack of response to antibiotics. Early detection and management reduce the morbidity and mortality associated with this condition.

Rawish Fatima (R)
Exploring the accuracy of the medication reconciliation process on the medical floor
Rawish Fatima MD, Sami Ghazaleh MD, Chad Jaenke BS, Omar Sajdeya MD, Samantha Davis MD, Saif-Eddin Malhas MD, Muhamad Ubby Kalifa MD, Omar Srour MD, Mohammed Mhanna MD, Neha Patel MD, William R. Barnett MS

Introduction: Medication reconciliation is an essential step in the admitting process and helps to ensure patients receive the appropriate and best medical care. Sometimes completion of this important task is inaccurate resulting in errors that can carry on during the hospital stay and ultimately to transition of care to other settings. As part of a resident-driven quality improvement project, we examined the accuracy of the medication reconciliation process for patients admitted to our Internal Medicine Service (IMS).
Methods: The medication list of patients admitted to IMS at the Toledo Hospital were audited by medical residents. The initial medication reconciliation was completed by an RN, whereafter the resident uses various means (e.g. verbal confirmation with patient or contacting the pharmacy) for verification. A medication list was considered inaccurate if there was a discrepancy in the medication count, route, dose, and/or frequency.
Results: Sixty-six patient charts were audited of which 26 charts (39.3%) had a discrepancy even after being reviewed by an RN. Two-thirds of charts had 3 or more discrepancies. The most common discrepancies were added or missing medications, which accounted for 74.4% of the total errors.
Conclusions: Through examination of the medication reconciliation process, we can quantify the errors and begin to take steps to improve the process. Our next focus should be on understanding why medication lists contain erroneous information because of added or missing medications.

Rawish Fatima (R)
Correlation of Autoimmune Pancreatitis and Malignancy: Systematic Review and Meta-Analysis
Rawish Fatima, Hossein Haghbin, Justin Chuang, Nuruddinkhodja Zakirkhodjaev, Wade Lee-Smith, Muhammad Aziz

Introduction: Given the lack of definite evidence, we aimed to pool and summarize data from available literature regarding prevalence of different malignancies in Autoimmune pancreatitis (AIP).
Methods: We conducted a systematic search of MEDLINE, EMBASE, Cochrane Register of Controlled Trials, and Web of Science through February 16, 2021, to include observational studies assessing the incidence of cancer in AIP. We used the DerSimonian-Laird method with random effects for meta-analysis. Pooled prevalence, 95% confidence interval (CI), and I^2 statistic are reported.
Results: A total of 17 studies with 2746 patients were included assessing the prevalence of cancer in AIP. The overall prevalence of cancer in AIP was 9.6% [95% confidence interval (CI), 5.7-13.5%]. The cancers with the highest prevalence in AIP population were gastric and colorectal cancer, with prevalence of 1.3% (95% CI, 0.5-2.1%) and 1.2% (95% CI, 0.6-1.8%), respectively.
Conclusion: We demonstrate the prevalence of different cancers in AIP. Inflammatory surge in AIP and subsequent carcinogenesis is one explanation for this association. Moreover, AIP can be a paraneoplastic syndrome manifestation of malignancies.

Rawish Fatima (R)
The association of low serum albumin level with severe covid-19: A systematic review and meta-analysis
Rawish Fatima, Muhammad Aziz, Wade Lee-Smith, Ragheb Assaly

Introduction: The coronavirus disease 2019 (COVID-19) pandemic necessitates identifying laboratory markers to assist the clinicians in early recognition of severe disease. Given the unclear association of hypoalbuminemia and severe COVID-19, we conducted a systematic review and meta-analysis.
Method: An extensive literature search of PubMed/MEDLINE, Embase, Cochrane, and Web of Science was conducted through April 3, 2020. Random-effects meta-analysis was conducted, and odds ratio (OR) and mean difference (MD)were computed. For each outcome, forest plot, 95% confidence interval (CI), *p* value (< 0.05 considered statistically

significant), and *I*2 statistic (> 50% considered as substantial heterogeneity) was generated using Open Meta Analyst (CEBM, Oxford, UK).
Results: A total of 11 studies (with 910 patients, mean age 47.6 ± 8.2 years and 47.0% females) were included. The weighted mean serum albumin on admission was 3.50 g/dL (CI 3.26–3.74 g/dL) and 4.05 g/dL (CI 3.82–4.27 g/dL) in severe and non-severe COVID-19 group, respectively. This was statistically significant (MD:− 0.56 g/dL, CI -0.69 to -0.42 g/dL, $p < 0.001$, $I^2 = 91.2\%$). Leave-one-out meta-analysis was consistent with point estimate (MD) ranging from -0.61 to -0.51 g/dL. The results were consistent on subgroup analysis of 8 studies that defined severe COVID-19 based on respiratory distress definition (MD -0.58 g/dL, 95% CI -0.78 to -0.37 g/dL, $p < 0.001$, $I^2 = 87.9\%$). Four studies assessed the hypoalbuminemia status and severe COVID-19 and increased risk was demonstrated (OR 12.6, 95% CI 7.5–21.1, $p < 0.001$, $I^2 = 0\%$).
Conclusion: We demonstrate the association of hypoalbuminemia and severe COVID-19. A low albumin level can potentially lead to early recognition of severe disease and assist clinicians in making informed decision for their patients.

Rawish Fatima (R)
Efficacy of tocilizumab in COVID-19: A systematic review and meta-analysis
Rawish Fatima, Muhammad Aziz, Hossein Haghbin, Emad Abu Sitta , Yusuf Nawras, Sachit Sharma, Wade Lee-Smith, Joan Duggan, Joel Kammeyer, Jennifer Hanrahan, Ragheb Assaly

Introduction: The efficacy of tocilizumab (TOC), monoclonal antibody against interleukin-6 (IL-6) receptor, in patients with coronavirus disease-2019 (COVID-19) patients has led to conflicting results. We performed a systematic review and meta-analysis to compare the efficacy of addition of TOC to standard of care (SOC) versus SOC in patients with COVID-19.
Method: We performed a comprehensive literature search of PubMed, Embase, Web of Science, WHO COVID, LitCOVID, and Cochrane databases. Pooled outcomes (overall mortality, need for mechanical ventilation, intensive care unit admission, and secondary infections) were compared using DerSimonian-Laird/Random-effects approach. Risk difference (RD), confidence interval (CI), and p values were generated. A total of 23 studies with 6279 patients (1897 in TOC and 4382 in SOC group, respectively) were included.
Results: The overall mortality was lower in TOC group compared to SOC group (RD: −0.06; CI: −0.12 to −0.01; p = .03). Subgroup analysis including studies with only severe cases revealed lower mortality (RD: −0.12; CI: −0.18 to −0.06; p < .01) and need for mechanical ventilation (RD: −0.11; CI: −0.19 to −0.02; p = .01) in TOC group compared to SOC group.
Conclusion: The addition of TOC to SOC has the potential to reduce mortality and need for mechanical ventilation in patients with severe COVID-19. Randomized controlled trials are needed to validate this.

Douglas Federman (F)
The association between cardiovascular diseases and several chronic inflammatory diseases
Douglas Federman, Sadik A. Khuder

Background and Objective: Do diseases with features of chronic inflammation have a stronger relationship with myocardial infarction? Prospective studies are lacking and other study methods have yielded varying estimates of risk. We propose a survey across multiple disease states using the same methodology to obtain estimates of the association.
Methods: We analyzed hospital admissions data from the 2017-2018 Nationwide Inpatient Sample and identified patients with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), scleroderma (SC), Sjogren's Syndrome (SS), psoriasis (PS), and HIV. We conducted descriptive statistics and bivariate analyses for factors associated with myocardial infarction (MI) and ischemic stroke (Cinfarct). Utilizing weighted logistic regression, we assessed the association between ADs and CVD and adjusting for demographic variables.
Results: Significant differences among the groups for MI. The highest prevalence is 4.95% for Lupus. The lowest prevalence is 2.59% for HIV. Significant increase in the risk was observed for SLE and SC. Significant decrease in the risk was observed for RA, PS, and HIV. Significant differences among the groups for Cinfarct. The highest prevalence is 1.55% for Arthritis. The lowest prevalence is 1.05% for Scleroderma. Significant decrease in the risk was observed for RA, PS, SC, SS and HIV.
Conclusions: Preliminary analysis demonstrates an inconsistent relationship between chronic inflammatory diseases and MI. The wide variety of treatments could have significant impact. Steroids and some HIV drugs contribute to glucose intolerance, a known risk factor. The effects of biologic treatments are unknown with respect to MI.

Saffa Iftikhar (R)

Efficacy of Alendronate for prevention of new fractures and vertebral deformities in patients with rheumatologic disorders on chronic glucocorticoid therapy- A systematic review and meta-analysis

Saffa Iftikhar MD, Waleed Khokher MD, Ashu Acharya MD, Joan Gekonde MD, Nithin Kesireddy MD, Rawish Fatima MD, Nezam Altorok MD

Introduction: Glucocorticoids are commonly used in patients with rheumatologic conditions. There is increased rate of bone resorption after the first few months of initiating glucocorticoid therapy. The risk of bone fractures increase before a decrease in bone mineral density is observed. Interventions to reduce the risk of fractures involve the use of alendronate. Alendronate is a bisphosphonate that works by inhibiting the osteoclast mediated bone resorption.
Methods: We conducted a systematic review and meta-analysis of studies that investigated the efficacy of alendronate for prevention of new fractures and vertebral deformities. We performed a comprehensive search of PubMed/MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials from 2006-2016. We considered RCTs. Primary outcome was the rate of new fractures. The random-effects model was used to calculate the RR, mean differences, and confidence intervals. A p value <0.05 was considered statistically significant.
Results: Six RCT's involving 898 patients were included in the meta analysis. Five studies showed that there was no significant difference in the rate of new fractures between the alendronate group in comparison to the control group. Four studies were analyzed to assess for new vertebral deformities in patients receiving alendronate versus control. There was no significant difference between the rate of vertebral deformities between the two groups.
Conclusion: This analysis demonstrated that the use of alendronate versus control in patients with rheumatologic conditions on chronic prednisone therapy, did not display any significant reduction in new fractures and vertebral deformities.

Yasmin Khader (R)

Should you get your covid-19 vaccine if you take rituximab?

Yasmin Khader, MD; Ashu Acharya, MD; Rawish Fatima, MD; Abdulaziz Aldhafeeri, MD; Cameron Burmeister, MD; Nezam Altorok, MD

Introduction: Rituximab is one of the biologic medications that is used in the management of rheumatoid arthritis. Rituximab depletes B cells, which are a key part of the immune system that helps create antibodies. Here we present a case of patient on rituximab who failed to develop antibodies after COVID-19 vaccine.
Case Presentation: A 66-year-old Caucasian lady with history of rheumatoid arthritis who presented to our office for routine follow-up. Patient was diagnosed with seropositive rheumatoid arthritis since 2015. She has been treated with intravenous rituximab infusion therapy at a dose of 375 mg/m^2 every six months since February 2020. Patient completed two doses of Pfizer-BioNTech COVID-19 vaccine in January 2021. She received her last infusion of rituximab 2 weeks after her last dose of COVID-19 vaccine.
Patient was seen in our office in May 2021. She reported flu like symptoms that started four weeks after the second dose of the vaccine. Patient's symptoms resolved after one week with supportive treatment. She didn't seek medical care at that time, and she was not tested for COVID-19. On examination, patient was afebrile and hemodynamically stable. Her lungs were clear to auscultation bilaterally. SARS-CoV-2 IgG test was sent, and it came back negative.
Conclusion: COVID-19 vaccines are now authorized for emergency use in the United States. Many questions have been arisen about whether people who take immunosuppressants can receive the vaccine. Further studies should be conducted regarding the effectiveness and the appropriate timing of COVID vaccine in patients receiving biologics.

Waleed Khokher (R)

Clinical outcomes of high flow nasal oxygen compared to standard oxygen therapy in the post-extubation setting: A systematic review and meta-analysis

W. Khokher, N. Kesireddy, S. Iftikhar, A. Beran, S. Ghazaleh, P. Mudiyanselage, M. Alom, M. Awad

Introduction: Acute respiratory failure (ARF), pneumonia and mortality are serious complications in the post-extubation setting. Several methods are being investigated in preventing these complications. This literature review looks at the role of high flow nasal oxygen (HFNO) compared to standard oxygen therapy (SOT) and the efficacy of HFNO in preventing post-extubation ARF, post-extubation pneumonia (PEP) and mortality.
Methods: Review of literature was conducted to perform a meta-analysis of the available studies that investigated the efficacy of HFNO compared to SOT in preventing post-exposure complications. This search was performed using

PubMed, Embase, and Cochrane from inception to April 20, 2021. We only considered randomized controlled trials (RCTs). The primary outcome was the occurrence of ARF requiring reintubation. Secondary outcomes were occurrence of PEP, need for rescue via non-invasive ventilation (NIV), and mortality. A p-value <0.05 was considered statistically significant.
Results: 5 RCTs involving 957 patients were including in the meta-analysis. The rate of reintubation was significantly lower in patients receiving HFNO when compared to those receiving SOT after extubation (5.2% vs. 13.2%, RR 0.42, 95% CI 0.25-0.71, p= 0.001, I^2= 12%). The rate of PEP, need for rescue via NIV and rate of ICU mortality after extubation was not significantly lower in patients who received HFNO compared to SOT.
Conclusion: Our meta-analysis demonstrates that the use of HFNO after extubation, when compared to SOT, significantly reduced the rate of reintubation. HFNO did not significantly reduce the rate of PEP, need for rescue via NIV, or mortality compared to SOT.

Waleed Khokher (R)

The role of ascorbic acid in reducing the incidence of stage 3 acute kidney injury in patients with septic shock: A systematic review and meta-analysis

W. Khokher, N. Kesireddy, S. Iftikhar, A. Beran, S. Ghazaleh, P. Mudiyanselage, M. Alom, M. Awad

Introduction: Some argue that the use of ascorbic acid decreases both morbidity and mortality in patients with septic shock, while others state that it provides no additional changes in a patient's outcome. This literature review looks at patients in septic shock, and investigates the role of high dose vitamin C (HDVC) in reducing the rate of stage 3 acute kidney injury (AKI), intensive care unit (ICU) mortality, and hospital mortality.
Methods: Review of the literature was conducted to perform a meta-analysis of the available studies that compared the efficacy of HDVC to standard care or placebo in patients with septic shock. This search was performed using PubMed, Embase, and Cochrane from inception to April 20, 2021. We only considered randomized controlled trials (RCTs) for our analysis. The primary outcome was the incidence of stage 3 AKI. Secondary outcomes were ICU mortality, and hospital mortality. A p-value <0.05 was considered statistically significant.
Results: 9 RCTs involving 1503 patients were including in the meta-analysis. 5 studies reported the rate of stage 3 AKI, and it was not significantly lower in those receiving HDVC when compared to standard care/placebo (39.0% vs. 37.5%, RR 1.03, 95% CI 0.89-1.20, p= 0.68). The rates of ICU mortality and hospital mortality was not significantly lower in those receiving HDVC when compared to standard care/placebo.
Conclusions: Our meta-analysis demonstrates that the use of HDVC for patients with septic shock does not significantly reduce the rate of stage 3 AKI, ICU mortality, and hospital mortality.

Waleed Khokher (R)

The role of oral chlorhexidine gluconate in mechanically ventilated pediatric patients in reducing ventilator associated pneumonias: A systematic review and meta-analysis

W. Khokher, N. Kesireddy, S. Iftikhar, A. Beran, S. Ghazaleh, P. Mudiyanselage, M. Alom, M. Awad

Introduction: The use of oral chlorhexidine gluconate (CHG) in mechanically ventilated patients is a topic of debate. Some argue it decreases the risk of ventilator associated pneumonias (VAPs), while others argue that is provides no additional benefits and increases the risk of altering the oral bacterial flora. This literature review looks at the mechanically ventilated pediatric population, and investigates the role of oral CHG care in reducing VAPs, length of intubation, and length of pediatric intensive care unit (PICU) stay.
Methods: Review of literature was conducted to compare the efficacy of oral CHG versus standard care or placebo among mechanically ventilated pediatric patients. This search was performed using PubMed, Embase, and Cochrane from inception to April 20, 2021. We considered only randomized controlled trials (RCTs) for this study. The primary outcome was the occurrence of VAP. Secondary outcomes were length of intubation and length of PICU stay. A p-value <0.05 was considered statistically significant.
Results: 4 RCTs involving 398 patients were including in the meta-analysis. Three studies reported the rate of VAP among mechanically ventilated pediatric patients, the occurrence was not significantly lower in those receiving oral CHG when compared to standard care/placebo (21.8% vs. 19.6%, RR 1.12, 95% CI 0.75-1.69, p= 0.57). Length of intubation and PICU stay was found to be similar between patients receiving oral CHG or standard care/placebo.
Conclusions: Our meta-analysis demonstrates that the use of oral CHG for mechanically ventilated pediatric patients does not significantly reduce the rate of VAPs when compared to standard care/placebo.

Sadik Khuder (F)

In-hospital mortality at teaching vs. non-teaching hospitals

Sadik A. Khuder, Basil E. Akpunonu, Lance D. Dworkin

Objective: The purpose of this study was to investigate, if there is a difference in in-hospital mortality in teaching hospitals as compared to non-teaching hospitals.
Methods: We used the NIS (2017-2018). The primary endpoint analyzed was death during the hospitalization. Secondary outcomes included length of stay (LOS), total charges. Statistical analysis was performed using weighted chi-square, ANOVA, and logistic regression via the SAS software. Significance was set at p value of 0.05.
Results: A total of 13,189, 682 hospital admissions (69.6% teaching hospitals) between 2017-2018 were analyzed. The mortality rate in teaching hospitals was 2.15% compared to 1.94% in urban non-teaching hospitals and 1.95% in rural hospitals. DRG risk of mortality was lower in rural hospitals compared to urban hospitals. DRG severity of illness was significantly higher in teaching hospitals. The percentage of Medicaid patients was significantly higher in teaching hospitals. The adjusted mortality rate was significantly lower in urban compared to rural hospitals. Length of stay and total charges was significantly higher in urban hospitals.
Conclusions: Teaching hospitals have lower mortality as compared to rural hospitals and slightly higher as compared to urban non-teaching hospitals.

Mohammed Mhanna (R)

A case of Takotsubo cardiomyopathy triggered by diabetic ketoacidosis and hypothermia

Mohammed Mhanna MD, Azizullah Beran MD, Ahmed Elzanaty MD, Omar Srour MD, Omar Sajdeya MD, Robert Grande MD

Background: Takotsubo cardiomyopathy (TC), also recognized as stress-induced cardiomyopathy, is a transient condition of left ventricular (LV) dysfunction, which presents similarly to acute coronary syndrome (ACS), but with normal coronaries. Physical or emotional stressors usually precipitate TC. It is typically a benign condition with the complete resolution once the triggering cause resolves. There have been a few cases of TC induced by diabetic ketoacidosis (DKA) that have been reported in the literature.
Case Presentation: A 50-year-old Caucasian female patient presented with lethargy, in addition to hypothermia and hypotension. Further investigation showed hyperglycemia with metabolic acidosis and ketonemia. Eventually, she was diagnosed with diabetic ketoacidosis (DKA). On day 2 of the admission, the patient's condition further deteriorated despite appropriate treatment of DKA. An EKG showed ST-segment elevation in inferior leads, and troponin levels were elevated. Cardiac catheterization showed non-obstructive coronary arteries but severely reduced cardiac index. Echocardiography showed an ejection fraction (EF) of 25% with global hypokinetic LV. Eventually, the patient was diagnosed with TC or stress-induced cardiomyopathy.
Conclusion: TC should always be suspected in any patient presenting with acute heart failure during DKA treatment. TC is a transient syndrome. However, it can result in dreadful complications, including cardiogenic shock, arrhythmias, or thromboembolic events. Early recognition and timely treatment are pivotal in such cases.

Mohammed Mhanna (R)

Social, racial, and gender disparities in sepsis-related in-hospital mortality

Mohammed Mhanna MD, Sadik A. Khuder PhD, Azizullah Beran MD, Omar Srour MD, Lukken R. Imel MD, Aadil Maqsood MD, Danae Hamouda MD, Ragheb Assaly MD

Background: Sepsis is a leading cause of in-hospital mortality, affecting almost 2 million patients annually and contributing to almost 300,000 deaths each year in the United States. The aim of this study is to assess the impact of social, racial, and gender status on in-hospital mortality of sepsis using data from the National Inpatient Sample.
Methods: The data for hospitalizations with sepsis were queried from the Healthcare Cost and Utilization Project National Inpatient Sample (HCUP-NIS) 2017 database. The associations between age, gender, race, median household income, and sepsis related in-hospital mortality were examined using logistic regression.
Results: Of 197979 patients admitted with sepsis, the mean age was 65.9±17.3 years with 49.9% were women. In-hospital mortality was higher for men compared with women (odds ratio [OR]: 1.04; 95% confidence interval [CI]: 1.01 to 1.07; $p < 0.004$) as well as for African American (OR:1.21; 95% CI: 1.16-1.26; $p = 0.002$) compared with white race. Furthermore, elderly population (+70 years) had higher odds of mortality when compared to a younger population (OR:

1.40; 95% CI: 1.35-1.45; p=< 0.0001). Medium household income was associated with significant lower mortality when compared to high income, however, this measure was based on patient ZIP Code (ZIPINC_QRTL classification).
Conclusions: There are significant social, racial, and sex differences in sepsis related in-hospital mortality. Men, as well as African American patients have a higher likelihood of death. Such observation of social disparities in sepsis related mortality should warrant further consideration, as well as integration, for future sepsis policies at the national level.

Mohammed Mhanna (R)

Single versus dual antiplatelet therapy following left atrial appendage occlusion in patients with high bleeding risk

Mohammed Mhanna MD, Azizullah Beran MD, Hazem Ayesh MD, MPH, Ziad Abuhelwa MD, Waleed Abdulsattar MD, Ehab A Eltahawy MD, MPH

Introduction: Left atrial appendage occlusion (LAAO) is an alternative therapy to prevent stroke in atrial fibrillation patients who are at high risk of bleeding. A short-term postprocedural antiplatelet therapy (APT) is recommended to prevent device-related thrombus. However, the optimal APT strategy following LAAO in patients who cannot tolerate OAC is debatable
Method: An extensive literature search of multiple databases was conducted to include all published studies that compared the use of SAPT with DAPT following LAAO in patients in whom OAC was deemed high-risk or contraindicated. The outcomes were device-related thrombosis (DRT), stroke and systemic embolization (SSE), and major bleeding (MB). A random-effects model was used to generate the risk difference (RD) and accompanying 95% confidence intervals (CI).
Results: A total of 14 observational studies (SAPT, n=1034; DAPT, n=2,117; 64.5% men; median follow-up duration 12 months; mean age 74.7±8.5 years; mean CHA2DS2-VASc score 4.3±1.6; mean HAS-BLED score 3.2±1.2) were included. There was no difference between SAPT and DAPT groups (RD: 0.01; 95%CI: 0.00-0.02; P=0.13; I2=0%). SSE was higher in SAPT compared to DAPT, but no statistically significant difference was found (RD: 0.00; 95% CI: -.0.02, 0.02; P=0.97; I2=0%). MB was with DAPT but there was no statistically significant difference between the two groups (RD: -0.01; 95%CI: -0.03, 0.01; P=0.48; I2=19%).
Conclusions: Our study shows that SAPT and DAPT following LAAO have a similar safety and efficacy profile in patients at high bleeding risk. Large scale Randomized Controlled Studies are warranted to validate and test if our results could be translated into the clinical practice.

Mohammed Mhanna (R)

Lung-ultrasound guided management to reduce hospitalization in chronic heart failure: a systematic review and meta-analysis

Mohammed Mhanna MD, Azizullah Beran MD, Salik Nazir MD, Omar Sajdeya MD, Omar Srour MD, Hazem Ayesh MD, MPH, Ehab A Eltahawy MD, MPH

Introduction: Pulmonary edema is a leading cause of hospital admissions, morbidity, and mortality in heart failure (HF) patients. A point-of-care lung ultrasound (LUS) is a useful tool to detect subclinical pulmonary edema.
Method: We performed a comprehensive literature search of multiple databases for studies that evaluated the clinical utility of LUS-guided management versus standard care for HF patients in the outpatient setting. The primary outcome of interest was HF hospitalization. The secondary outcomes were all-cause mortality, urgent visits for HF worsening, acute kidney injury (AKI), and hypokalemia rates. Pooled risk ratio (RR) and corresponding 95% confidence intervals (CIs) were calculated and combined using random effects model meta-analysis.
Results: A total of 3 randomized controlled trials including 493 HF patients managed in outpatient setting (251 managed with LUS plus physical examination (PE)-guided therapy vs. 242 managed with PE-guided therapy alone) were included in the final analysis. The mean follow-up period was 5 months. There was no significant difference in HF hospitalization rate between the two groups (RR:0.65; 95% CI:0.34-1.22; *P*=0.18). Similarly, there was no significant difference in all-cause mortality (RR:1.39; 95% CI:0.68-2.82; *P*=0.37), AKI (RR:1.27; 95% CI:0.60-2.69; *P*=0.52), and hypokalemia (RR:0.72; 95% CI:0.21-2.44; *P*=0.59). However, LUS-guided therapy was associated with lower rate for urgent care visits (RR: 0.32; 95% CI: 0.18- 0.59; *P* = 0.0002).
Conclusions: Our study demonstrated that outpatient LUS-guided diuretic therapy of pulmonary congestion reduces urgent visits for worsening symptoms of HF. Further studies are needed to evaluate LUS utility in the outpatient treatment of HF.

Mohammed Mhanna (R)

Ivermectin for treatment of SARS-CoV-2 infection: A systematic review and meta-analysis of randomized clinical trial studies

Mohammed Mhanna MD, Sadik A. Khuder PhD, Azizullah Beran MD, Omar Srour MD, Ragheb Assaly MD

Introduction: Ivermectin has a broad antiviral activity. This study aims to investigate the utility of Ivermectin for SARS-CoV-2 infection.
Method: Multiple databases were searched for randomized clinical trials (RCTs) that evaluated the clinical efficacy of Ivermectin for SARS-CoV-2 infection. The primary outcome was all-cause mortality. The secondary outcomes were negative RT-PCR test results rate, time to negative RT-PCR test results, and time to hospital discharge. Pooled relative risk (RR) or the mean difference (MD) and corresponding 95% confidence intervals (CIs) were calculated and combined using a random-effects model.
Results: A total of 10 RCTs, including 1,491 COVID-19 patients (686 managed with Ivermectin vs. 805 managed with SOC) were included. There was no significant difference in all-cause mortality rate between the two groups (RR:0.87; 95%CI: 0.56-1.35; P=0.54). Similarly, there was no significant difference in conversation rate to negative RT-PCR test (RR:1.72, 95%CI: 0.79-3.77, P=0.17). However, Ivermectin therapy was associated with shorter time to achieve negative RT-PCR test (MD, days: - 2.31; 95%CI: -4.27, -0.35; P=0.02) and shorter hospital stay (MD, days: - 1.33; 95%CI: -1.59, -1.08; P< 0.001).
Conclusions: Our study demonstrated that despite no effect on mortality, Ivermectin was associated with shorter hospital stay and time to negative RT-PCR test. Further studies are required to evaluate the role of Ivermectin in reducing COVID-19 transmissibility.

Mohammed Mhanna (R)

Distal versus Conventional Transradial Access for Coronary Angiography and Intervention: A Systematic Review and Meta-Analysis

Mohammed Mhanna MD, Azizullah Beran MD, Salik Nazir MD, Ahmad Al-Abdouh MD, Mahmoud Barbarawi MD, Omar Sajdeya MD, Omar Srour MD, Cameron Burmeister MD, Saif-Eddin Malhas MD, Ehab A Eltahawy MD, MPH

Introduction: Distal transradial artery access (DTRA) has recently gained attention due to potential benefits in terms of local complications. In this meta-analysis, we aimed to evaluate the utility of DTRA compared to conventional transradial artery access (CTRA) for coronary angiography and intervention.
Method: Multiple databases were searched from inception through February,2021 for all the studies that evaluated the efficacy and safety of DTRA in the coronary field. The primary outcome of interest was the access success rate. The secondary outcomes were periprocedural local complications (site hematoma, radial artery occlusion or spasm) and procedural characteristics (cannulation, fluoroscopy, and radial artery compression times). All meta-analyses were conducted using a random-effect model.
Results: A total of 8 studies (including three randomized control trials) with 805 patients who underwent DTRA vs. 825 with CTRA, were included in the final analysis. The access success rate was similar in the two groups (odds ratio (OR):0.61; 95% confidence interval (CI):0.18-2.09; P=0.43; I2=72 %). Similarly, no difference was observed in the overall periprocedural local complications rate (OR:0.63, 95% CI:0.38-1.04, P = 0.07, I2=25%). On subgroup analysis, the rate of radial artery occlusion was significantly lower in DRTA group (OR 0.33, 95% CI 0.13-0.82, P = 0.02, I2=0%). Regarding the procedural characteristics, the two approaches were different only in the cannulation time favoring the CTRA group (mean difference (min.) [MD] 0.96, 95% CI 0.16-1.76; P=0.02).
Conclusions: Our meta-analysis demonstrates that the DTRA is effective and safe with statistical superiority in preventing radial artery occlusion when compared to CTRA.

Mohammed Mhanna (R)

Direct oral anticoagulants versus warfarin in morbidly obese patients with non-valvular atrial fibrillation: A systematic review and meta-analysis

Mohammed Mhanna MD, Azizullah Beran MD, Ahmad Al-Abdouh MD, Omar Sajdeya MD, Waleed Abdulsattar MD, Omar Srour MD, Hazem Ayesh MD, MPH, Modar Alom MD, Sadik A. Khuder PhD, Danae Hamouda MD, Ragheb Assaly MD

Introduction: Direct oral anticoagulants (DOACs) have been increasingly preferred over warfarin; however, The International Society of Thrombosis and Hemostasis recommended avoiding the use of DOACs in morbidly obese patients (BMI > 40 or weight > 120 kg) because of limited clinical data.
Method: We performed a comprehensive search for multiple databased for studies that evaluated the efficacy and safety of DOACs in morbidly obese patients with NVAF. The primary outcome of interest was stroke or systemic embolism (SSE) rate. The secondary outcome was major bleeding (MB).
Results: A total of 10 studies including, 89,494 morbidly obese patients with NVAF on oral anticoagulation therapy (45427 on DOACs vs. 44067 on warfarin), were included in the final analysis. The SSE rate was significantly lower in DOACs group compared to warfarin group (odds ratio (OR): 0.71; 95% confidence interval (CI): 0.62, 0.81; $p < 0.0001$; $I2 = 0$ %). MB rate was also significantly lower in DOACs group compared to the warfarin group (OR 0.60, 95% CI 0.46-0.78, $P < 0.0001$, $I2 = 86\%$). On subgroup analysis, SSE and MB event rates were significantly lower in rivaroxaban and apixaban than warfarin; however, dabigatran showed non-inferiority to warfarin in SSE rate but superiority in the safety outcome.
Conclusions: Our meta-analysis demonstrated that DOACs are effective and safe with statistical superiority when compared to warfarin in morbidly obese patients. Large-scale randomized clinical trials are needed to further evaluate the efficacy and safety of DOACs in this cohort of patients.

Mohammed Mhanna (R)

Social, racial, and gender disparities in cardiovascular disease-related in-hospital mortality

Mohammed Mhanna MD, Azizullah Beran MD, Sadik A. Khuder PhD, Omar Srou MD, Omar Sajdeya MD, Hazem Ayesh MD, MPH, Ehab A. Eltahawy MD, MPH, Ragheb Assaly MD

Introduction: Cardiovascular diseases (CVD) including coronary artery disease (CAD), myocardial infarction (MI), and heart failure (HF) are the leading causes of mortality for men, women, and people of most racial groups in the United States. Each 36 seconds, one person in the US dies from CVD, yielding 655,000 deaths annually. The aim of this study is to assess the impact of social, racial, and gender status on in-hospital mortality of CVD using data from the National Inpatient Sample.
Methods: The data for hospitalizations with CAD, MI, and HF were queried from the Healthcare Cost and Utilization Project National Inpatient Sample (HCUP-NIS) 2017 database. The associations between age, gender, race, and CVD related in-hospital mortality were examined using logistic regression.
Results: Of 997870 patients admitted with CVD, the mean age was 71.7±13.0 years with 54.5% were women. In-hospital mortality was higher for male compared with female (odds ratio [OR]: 1.04; 95% confidence interval [CI]: 1.02 to 1.06; $p < 0.001$) as well as for minority races (OR: 1.06; 95% CI: 1.01 to 1.10; $p < 0.0001$) compared with white race. Furthermore, elderly population (+70 years) had higher odds of mortality when compared to a younger population (OR: 1.54; 95% CI: 1.49 to 1.58; $p < 0.0001$).
Conclusions: There are significant social, racial, and sex differences in cardiovascular diseases related in-hospital mortality. Males and minority races patients have a higher likelihood of death. Such observation of social disparities should warrant personalized assessments and innovative prevention and treatment strategies focusing on these populations with a higher risk.

Mohammed Mhanna (R)

Efficacy and safety of direct oral anticoagulants versus low molecular weight heparin in cancer-associated venous thromboembolism: A systematic review and meta analysis

Mohammed Mhanna MD, Azizullah Beran MD, Omar Sajdeya MD, Omar Srour MD, Hazem Ayesh MD, Ehab E. Eltahawy MD

Introduction: Low molecular weight heparin (LMWH) is considered as the mainstay treatment for cancer associated venous thromboembolism (CA-VTE). However, recent studies showed a promising role of direct oral anticoagulants (DOAC) in the management of VTE in cancer patients.
Method: We performed a comprehensive literature search using multiple databases for all the studies that evaluated the efficacy and safety of DOACs in CA-VTE. The primary outcomes of interest were VTE recurrence and major bleeding (MB) at 6 months. The secondary outcomes were clinically relevant non-major bleeding (CRNMB) and all cause-mortality. Pooled relative risk (RR) and 95% confidence intervals (CIs) were obtained.
Results: A total of 6 studies (4 randomized controlled trials and 2 cohort studies) including 3715 cancer patients with VTE (1881 on DOACs vs. 1834 on LMWH) were included. The risk of VTE recurrence was significantly lower in DOACs

group compared to LMWH group (RR: 0.60; 95% confidence interval (CI): 0.42, 0.86; $P = 0.006$; $I^2 = 44$ %). There was no statistically significant difference between DOACs and LMWH in major bleeding events (RR: 1.23; 95% CI: 0.92, 1.65; $P = 0.17$; $I^2 = 0\%$). The incidence of all-cause mortality was similar between the two groups (RR: 0.95; 95% CI: 0.83, 1.09; $P = 0.45$; $I^2 = 44\%$). However, there was a significant increase in CRNMB among DOACs group (RR: 1.53; 95% CI: 1.13, 2.08; $P = 0.006$; $I^2 = 33\%$).
Conclusions: Our meta-analysis demonstrated that DOACs are superior to LMWH in preventing CA-VTE recurrence. However, the risk of CRNMB is increased with DOACs.

Mohammed Mhanna (R)
Dexamethasone for cocaine-induced Cardio-auditory Syndrome
Mohammed Mhanna MD, Azizullah Beran MD, Omar Sajdeya MD, Adam T Mierzwa MD, Nicholas G Horen MD, FACP, Ragheb Assaly MD
Background: Cocaine use is associated with various cardiovascular complications including long QT syndrome (LQTS), which is associated with an increased risk of torsades de pointes and potentially sudden cardiac death. Furthermore, acute-onset hearing loss following cocaine abuse is infrequent, and sensorineural hearing loss (SNHL) with cocaine use has been described only in a few reports.
Case presentation: A 28-year-old male patient with no significant past medical history presented to the emergency department with sudden bilateral hearing loss. The patient admitted consuming cocaine intravenously the day before symptom onset. Bedside Weber and Rinne tests disclosed profound bilateral SNHL with no other focal neurological deficits. Urine drug screen tested positive for cocaine. EKG showed normal sinus rhythm but a prolonged QTc of 521 ms. Initial workup with basic metabolic profile, HIV, and thyroid-stimulating hormone all were within normal limits. Patient was started on oral dexamethasone (10 mg daily), his hearing loss dramatically improved within 24 hours of admission and ultimately resolved after day 3 of hospitalization. Repeat EKG on day 3 showed QT interval normalization with a QTc of 420. The patient was discharged home with no reportable complications on a 14-day tapering dose of oral dexamethasone.
Conclusion: To the best of our knowledge, this is the first report in the literature to describe the simultaneous cardio-auditory adverse effects of acute cocaine intoxication. In our case, dexamethasone successfully eliminated the patient's hearing loss and normalized the QT interval. Our case would add more insight into the potential role of glucocorticoids in the treatment of LQTS.

Scott Pappada (F)
Development of a Novel Machine Learning-based Sepsis Risk Index for use in an Intelligent Antibiotic Decision Support System for the Hospital/Critical Care Setting
Scott Pappada, PhD; Brian Hinch, MD

Background: Appropriate antibiotic therapy is critical to patient outcomes for both civilian and military patients. A significant challenge facing healthcare providers (HCPs) is early detection and diagnosis of sepsis and septic shock. This is especially important when treating military combat casualties in future prolonged field care and/or austere environments. Critically ill patients experience significant organ dysfunction and early signs/symptoms of sepsis and/or septic shock may be difficult to detect. Several diagnostic criteria and guidelines for sepsis/septic shock have been promulgated over the years, including system inflammatory response syndrome (SIRS) criteria, and more recently, Sepsis-3 guidelines, which serve to support these diagnoses based on changes in Sequential Organ Failure Assessment (SOFA) scores. The optimization of antibiotic therapy in terms of timing, dosing, and appropriate antibiotic selection for a given infection source/organism are extremely important. Previous studies have shown that there is a significant increase in mortality with as little as a single hour delay in the initiation of antibiotic therapy. To address these challenges our team is developing a novel clinical decision support system (CDSS) to assist healthcare providers in optimizing antibiotic therapy in critical care settings. This CDSS consists of a set of machine learning-based models intended to support HCPs in optimizing preventive and directive antibiotic therapy. These models and algorithms serve to generate a Sepsis Risk Index (SRI), which is predictive of the onset of sepsis and septic shock. The CDSS generates alerts for HCPs that prompt consideration of antibiotic initiation.
Methods: The CDSS uses multiple machine-learning models that operate in tandem to generate a SRI ranging from 0 to 100 (with 100 having the highest probability or risk of a patient developing sepsis). Machine learning models are well suited to identify patterns and trends in data that are not readily detectable by healthcare professionals. The first set of machine learning models used to derive the SRI are predictive models designed to forecast a complete trajectory of changes in key patient vital signs that include heart rate, systolic blood pressure, and mean arterial pressure. The

predictive model output is rate of change in a patient's vital signs over the course of the next three hours. The output of the predictive model is leveraged as an input to the second machine learning model which serves to generate an output between 0 to 1 which represents the overall risk for or probability of sepsis. Both machine learning models are designed as multilayer perceptrons (MLPs), a specific class of feedforward artificial neural network. The model inputs include: vital signs, laboratory results, and certain medications (e.g. vasopressors). The SRI model inputs included: vital signs, medications, lab results, and a continuous SOFA score derived by an algorithm that queries required electronic medical record (EMR) data for its calculation. The model uses a sigmoid transfer function to constrain/normalize model inputs and outputs to a range of 0 to 1. Results are then multiplied by 100 to scale the SRI output between 0-100. SRI values closer to 0 indicate the patient is not trending towards a sepsis/septic shock state, and values closer to 100 indicate a higher probability that the patient is in a sepsis/septic shock state or trending towards one. The model output is used to represent a class membership either with or without sepsis. When the SRI exceeds a threshold of 50 (higher probability of sepsis/septic shock versus not) the CDSS generates an alert.
The MIMIC-III (Medical Information Mart for Intensive Care III) database was used to develop the aforementioned machine learning-based models. This database consists of over 45,000 critical care patients admitted from the ICUs of the Beth Israel Deaconess Medical Center from 2001-2012. Model training sets were generated for each MLP using a custom software application. To develop the continuous value for sepsis and septic shock diagnosis (i.e. target model output) for the training set, patient data was evaluated every hour with respect to a modified SIRS criteria if patients had a ICD-9 diagnosis of sepsis or septic shock during their intensive care unit (ICU) stay. Our modified SIRS criteria were met if a patient met > three SIRS criteria previously defined by the Surviving Sepsis Campaign. If patients met this modified criteria, as well as having been diagnosed with sepsis or septic shock, a "1" was used as the target model output at each time stamp this condition held true throughout the patient's ICU stay. Where this condition was not true, a "0" was used as the target or desired model output at each corresponding time stamp.
To assess model accuracy, we used a completely independent dataset the eICU Collaborative Research Database. This database includes time stamped ICD-9 diagnoses of sepsis and septic shock, and provided the ability to evaluate the accuracy of developed models in the detection and prediction of sepsis/septic shock. The models were validated using 35,721 patients with 1,036 of these patients having a positive sepsis or septic shock diagnosis. Patients were eliminated from the validation/testing set if the diagnosis was less than four hours from ICU admission (i.e. preexisting diagnosis). Sensitivity and specificity of the SRI was evaluated using a static threshold of 50. The area under a receiver operating characteristic curve (AUROC) was generated to evaluate diagnostic capabilities. Additionally, the predictive capacity of the index (% of patients where the SRI alerted before diagnosis) was calculated.
Results: The SRI effectively assisted in sepsis/septic shock Dx and predicted onset amongst a significant proportion of patients present in the eICU dataset. The SRI achieved a TPR and SPC of 0.79 and 0.73 respectively for sepsis diagnoses. Conversely, the SRI achieved a higher TPR and SPC of 0.86 and 0.77 respectively for septic shock diagnoses. The AUROC curve for sepsis and septic shock diagnoses was 0.84 and 0.87, respectively. The SRI successfully predicted sepsis and septic shock in 62.5% and 73.9% of the patients in each subgroup (N = 293 and N = 498), respectively. For the entire dataset, when sepsis onset was predicted, the SRI alerted an average of 42.2 hours before Dx compared to 37.4 hours before Dx of septic shock as indicated by ICD-9 code time stamps. The distribution of predicted Dx times was non-Gaussian, and as such a better measures of performance included the interquartile range (IQR) and median lead Dx times. For sepsis the IQR was [7 to 51] with a median lead Dx time of 17 hours whereas the IQR for septic shock was [6 to 45] with a median lead Dx time of 16 hours.
Conclusions: Our results demonstrate the accuracy and applicability of our model in real-world ICUs. The validation set was independent of the data used to develop the models used and is representative of the proportion of patients that acquired sepsis/septic shock during their ICU stay across a 35,000+ patient population. The Toledo Hospital. Future research includes CDSS evaluation and validation at these centers. We have integrated a CDSS software application into the EMR in the ICU of UTMC that generates alerts based on the model-generated SRI which will be subject of future investigation and research.

Tia Rahman (MS)
Use of clobazam monotherapy to treat refractory generalized seizures in a patient with variant of ITPA gene
Tia Rahman, Ajaz Sheikh, Naeem Mahfooz

Introduction: We present the case of a 4-year old male with ITPA gene variant of unknown significance, c323A>G (p.Glu108Gly), which has thus far not been correlated to medically refractory epilepsy in a developmentally normal child having significant response to clobazam therapy.
Method: Case report.

Results: A four-year-old male, who has a strong maternal family history of epilepsy, initially had complex febrile seizures at age 3 years with generalized shaking, unresponsiveness, and respiratory arrest requiring CPR. His subsequent seizures were staring spells with unresponsiveness. Afebrile seizures started at age 4 as similar unresponsive staring spells lasting 2 to 120 sec. Interictal EEG showed generalized spike/polyspike and waves discharges that intermittently evolved into generalized electrographic seizures. His seizures were refractory to combinations of various anti-epileptic medications, including levetiracetam (up to 500mg/day – behavior issues), lamotrigine (100mg/day - rash), valproic acid (up to 250mg/day - insomnia), and topiramate (50mg/day – burning of throat). He finally responded to clobazam (10 mg/day) which reduced seizures from 2-6/hour to 2-3/week and normalized his routine EEG. An epilepsy genetic panel (INVITAE™) showed ITPA gene heterozygous variant of unknown significance, c323A>G (p.Glu108Gly).
Conclusion: ITPA gene mutations have been associated with severe encephalopathy with epilepsy, microcephaly, dilated cardiomyopathy, developmental retardation, and early death. However, our patient with heterozygous variant c323A>G (p.Glu108Gly) is developmentally normal with generalized seizures. He exemplifies a unique case of a significant response to clobazam monotherapy, which may be related to the genetic component of his epilepsy. Additionally, his case suggests that the ITPA mutation is likely to be clinically significant.

Brian Rao (MS)
Systematic review of the surgical outcomes of interprosthetic femur fractures
Brian Rao (Medical Student); Jiayong Liu, MD

Introduction: Interprosthetic femur fractures (IFFs) are a rare but debilitating diagnosis, and the treatment is challenging. Currently, there are many treatment methods utilized, but comparison of these different surgical outcomes has not been thoroughly investigated. The purpose of this study was to compare outcomes of different IFF treatment methods and to determine which has the most favorable outcomes.
Methods: A systematic review of retrospective studies was conducted. The research databases of PubMed, Cochrane, and Embase were searched using a combination of the keywords involving IFFs and surgical outcomes. Research articles from inception through June 2021 that included IFF treatments and outcomes were included in the review. Data collected included patient demographics, intraoperative data, and postoperative outcomes. Functional scores and healing times were also recorded when available. Statistical analysis was performed to compare data between different treatment groups using a significant p-value of 0.05.
Results: Forty studies were included for review with a total of 508 patients. Union rates were highest in the plate + nail/rod and plate + prosthetic revision groups with each having 100% union rates. The femur replacement group had the lowest union rate of 50%. The Ilizarov external fixator method proved to be a viable option with few complications, low healing time, and high union rates.
Conclusion: Each treatment method should be carefully considered by the surgeon depending on the patient. However, the Ilizarov external fixator method proved to be favorable, although more research needs be done with larger population sizes in for further comparison and analyses.

Hadeel Rushdi (R)
Mesenteric mesothelial cyst a relatively rare complication of peritoneal dialysis and intra-abdominal surgical sequel, case presentation
Hadeel I Rushdi MD, Raied T Hufdhi MD, Ziad Abuhelwa MD, Kirubel Zerihun MD, Ahmed Abdelrahman MD, Joanna Kilbane Myers, Casey Ryan, Andrew Jessen, Basil E Akpunonu MD

Introduction: Mesenteric mesothelial cysts are relatively rare intra-abdominal lesions that are often asymptomatic, they can be multiple and variable in sizes even in the same individual. Often identified incidentally on radiological studies for intra-abdominal symptoms. Some can be infected and show various inflammatory changes. We present a case of a patient with multiple cysts in which simultaneous sampling of different lesions yielded a sterile result and heavy growth of MRSA pointing to need for multiple sampling.
Case presentation: A 33-year-old African American male with past medical history of ESRD post renal transplant currently on hemodialysis. Presented with shortness of breath, cough, mild abdominal discomfort. He reported missing last two hemodialysis session, vitals on presentation were only remarkable for hypertension (SBP156) and pulse of 102, on physical exam a positive JVD and HJR was noted with normal first and second heart sounds, S4 gallop noted. Abdomen was distended and a palpable mass in the epigastrium. Lab work was remarkable for Hgb 7.1, normal WBC, elevated procalcitonin, Cr of 10.88 and BUN of 50. Abdominal ultrasound showed 4 complex cystic lesions with loculation and septation of varying degrees, two in midline (epigastric) with one measuring 10.5 X 8.6X 9.2and another 2

in the left flank with largest measuring 15.4X 5.4 x 5.0. Bilateral atrophic native kidneys and transplanted kidney were noted. Aspiration of the midline epigastric lesion yielded 40cc of blood-tinged material with 257962 RBC, 318 nucleated cells, 20% lymphocytes, 28% neutrophils and mesothelial cells and core biopsy was unsuccessful while left upper quadrant cyst yielded 300cc of amber fluid with >25 WBC, many gram positive and heavy growth of MRSA. Intravenous Vancomycin was given with significant improvement of the culprit lesions on repeat CT abdomen.
Discussion: Mesenteric mesothelial cysts can be located anywhere in the abdomen. They may result from trauma, lymphatic malformation or infection. Rare complications may include infection, obstruction, rupture or torsion. Presenting symptoms include abdominal pain, heaviness and other nonspecific symptoms. The cysts can be single, multiple, simple, loculated or septated and complex in character with varying sizes and can contain serous, bloody and chylous and infected materials. The exact etiology has never been fully elucidated but lymphatic drainage failure and inflammatory processes have been postulated. Imaging modalities include ultrasonography, computed tomographic studies and magnetic resonance imaging. Diagnostic aspiration studies help in tailoring treatment and while surgery is felt to be the gold standard for treatment, care must be exercised to avoid other organ perforation that may occur with adherent tissues. In this case we believe that the cysts were complications of previous peritoneal dialysis treatments and peritonitis and recommend synchronous sampling of multiple cysts since benign and infected cysts can coexist.

Omar Sajdeya (R)

Racial differences in hypercholesterolemia prevalence: A cross-sectional study using 2017-2018 national health and nutrition examination survey data

Omar Sajdeya, MD; Ruba Sajdeya, MD; Mohamad B Taha, MD; Mohammad As Sayaideh, MD; Osama Dasa, MD, MPH

Introduction: African Americans (AA) have a 20% higher risk of CVD death than Whites. Treating hypercholesterolemia (HCL) is paramount in CVD primary prevention. Some evidence showed that AA have a lower risk of HCL compared to whites.
Methods: A cross-sectional study using the 2017-18 National Health and Nutrition Examination Survey data. Logistic regression analysis was used to compare the prevalence of diagnosed HCL in AA and whites aged 18-80 years old. Serum total cholesterol (TC) and high-density lipoprotein (HDL) levels were compared by multiple linear regression.
Results: Among 2549 participants, 51.7% were females, and 63.4% were white. The mean (SD) age was 51.6 (19.1) years. AA had a 24 % reduced risk of HCL diagnosis than whites after adjusting for age, Body Mass Index (BMI), diabetes, hypertension, and smoking; OR [95%CI]= 0.767 [0.621, 0.923]. There was no difference in TC level ($p=0.7242$), while HDL was higher among AA ($p<0.0001$, $\beta=3.83$), adjusting for age, gender, BMI, smoking, diabetes, education level, and use of cholesterol medications.
Conclusion: Consistent with some evidence, AA had a lower prevalence of HCL diagnosis and higher HDL levels.

Omar Sajdeya (R)

Efficacy and safety of intravascular lithotripsy in the treatment of calcified peripheral artery disease: a systematic review and meta-analysis

Omar Sajdeya, Mohammed Mhanna, Pinang Shastri, Cameron Burmeister, Jeremy Tomcho, Mitra Patel, Ahmed Elzanaty, Sapan Bhuta, Neha Patel, Sami Ghazaleh, Azizullah Beran

Background: Intravascular lithotripsy (IVL) is a novel endovascular calcified peripheral artery disease (PAD) therapy technique. However, data regarding its clinical utility for PAD remain sparse. We aimed to evaluate the safety and efficacy of IVL in managing calcified PAD.
Methods: We performed a comprehensive literature search, using PubMed and Embase databases through November 2020, to identify studies evaluating the clinical outcomes of IVL use in the management of calcified PAD. The primary outcomes were the IVL delivery success rate, the pooled mean of acute lumen gain, minimal lumen diameter (MLD), and residual stenosis. Secondary outcomes were 30- day major adverse effects (MAEs), including dissection, perforation, thrombus formation, and distal embolization rates. Meta-analyses were conducted using a random-effect model.
Results: Seven studies, including 503 patients with 605 lesions who underwent IVL for calcified PAD, were included. The IVL success rate was 99.6% (95% CI: 0.991-1.002), while the pooled mean acute lumen gain was 2.745 mm (95% CI: 1.826-3.664), and minimal diameter (MLD) was 4.017 (95% CI: 2.910-5.123). Mean residual stenosis (MRS) was 21.737 mm (95% CI: 17.749-25.724). 30-day MAE rate was 0.018 (95% CI: -0.002-0.038), including dissection rate of 0.03 (95% CI: -0.003-0.047) and perforation rate of 0.004 (95% CI: -0.001-0.009). No studies reported embolization or thrombus formation.

Conclusion: IVL is an effective and safe technique in managing calcified PAD, achieving significant improvement of acute lumen gain and low 30-day MAEs. However, further studies with large sample sizes are needed to determine the long-term efficacy and safety of IVL in PAD.

HEMATOLOGY/ONCOLOGY

James William Antonisamy (RF)

IQGAP1 Control of Centrosome Division Defines Distinct Variants of Triple Negative Breast Cancer

William James Antonisamy, Samhitha Dasari, Rawan Moussa, Joseph Granata and Mahasin Osman

Triple negative breast cancer (TNBC) is a heterogenous and lethal disease that lacks diagnostic markers and therapeutic targets; as such common targets are highly sought after. IQGAP1 is a signaling scaffold implicated in TNBC but its mechanism is unknown. Here we show that IQGAP1 localizes to the centrosome, interacts with and controls expression level and localization of key centrosome proteins like BRCA1 and thus regulates centrosome division. Genetic mutant analyses reveal that phosphorylation of IQGAP1 regulates its subcellular localization and centrosome-nuclear shuttling of BRCA1; dysfunction of this process defines distinct mechanisms associated with cell proliferation. TNBC cell lines and patient tumor tissues phenocopy these mechanisms supporting clinical existence of molecularly distinct variants of TNBC defined by IQGAP1 pathways. These variants are defined, at least in part, by differential mis-localization of IQGAP1-BRCA1 and activation of a novel Erk1/2-MNK1-JNK-Akt-β-catenin signaling signature. We discuss a model in which IQGAP1 modulates centrosome-nuclear crosstalk to regulate cell division. Our data provides molecular tools for classification of TNBC and present IQGAP1 as a common target amenable to personalized medicine.

Luis Cedeño-Rosario (GS)

Regulation of MLK3 and JNK during ovarian cancer cell cycle progression

Luis Cedeño-Rosario; David Honda; Autumn Sunderland; William R. Taylor, PhD; Deborah N. Chadee, PhD

Mixed lineage kinase 3 (MLK3) is a serine/threonine MAP3K that promotes the activation of multiple mitogen-activated protein kinase pathways, and is required for invasion and proliferation of ovarian cancer cells. Often, ovarian cancer patients are diagnosed when ovarian cancer is in the late stages and treatment options are limited. Therefore, understanding the molecular mechanisms that cause aberrant division of ovarian cancer cells will give us insights to create novel cancer therapies. It has been demonstrated that inhibition of MLK activity causes G2/M arrest in HeLa cells; however, the regulation of MLK3 during ovarian cancer cell cycle progression is not known. We hypothesize that a Cyclin-dependent kinase (CDK) regulates MLK3 during ovarian cancer cell division. We found that MLK3 is phosphorylated in mitosis and that inhibition of CDK1 prevented MLK3 phosphorylation. In addition, we observed that c-Jun N-terminal Kinase (JNK), a downstream target of MLK3, was activated in G2 when CDK2 activity is increased and then inactivated at the beginning of mitosis concurrent with the increase in CDK1 and MLK3 phosphorylation. Furthermore, we discovered that CDK1 phosphorylates MLK3 in vitro on Ser^{548}, and CDK2 phosphorylates MLK3 in vitro on Ser^{770}. We also found that MLK3 inhibition causes a G1 arrest in ovarian cancer cells but not in normal ovarian epithelial cells, suggesting that MLK3 is required for ovarian cancer cell cycle progression. Taken together, we propose a model where phosphorylation of MLK3 by CDK1 and CDK2 during G2 and M regulate MLK3/JNK activity and proper G2/M transition in ovarian cancer cells.

Justin Creeden (GS)

PDX1-BIRC5 Axis in Pancreatic Ductal Adenocarcinoma

J. F. Creeden, Zach N. Herron, S. Liu, T. D. Hinds, I. de la Serna, R. Trumbly, F. C. Brunicardi, R. McCullumsmith

Introduction: The majority of pancreatic ductal adenocarcinoma (PDAC) patients display significantly increased levels of the anti-apoptotic protein BIRC5 (also called survivin). BIRC5 has been identified as a potential anti-cancer therapeutic target. Targeting BIRC5 proteins directly remains problematic. Instead, BIRC5 may be indirectly targeted by modulating the activity of its transcription factors. Preliminary data suggest a novel relationship between the transcription factor pancreas/duodenum homeobox protein 1 (PDX1) and BIRC5 gene regulation.
Methods: Bioinformatic query, *in-vivo* genetic engineering, chromatin immunoprecipitation (ChIP), real-time quantitative polymerase chain reaction (RT-qPCR).

Results: ChIP-PCR assays using pancreatic ductal adenocarcinoma cells constitutively overexpressing PDX1 demonstrate direct binding between the transcription factor protein PDX1 and bioinformatically-predicted PDX1 binding motifs within the BIRC5 gene and its upstream 5' untranslated region.
Conclusions: The PDX1-BIRC5 axis may provide insight into the development of more effective BIRC5 inhibitors and improved PDAC treatment outcomes. Furthermore, the PDX1-BIRC5 axis is a potential new source of information concerning PDX1's role as an oncogenic transcription factor.

Monika Devanaboyina (MS)

A retrospective study of characteristics and survival in patients with breast cancer brain metastases classified by subtype using NCI SEER registry.

Monika Devanaboyina B.S., Morgan Marie Bailey B.S., Danae M. Hamouda M.D.
Introduction: Breast cancer brain metastasis (BCBM) de novo is associated with the worst prognosis among all metastases in breast cancer (BC) and earlier identification of metastasis could improve survival.
Methods: 1,268 patients with BCBM at diagnosis and known subtype who were ≥20 years of age from 2010-2017 were identified using the NCI's Surveillance, Epidemiology, and End Results (SEER) registry. Chi-Square and Kaplan-Meier analyses were used for baseline characteristics and survival.
Results: Patients with HR-/HER2+ BC were most likely to present with BCBM compared to all BC patients (prevalence of 13.9% vs. 4.7%; $p<0.001$). Further analysis demonstrated that HER2+ patients had an odds ratio of 2.52 (95% CI: 2.24-2.84) of presenting with BCBM compared to HER2- patients. In patients ages 20-39 with HR-/HER2+ BC, higher rates of brain metastases are noted within the BCBM group compared to all HR-/HER2+ BC cases (28% vs. 7.6%; $p<0.001$). This trend is observed within HR-/HER2+ African Americans (14.3% vs. 5.9%; $p<0.001$) and uninsured BCBM patients (14.8% vs. 6.4%; $p=0.001$) showing higher rates of brain metastases. Patients with T4 or N3 status with HR-/HER2+ BCBM exhibited much higher rates of metastases ($p<0.001$). Median overall survival was 12 months for patients with HR-/HER2+ BCBM. HR-/HER2- BCBM patients had the lowest 5-year percent survival, while HR+/HER2+ BCBM patients had the highest survival.
Conclusions: This SEER study shows increased rates of brain metastases in high-risk populations among HR-/HER2+ BC patients compared to the general BC population. Earlier identification of brain metastases within the HR-/HER2+ cohort could improve patient survival.

Dylan Fortman (MS)

HER2-positive metastatic cervical cancer responsive to first and second-line treatment: A case report

Dylan Fortman, Rochell Issa, Laura Stanbery, Mary Albrethsen, John Nemunaitis, and Timothy Kasunic

Introduction: Cervical cancer is the fourth most common malignant disease among women, with metastatic disease having a dismal survival rate compared to localized disease. Next-generation sequencing (NGS) has allowed for targeted treatments in patients who progressed on first-line therapy. We present a 46 year-old female with advanced cervical adenocarcinoma and pulmonary metastatic recurrence found to have HER-2 mutation who underwent first and second-line HER-2-targeted therapy with sustained response.
Methods: Review of the patient's medical record.
Results: The patient progressed on first-line combination chemoradiation with cisplatin therapy, as well as second-line topotecan, paclitaxel, and bevacizumab combination therapy with confirmed pulmonary metastasis. FoundationOne genetic testing revealed ERBB2 (HER-2) amplification. Her disease was stable for two years on trastuzumab-pertuzumab until progression was noted. She received SBRT and was switched to ado-trastuzumab-emtansine (TDM-1) therapy in 01/2018 and remains without evidence of residual or recurrent disease.
Conclusions: HER-2 amplification is found in approximately 1-2% of cervical cancer. Early data from the phase II SUMMIT 'basket' trial shows beneficial use of HER-2 therapy in patients with somatic HER-2 mutant cervical cancer. Targeted therapies have been shown to be advantageous over systemic chemotherapy with regards to improved overall survival, improved response rate, and improved time to progression.

Joseph Granata (GS)

The Signaling Scaffold IQGAP1 is a Target of the Antipsychotic Drug Haloperidol in Cancer

Joseph P. Granata, William J. Antonisamy, Robert E. McCullumsmith and Mahasin A. Osman

IQGAP1 is a phosphorylation-dependent conformation switch that generates a wide range of carcinomas in a context-dependent manner via pathways including, at least, mTORC1-S6K-Akt1, MAPK-Mnk1 and/or E-Cadherin-β-catenin axes. Previously, we identified rapamycin and LY29004 as specific inhibitors of phosphorylated (active) IQGAP1. Here

we used pharmaco-genetic analyses and identified Haloperidol (Haldol) as specific inhibitor of inactive IQGAP1. Haldol is a typical antipsychotic drug used to treat schizophrenia and other brain disorders. Ten micromolar of Haldol potently inhibited proliferation of cells stably expressing the dominant negative $IQGAP1^{IR\text{-}WW}$ by activating JNK stress signal. Using cell proliferation assays in panels of cancer cell lines, we find that Haldol effectively inhibited proliferation of a number of breast and glioblastoma cell lines. Interestingly however, a panel of lung cancer cell lines required longer time and twice the concentration of Haldol used for other cell lines, and exhibited variable response ranging from 0% to 89% proliferation inhibition. Haldol significantly blunted migration of IQGAP1 mutants and cancer cell lines, suggesting potential role as anti-metastatic agent. Studies are underway to define the mechanism by which Haldol inhibits cell proliferation and migration and how that translates in *iqgap1-/-* knockout mice. Overall, these findings present potential for repurposing the FDA-approved Haldol in precision anticancer medicine for tumors marked by the prevalent dysfunction of IQGAP1 pathway.

Michael Hajduk (R)

Dosimetric comparison of VMAT prostate plans designed with 10MV vs 18MV photon beams.

Michael Hajduk

Purpose: To compare prostate volumetrically modulated arc therapy (VMAT) treatments planned with 10MV vs 18MV photon beams to determine the practicality of 18 MV VMAT treatments. Recent studies indicate significantly lower than previously reported neutron doses associated with high-energy photon beams.
Methods: Clinically delivered prostate patient treatments planned using a 10MV photon VMAT technique were selected and re-planned with 18MV photon beams. Both sets of plans were made to meet the same clinical goals and follow the same optimization constraints. The resultant plans were then compared across criteria such as modulation factor, 50% isodose volume, and average dose to OARs. Treatments were planned in RayStation v8 utilizing clinically accepted beam model data.
Results: On average, 18MV photon plans were delivered with a ~17% lower modulation factor than the corresponding 10MV plans. The average 50% isodose volume of 18MV plans was found to be ~10 % larger than that of the 10MV treatments and average doses to the bladder and rectum were also larger on average. It was consistently observed however that in plans designed to treat larger patients 18MV photon plans were more likely to outperform their 10MV counterparts.
Conclusion: On average treatments planned with 10 MV photons proved to be superior in 50% isodose volume and OAR averages doses. For larger patients 18MV prostate treatments are likely to produce dosimetrically preferable plans. Criteria used to distinguish that patient population will be presented.

Abdul-Rizaq Hamoud (GS)

Examining differential cancer rates in schizophrenia

Abdul-rizaq Hamoud, Jacob Rethman, Sadik Khuder, Jarek Meller, James Riegle, Robert McCullumsmith

Introduction: Schizophrenia is a devastating psychiatric disorder that has a global prevalence of about 1%. Interestingly, overall cancer rates in schizophrenia are lower than the general population. Previous epidemiological studies of cancer rates in schizophrenia did not fully account for confounding variables such as smoking and substance abuse. We sought to confirm lower cancer rates in schizophrenia and explore mechanisms responsible for this unexpected observation. Cell culture studies have shown dysregulation of kinase networks driven by antipsychotic administration with a focus on Dopamine 2 Receptor antagonism. Gene expression analysis of cancer cells treated with antipsychotic drugs has shown decreased expression of kinases including PIM1. We hypothesize that typical antipsychotics are competitive inhibitors PIM kinases.
Methods: We applied a three-pronged approach to answer this question: 1) Epidemiological confirmation of reduced cancer incidence rates in patients with schizophrenia, 2) bioinformatics analyses of structural moieties and gene expression data, and 3) in vitro kinase activity screening.
Results: Epidemiological data confirmed reduced risk of cancer incidence in patients with schizophrenia when accounting for age and smoking rates using the Healthcare Cost and Utilization Project (HCUP). Bioinformatics analyses of perturbagen structure and transcriptional profiles suggest a medication effect, driving reduced cancer rates. In vitro kinase activity and protein expression will be measured in non-small cell lung cancer cells.
Conclusion: In summary, we have identified PIM kinases as possible novel targets of typical antipsychotics. Our data suggest that typical antipsychotics act directly on protein kinases to lower cancer risk.

Danae Hamouda (F)

The association between non-Hodgkin lymphoma and autoimmune diseases

Sadik Khuder, Roland Skeel, Danae Hamouda

Background and Objective: Epidemiologic studies reveal an increased risk of non-Hodgkin lymphoma (NHL) in patients with autoimmune diseases (AD). The aim of this study was to examine the prevalence of NHL in patients with ADs and define demographic characteristics.
Methods: We analyzed hospital admissions data from the 2017-2018 Nationwide Inpatient Sample and identified 138,130 patients with rheumatoid arthritis (RA), 36,297 patients with systemic lupus erythematosus (SLE), 5763 patients with scleroderma (SC), and 623 patients with Sjogren's Syndrome (SS). We conducted descriptive statistics and bivariate analyses for factors associated with NHL. Utilizing weighted logistic regression, we assessed the association between ADs and NHL and adjusting for demographic variables.
Results: Significant differences in the prevalence of NHL among the autoimmune diseases were found. The highest prevalence (0.48%) was in SS and the lowest prevalence (0.23%) was in SLE. The prevalence of NHL in patients without an autoimmune disease was 0.17%. The minimum age for NHL was seen in SLE (19 years) and the mean age was 61.6 years. The risk of NHL was significantly increased in patients with autoimmune disease. The highest risk was for SS (OR = 3.04, 95% CI 2.35 – 3.95).
Conclusions: Taken together, the data suggest that a broad spectrum of ADs is associated with NHL, and AD-associated NHL may be manifested at an earlier age. Of the ADs evaluated, SS was associated with the highest risk of developing NHL.

Zach Herron (MS)

Multitudinal validation of kinase's function, related to desmoplasia in pancreatic ductal adendocarcinoma by simple western

Zach N. Herron, Justin F. Creeden, Nicholas Henkel, Rob McCullumsmith

Introduction: Pancreatic ductal adenocarcinoma (PDAC) is the most common forms of pancreatic cancer and is characterized by its unique peritumoral proliferation of fibroblast and extracellular matrix (ECM) proteins known as desmoplasia. These characteristics make it one of the most lethal diseases with an average 5-year survival rate of less than 10% (3). While, traditional treatments such as chemotherapy, surgery and radiation have not been shown to significantly improve survival (4), studies have revealed interactions of ECM proteins and desmoplastic secreted growth factors that suggest they play a key role in regulating carcinogenesis..
Method: Western blotting with cell lysates was performed following Simple Western™ assays (ProteinSimple, Santa Clara, CA, USA) according to the manufacturers' instructions. Colorimetric method for estimating protein concentration via Bicinchoninic acid (BCA) assay.
Results: Pending.
Conclusion: The aim of our research was to study these interaction using a multiplex validation approach focused on multiple kinases we believe play a vital role in PDAC desmoplasia. With the use of Simple Western's multiple detection apparatuses Peggy Sue we were able to use a sized-based protein detection method via capillary electrophoresis to identify and quantitate those proteins of interest (5) against four different pancreatic cell lines. Better understanding of the biology of desmoplasia in the mechanism of PDAC will likely provide significant opportunities for better treatments for this devastating cancer.

Ying Ning (CF)

Lifestyle and Socioeconomic Disparities in Men and Women with Breast Cancer

Ying Ning, Ziad Abuhelwa, Saba Mehra, Sadik Khuder, Danae Hamouda

Introduction: Breast cancer in men and women shares many similarities, but important differences were reported.
Methods: Retrospective data were obtained from Healthcare Cost and Utilization Project Nationwide Inpatient Sample (HCUP-NIS) 2017-2018. Weighted chi-square tests were used to examine the association of lifestyle (alcohol, smoking, obesity) and socioeconomic factors (race, median household income) with the diagnosis of male or female breast cancer. $P<0.05$ was considered statistically significant.
Results: Among 5,689,722 male patients and 7, 498, 636 female patients hospitalized, 500 male breast cancer patients and 47,215 female breast cancer patients were identified. Alcohol use is associated with a lower risk of breast cancer in both men and women (*P-value* 0.0007 vs. <0.0001). Smoking is associated with a higher risk of breast cancer in women but no

difference in men (*P-value* <0.0001 vs. 0.1669). On the other hand, obesity is associated with a higher risk of breast cancer in men but not in women (*P-value* 0.0006 vs. 0.9853). Race disparities are noticed in female breast cancer (risk is lower in Hispanic and Native American) but not in males (*P-value* <0.0001 vs. 0.121). Finally, median family income makes a difference in female (higher income is associated with higher risk) but not in male breast cancer (*P-value* <0.0001 vs. 0.124).
Conclusions: Among hospitalized patients with breast cancer, lifestyles (alcohol use, smoking, and obesity), race, median household income seem to play distinctive roles in the risk of breast cancer in men and women.

Nealie T Ngo (MS)
Bifidobacterium spp: the Promising Trojan Horse in the Era of Precision Oncology

Nealie T Ngo; Khalil Choucair, MD; Justin F Creeden (Medical Student); Hanan Qaqish (Medical Student); Krupa Bhavsar (Medical Student); Chantal Murphy (Medical Student); Kendra Lian (Medical Student); Mary T Albrethsen (NP, Toledo Clinic), Laura Stanbery (UTMC Volunteer), Richard C Phinney, MD; F Charles Brunicardi, MD; Lance Dworkin, MD; John Nemunaitis, MD

Introduction: Selective delivery of therapeutic agents into solid tumors has challenged the achievement of long-term disease remission and cure. There is a need to develop alternative drug delivery routes to achieve better efficacy. Bifidobacterium spp. are anaerobic, nonpathogenic, gram-positive bacteria, commensal to the human gut that are a possible anticancer drug-delivery vehicle.
Methods: In this review, we describe Bifidobacterium's microbiology, current clinical applications, Bifidobacterium's potential to deliver anticancer therapy, and challenges and future prospects.
Results: Studies have demonstrated successful and exclusive localization of the bacteria to anoxic environments within malignant microenvironments and their ability to carry genes in situ. Agents successfully delivered via Bifidobacterium spp have been shown to achieve: sensitization to known chemotherapy, induction of apoptosis, angiogenesis blockade, immune-stimulation, modulation of molecular signaling, and bio-conversion of inactive pro-drug to active drug. No significant safety concerns/toxicities were reported regardless of administration routes, but due to the introduction of a bacterial product into human blood, there are potential risks of fever, tachycardia, and hypotension.
Conclusions: Advantages of Bifidobacterium spp include selective targeting of tumors, being non-pathogenic, and being susceptible to genetic manipulation. These characteristics offer unlimited possibilities for gene-based therapies, therefore making Bifidobacterium spp a promising vehicle for cancer delivery.

Olivia Noe (MS)
Importance of APC in Cancer and Therapeutic Implications

Olivia Noe; Louis Filipiak; Taha Sheik, MD; Rachel Royfman; Laura Stanbery, PhD; John Nemunaitis, MD
Introduction: Inactivating mutations of the adenomatous polyposis coli (APC) gene and consequential overaction of the Wnt signaling pathway are critical initiators in the development of colorectal cancer (CRC), the third most common cancer in the United States. The APC gene is responsible for negatively regulating the beta-catenin/Wnt pathway via a destruction complex with Axin/Axin 2 and GASK-3 beta. In the event of an APC mutation, beta-catenin accumulates, translocates to the cell nucleus and increases the transcription of Wnt target genes that have carcinogenic consequences in gastrointestinal epithelial stem cells.
Methods: A literature review was conducted to highlight carcinogenesis related to APC mutations and potential therapies targeting steps in inflammatory and Wnt pathway signaling regulation.
Results: While studies have addressed targeting upregulated inflammatory factors in CRC, therapies more specific to cytokine mediated transcription factors and Wnt pathway signalers are increasingly being explored. Some potential molecular targets in murine models include IL-6 signal transducers (YAP, Src, STAT3, Notch), tankyrase enzymes, Traf2- and Nck-interacting kinase, and Frizzled 7 Wnt receptors.
Conclusion: To date, relatively few pharmacological agents have led to substantial increases in survival for CRC patients. Here we review molecular targets that may be efficacious for patients suffering from APC mutations.

Hannah Staats (MS)

Targeted Molecular Therapy in Palliative Cancer Management

Hannah Staats, Christine Cassidy, Jesse Kelso, Sean Mack, Susan Morand, Khalil Choucair, MD, Hanan Qaqish, Owen Willis, Daniel Craig PhD, Joseph Duff, Laura Stanbery PhD, Gerald Edelman, MD, PhD, Lance Dworkin, MD, John Nemunaitis, MD

Introduction: Acknowledging the correlation of response to therapy based on the "targeting the target" concept, FDA demonstrated confidence in precision therapy approaches by approving FoundationOne® CDx test in late 2017 as an indicated diagnostic for cancer patients. More than 100 precision therapies involving both solid and liquid malignancy have since been approved by FDA as indicated therapy in a variety of cancer types as related to correlated molecular target.
Methods/Results: Through analysis of use of precision therapy in and outside of FDA approved indications. We found various studies and case reports that prove the effectiveness of using precision therapies on cancer populations outside of the FDA approved indications if the cancer matches the relevant molecular target.
Conclusion: The introduction of genotyping studies (CGP) revealed genetic and molecular abnormalities in the various subtypes of cancer. These results are shifting the current and future paradigm of cancer management from histologically-driven therapeutic strategies, to molecular-driven precision therapies. This review provides clinical justification of consideration for precision therapy guided by matched molecular target for advanced disease cancer patients who previously failed optimal NCCN guideline directed standard of care.

Hannah Staats (MS)

Molecular Mechanisms Underlying Rheumatoid Arthritis and Cancer Development and Treatment

Susan Morand, Hannah Staats, Justin Fortune Creeden, Laura Stanbery, PhD, Bashar Kahaleh, MD, John Nemunaitis, MD

Introduction: With recent advances in cancer immune therapy, specifically checkpoint inhibitors, understanding the link between autoimmunity and cancer is essential. In one of the most prevalent autoimmune diseases, Rheumatoid arthritis (RA), management consists of disease-modifying anti-rheumatic drugs. These drugs alter normal immunologic pathways, which could affect malignancy growth and survival. The link between RA and cancer is complex. Both diseases have similar complex etiologies including environmental and genetic factors which relates to immune dysregulation.
Method: Through literature review pertaining to mechanisms of RA, inflammation, and malignancy we analyzed their connections and possible relationships.
Results: Prolonged immune dysregulation and the resulting inflammatory response associated with development of RA may lead to increase cancer development risk. RA has long been associated with increased risk of non-Hodgkin's lymphoma and evidence supports relationship to lung cancer.
Conclusion: While it appears that there is a risk of RA patients to develop certain cancers, the exact mechanism remains unclear due to complex etiology. While much research has been done to understand links between RA and cancer, more work needs to be done to understand links between cancer and development of immune related adverse events, especially with use of immune therapy like checkpoint inhibitors.

HOSPITAL MEDICINE

Zohaib Ahmed (F)

Vitamin D and autoimmune hepatitis: systemic review and meta-analysis

Dr. Zohaib Ahmed, Dr. Umair Iqbal, Wade Lee, Dr. Faisal Kamal, Dr. Ahmad Nawaz, Dr. Asif Mahmood, Dr. Ali Nawras, Dr. Mona Hassan

Background: Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease that, if left untreated, can lead to liver failure and/or cirrhosis. AIH affects children and adults of all ages. It has a variable course, with periods of increased or decreased activity. A low Vitamin D level has been associated with autoimmune illnesses such as primary sclerosis cholangitis and primary biliary cirrhosis in several studies. Even though vitamin D has been demonstrated to have various immunomodulatory effects, little is known regarding its impact on the severity of autoimmune hepatitis. To determine the effects of low vitamin D levels on the severity of autoimmune hepatitis, including progression of advanced fibrosis, we conducted a systematic review and meta-analysis of the available studies.
Methods: We systematically searched the following databases: PubMed/Medline, Embase, Cochrane Register of Controlled Trials, and Web of Science through April 2021 to include all the cross-sectional studies. The individuals'

characteristics, as well as outcome measurements such as advanced liver fibrosis, were analyzed. Random effects model using the DerSimonian-Laird approach was employed, and odds ratios (OR) with 95% confidence interval (CI) were calculated.
Results: 4 Studies (3 Cohort studies and 1 Abstract) with a total of 406 patients were included. The patients were 43 years old on average when they were diagnosed with AIH, and 79 percent of them were female. Each study used a different cut-off value for vitamin D. Patients with comparatively low vitamin D levels had a lower risk of advanced fibrosis (pooled OR 0.47 95% CI 0.26-0.87, P-value 0.02). Heterogeneity among studies was low as seen by the I^2 of 23% for Hepatic Fibrosis.
Conclusion: Vitamin D has been demonstrated to have several immunomodulatory effects and lower vitamin D levels have been linked to a lower risk of advanced fibrosis in this meta-analysis and systemic review. However, further studies, including randomized controlled trials, are warranted to further establish this association.

Enrico DeLuca (R)
An evaluation of complex plan quality using RayStation's collapsed cone convolution (CCC) algorithm as a function of differing hardware given a time constraint
Enrico DeLuca; Nicholas Sperling
Purpose: The introduction of graphical processing unit (GPU) acceleration for RayStation's collapsed cone convolution (CCC) algorithm saw tremendous increases in the speed of dose calculations, but these increases and their effect on plan quality has not been extensively documented. The complexity of the optimization problem provides no guarantee of reaching acceptable plan results in reasonable timeframes. This study investigates the impact of hardware on radiation treatment plan quality.
Methods: Complex treatment plans were developed in RayStation v8A SP1 with criteria that produce clinically acceptable plans without additional input. These criteria were optimized using different sets of initializations and iterations (1x240, 2x120…). These were evaluated for speed and plan quality under GPU acceleration. CPU optimized plans were created under time constraints matching the accelerated plans, and results compared to evaluate the impact of acceleration on plan quality.
Results: CCC calculations entailed five-fold increases in runtime in the CPU-accelerated environment over GPU-accelerated. Total runtime increases quadratically for long, continuous optimization runs, with decreasing returns on time invested. The 1x240 optimization resulted in a plan with the most volume exceeding Rx (58.7%), while the 4x60 optimization resulted in the least excess (6.92%).
Conclusion: The downside of increasing runtime for long optimizations and the improved dosimetry of multi-initialized plans suggest these are clearly superior. When given a time constraint, GPU-accelerated optimizations can perform more iterations than CPU-accelerated optimizations by completing CCC evaluations efficiently – producing better treatment plans; thus clinics using RayStation's CCC algorithm within tight timeframes can produce better plans with improved hardware.

Manesh Kumar Gangwani (F)
Re-expansion Pulmonary Edema After Pneumothorax Drainage: An Uncommon Under-Recognized Complication
Manesh Kumar Gangwani, MD; Anup Katyal, MD

Introduction: Re-expansion pulmonary edema can present as a rare complication after chest tube placement for pneumothorax with approximately twenty percent case fatality. Risk factors include chronicity greater than seventy-two hours, young age and large-volume thoracentesis. Pathophysiological considerations include potential free-radical induced increased vascular permeability and alterations of hydrostatic mechanisms.
Case: A healthy 35-year-old male with history of vaping presented with shortness of breath with right-sided chest pain for one week. Initial vitals were stable. A large right-sided pneumothorax was identified and the patient underwent chest tube drainage with negative pressure suction placement. The patient underwent complete re-expansion of the right lung. The patient's hemodynamic and respiratory status worsened within an hour after chest tube placement with profound hypoxia and shock progressing from room air to worsening hemodynamic instability, requiring intubation. Interval chest x-ray showed an increase in diffuse alveolar infiltration on the right side attributing to re-expansion pulmonary edema. Other etiologies were ruled out. The etiology of pneumothorax was attributed to vaping with the use of the Valsalva maneuver to increase absorption. The patient subsequently made complete recovery.
Conclusion: Re-expansion pulmonary edema is rare, however a very important complication to recognize early to yield favorable outcomes to prevent a very rapidly progressive respiratory failure. The complication is self-limiting and management is supportive. Re-expansion pulmonary edema may be prevented by placing a chest tube under water-seal

drainage and reserving the negative pressure for patients with no or clinically insignificant lung expansion. The role of vaping also needs to be looked into.

Manesh Kumar Gangwani (F)

Reducing unnecessary treatment of asymptomatic Hypertension with Intravenous Medications: A QI initiative

Manesh Kumar Gangwani, MD; Andrew Crannage, Pharm.D. ; Katherine Garland, MD

Background: Hypertensive urgency requires a gradual blood pressure reduction with oral agents whereas hypertensive emergency requires emergent blood pressure reduction to limit end-organ damage. Labetalol and hydralazine are the most commonly used intravenous medications. There is disproportionate utility of IV medications relative to true hypertensive emergency which could increase harm and inappropriate use of resources.
Methods: We aimed to reduce inappropriate orders for IV labetalol and hydralazine for hypertensive urgency management for hospitalized patients under medicine resident service by 20%. Three-month pre and three-month post intervention data was collected for IV Hydralazine and Labetalol at end of each month. Interventions included generating an EMR smart phrase for appropriate algorithm and systematic resident education. Alternative etiologies for elevated blood pressure such as pain, anxiety, withdrawal of home medications were also considered.
Results: The overall IV reduction was 29% orders with consistent drop in both IV Hydralazine and Labetalol. There was subsequent decrease in month-on-month IV orders in post intervention months. Mild uptick noted in 3rd month of intervention relative to initial 2 months. Limitations of the study include small sample size, short follow up and COVID 19 pandemic leading to reinforcement gaps.
Conclusion: Re-enforcement and education with multidisciplinary approach can successfully impact in reduction of overall inappropriate intravenous hypertensive agents. EMR based interventions can assist in tracking and determining appropriate utility. It is essential to recognize other etiologies including withholding of home medications, pain, anxiety as etiologies for elevated blood pressure.

Manesh Kumar Gangwani (F)

Optimizing MitraClip procedure with high frequency jet ventilation: First reported case

Manesh Kumar Gangwani, MD Anthony Sonn, MD FACC

Introduction: MitraClip delivery system is approved for surgically prohibitive candidates to reduce symptomatic mitral regurgitation. High-frequency jet ventilation(HFJV) can be employed to minimize cardiopulmonary motion during procedure. In a first of its kind, we employed HFJV for a successful MitraClip procedure.
Case: A74-year-old female with significant past medical history of CAD and CHF presented with shortness of breath, orthopnea and leg swelling. Patient's symptoms were attributed to severe mitral regurgitation. Patient was a poor surgical candidate and was planned to undergo MitraClip procedure. Intra-operatively, it was technically challenging achieve adequate orientation to grasp for clip deployment. HFJV technique was applied which improved respiratory variation to allow optimized and near static surgical field leading to successful MitraClip application.
Discussion: Advancement has led to increase of minimally invasive procedures including MitraClip which has increased operative complexity requiring ever increasing operative precision. HFJV has been successfully employed in atrial fibrillation ablation procedures to reduce posterior atrial motion to achieve catheter stabilization. On occasion, MitraClip procedure can present with operative challenges secondary to multiple anatomic and functional variations. It became technically challenging to apply the clip secondary increased cardiac motion with respiratory variations in our case. As a first of its kind technique for MitraClip procedure, HFJV was applied to optimize surgical field to provide near static conditions, leading to a successful MitraClip application.
Conclusion: HFJV provides near stationary operative site to provide optimal position navigating operative complexities to increases success rate, decrease operative time and complications in technically challenging cases.

Manesh Kumar Gangwani (F)

Cilostazol therapy: not for the faint of heart

Manesh Kumar Gangwani, MD; Sarah Foley Horn, MD

Introduction: Cilostazol, a phosphodiesterase inhibitor, causes arterial vasodilation to improve flow and inhibit platelets, is shown to be used for improving cerebral blood flow in intracranial stenosis and secondary prevention of stroke. Post market surveillance data have found an association with QT prolongation syndromes of torsades with pre-existing cardiac

conditions. We describe the first case report of QT prolongation with initiation of Cilostazol in true clinical settings and without any significant cardiac history.
Case: A 66 year old male with history of HTN and left MCA stroke with to ED with syncope few days after starting Cilostazol. Patient was started on DAPT a month prior to admission due to left basal ganglia stroke and infarcts in the white matter of the left frontal and parietal lobes and left ICA stenosis. Patient presented back with recurrent symptoms and repeat work up re-demonstrated symptoms secondary to intracranial cerebral artery stenosis and patient was switched from clopidogrel to cilostazol and discharged home. Patient presented back with syncope and noted to have prolonged QTc of 562 with QTc of 412. Other etiologies were ruled out. Patient's symptoms were attributed to acute QT prolongation neurocardiogenic syncope. Cilostazol was discontinued and QTc returned to 460 consistent with drug half-life of 11-13 hours.
Discussion/Conclusion: This case illustrates an important association between cilostazol and significant QTc prolongation. Recognition of this association is essential to prevent fatal arrythmias paving way for electrocardiographic surveillance in appropriate cases. Further studies are needed to identify high risk patient populations.

Manesh Kumar Gangwani (F)
Short versus long duration of dual antiplatelet therapy after second generation drug-eluting stents implantation in diabetics
Manesh Kumar Gangwani, MD

Background: Dual-antiplatelet therapy (DAPT) duration in patients undergoing PCI has increasing data suggestive of acceptable short-term duration. Metabolically accelerated atherosclerosis associated with diabetes makes it essential to study short term DAPT in this subgroup. With limited studies determining optimal DAPT strategies after second-generation stents in this subset, we aimed to establish the optimal duration.
Methods: Database search of randomized controlled trials was performed. Meta-analysis was conducted comparing the outcomes of short term (3-6 month) vs long term (≥12 months) DAPT therapy. Subgroup analysis comparing 6 vs 12 months was also conducted. Primary endpoints included a composite of NACCE/MACE. Secondary outcomes included mortality, myocardial infarction (MI), stent thrombosis (ST), stroke, and target vessel revascularization (TVR).
Results: 5 RCTs were included with a total of 3117 diabetic patients. Short term DAPT did not show any statistical difference from long term DAPT in primary outcomes (RR: 0.96, 95%CI 0.68-1.35,P=0.84). Overall mortality (OR 0.92; 95% CI, 0.52-1.63, P = 0.98), MI (OR 1.02; 95% CI, 0.53 - 1.94, P = 0.85), ST (OR 1.20; 95% CI, 0.55-2.60, P = 0.55), TVR (OR 1.10; 95% CI, 0.45 -2.73, P = 0.74) and stroke (OR 0.50; 95% CI, 0.082- 2.43, P = 0.81), did not show any statistical difference between the two groups. No difference was noted in 6 vs 12 month primary outcome (RR: 0.86, 95%CI 0.45 - 1.45, P = 0.60).
Conclusion: This meta-analysis showed no statistically significant benefit of longer DAPT over shorter DAPT therapy in patients undergoing PCI with DES in diabetics.

Nathaniel Locke (MS)
A case of anti-myelin oligodendrocyte glycoprotein (MOG) associated acute disseminated encephalomyelitis (ADEM): Differentiating multiphasic versus monophasic disease
Nathaniel Locke; N. Ali, DO; A. Taneja, MD; M. Nagel, MD; N. Mahfooz, MD

Introduction: ADEM is an autoimmune inflammatory demyelination of white matter in the CNS that occurs after a viral illness. It may present as monophasic or multiphasic disease. Anti-MOG associated ADEM has higher risk of relapse.
Methods: Case report.
Results: Four-year-old female presented with one-week history of URI symptoms, conjunctivitis, headache, fever, somnolence, and vomiting. Intermittent episodes of staring, and speech slowing started after admission. CT head and lumbar puncture concerning for increased ICP while EEG was normal. MRI brain showed non-enhancing FLAIR signals in the anterior left basal ganglia and medial right occipital lobe. Symptoms progressed to altered mental status, hallucinations, and increased agitation. Repeat MRI brain showed non-enhancing hyperintense T2 lesion in the left putamen, bifrontal, bi-occipital medial cortex, and right parietal region. MRI spine showed abnormal T2 hyperintensity in the right hemi-cord at the C6-C7 level. Serum Myelin Oligodendrocyte Glycoprotein (MOG) Antibody was positive (1:1000). Symptoms improved with five days methylprednisolone. Headaches returned 2-3 days after completing weeklong oral prednisone taper. She also developed fever, vomiting, and loss of vision. After readmission, MRI brain showed extensive white matter T2/FLAIR hyperintense lesions involving all cerebral lobes, the corpus callosum, basal ganglia, and left optic chiasm/nerve. Bilateral optic neuritis noted on ophthalmologic exam. Initiation of intravenous

immunoglobulins (IVIG) with methylprednisolone immediately improved her symptoms. One-month oral prednisone taper given at discharge.
Conclusion: Monophasic ADEM must be differentiated from multiphasic disseminated encephalomyelitis (MDEM) to ensure appropriate treatment and early IVIG initiation can be beneficial. Long-term follow-up required given anti-MOG association.

Adam Pasquinelly (MS)
Just like the simulations: Assessing medical student confidence before and after completion of a transitional education program simulating procedures for students entering emergency medicine residency
Adam Pasquinelly; AJ Luna; Alex Belaia; S. Aouthmany, MD
Introduction: Incoming emergency medicine residents may feel underprepared to handle common emergency room scenarios. This stems not only from a lack of skill, but also from a lack of confidence in the skills they already have. We look to establish a link between perceived self-confidence in the capacity to perform common EM procedures and the completion of simulation-based training in incoming emergency medicine interns.
Methods: Fourth year medical students who matched into an emergency medicine residency program participated in a Transitional Educational Program (TEP) at the Interprofessional Immersive Simulation Center at the University of Toledo. Subjects were given pre- and post-TEP survey questionnaires assessing their confidence in common emergency medicine clinical scenarios using a 5-grade Likert scale. Data was analyzed using a one-tailed Wilcoxon signed-rank matched-pairs test.
Results: Of 19 subjects who participated, 16 (84.2%) responded to the pre-survey and consented. Out of those 16 subjects, 10 (62.5%) completed the surveys at the correct time and order. The pre- and post- surveys consisted of the same 14 questions, with one question for each simulated procedure. In 11 of 14 questions, there was a significant increase in perceived subject confidence e ($p<.05$) after simulation. The TEP and associated surveys were completed over an eight hour time period, with costs and training included the general maintenance of the simulation center, simulation center techs and certified emergency medicine physician faculty.
Conclusions: Simulation-based training in the setting of hi-fidelity equipment and faculty guidance significantly improved the confidence of incoming emergency medicine interns

Logan Roebke (MS), Josh Vander Maten (MS), and Ghattas Alkhoury (F)
Hyperbaric Oxygen Management of Recurrent Cellulitis in Poikiloderma with Neutropenia
Logan J. Roebke; Josh W. Vander Maten; G. Alkhoury, MD

Poikiloderma with neutropenia (PN), is a rare autosomal recessive condition with many associated complications and manifestations. Here we present a patient with confirmed Poikiloderma with Neutropenia (PN) who is of one-quarter Chucktaw or Cherokee heritage with no known descent from the Navajo tribe. The patient's condition was complicated by chronic bilateral lower limb cellulitis and associated osteomyelitis which was unresponsive to extensive antibiotic regimens. Subsequent treatment with hyperbaric oxygen therapy was successful. To date, no author has reported on the treatment of recurrent cellulitis using hyperbaric oxygen therapy in this patient population. Based on our experience, hyperbaric oxygen therapy should be considered in patients with Poikiloderma with Neutropenia who present with recurrent cellulitis.

INFECTIOUS DISEASES

Sapan Bhuta (R)
Cardiac Magnetic Resonance Imaging for the Diagnosis of Infective Endocarditis in the COVID-19 Era
S. Bhuta, MD (resident); N.J. Patel, MD; R. Redfern; J.A. Ciricillo; M.N. Haddad; H. Malas, DO; H. Elsaghir, MD; J.A. Kammeyer, MD, MPH

Introduction: Transesophageal echocardiogram (TEE) is widely used as a sensitive and specific imaging modality for diagnosis of infective endocarditis (IE). However, TEE is an aerosol-generating procedure (AGP). We evaluate the utility of cardiac MRI (CMR) as an alternative to TEE for diagnosing IE in patients growing typical microorganisms on blood cultures or meeting modified Duke criteria.
Methods: This retrospective study was conducted at a single medical center using data from 14 patients that underwent CMR for evaluation of IE during the COVID-19 pandemic, 03/14/2020 – 02/14/2021.

Results: All patients had multiple positive blood cultures (MRSA 7%, MSSA 50%, Enterococcus 29%, Streptococcus 7%, other 6%). Modified Duke criteria were met in 4 cases (29%). On CMR, 1 case (7%) was notable for leaflet vegetation and 5 cases (36%) for non-specific delayed myocardial enhancement. TEE was performed in 3 cases (21%), and in all 3 cases leaflet vegetations were visualized on TEE but in 2 of 3 cases missed on CMR. Average duration of antibiotics was 5.7 weeks, with no significant difference based on CMR results, though 9 cases had additional indications for prolonged antibiotics. All 5 patients that completed repeat cultures after antibiotics, remained negative.
Conclusions: CMR may provide an alternative to TEE in settings where AGPs should be minimized. However, in our study, CMR results did not affect duration of therapy, suggesting empiric treatment and a lack of confidence in CMR as a valid diagnostic modality. Further studies are needed to compare the diagnostic utility of CMR versus TEE in IE.

Caitlyn Hollingshead (F)

Outcomes in Prosthetic Fungal Infection

Caitlyn Hollingshead, MD; Joan Duggan, MD; Roberta Redfern, PhD; Gregory Georgiadis, MD, and Jason Tank, MD
Background: There is a paucity of data in the literature regarding the most effective treatment and related outcomes of fungal prosthetic joint infection. The majority of reported cases are treated using a two-stage revision method. Alternately, others have suggested a one-stage revision in order to prevent a period of significant functional impairment and lower overall costs.
Methods: A retrospective record review of patients admitted within two health systems between January 1, 2007 and December 31, 2018 with prosthetic joints and a deep culture of the joint positive for fungal organisms was performed.
Results: Eighteen patients fit criteria. Nine patients had knee replacements and nine patients had hip replacements. The average age at time of infection was 61. Ten patients were female. Average BMI was 32.1. Twelve presented with a painful joint, eight presented with drainage, and one with dehiscence. Average WBC count was 9.3, average ESR was 47, and average CRP was 11.8. All patients were noted with Candida species. Eight patients were treated with two-stage revisions, three received one-stage revisions as destination therapy. One required amputation. All but one patient was associated with concurrent bacterial infection. Of the twelve patients that had known outcomes, six were noted with cure and six were noted with relapse. All patients that were cured received two-stage exchange or girdlestone procedure.
Conclusion: Fungal prosthetic joint infection was associated with poor outcomes. All of the patients were noted with Candida species, which is in concordance with the literature. Two-stage exchange was associated with better outcomes.

Caitlyn Hollingshead (F)

A Needs Assessment for Infectious Diseases Consultation at Rural Hospitals

Caitlyn Hollingshead, MD; Ana Khazan, MD; Jacob Ciricillo, MD; Justin Franco (Medical Student); Roberta Redfern, PhD; Michael Haddad (Medical Student); Julia Berry (Medical Student); Joel Kammeyer, MD

Background: Consultations by a specialist trained in infectious diseases (ID) have been demonstrated to improve patient outcomes in many arenas. ID specialists generally practice in large or mid-size hospitals in urban or centers that can support robust inpatient practices. In the United States, 79.5% of counties do not have ID physicians, leaving 208 million citizens with no or below-average ID coverage. Little is known regarding the treatment of infections in rural hospitals with no coverage from an ID specialist.
Methods: 2336 patients received antibiotics at seven community hospitals with no ID physician from May 15, 2019 – November 30, 2019. Patients that received antibiotics for 3 days or more were included. Cases were reviewed by an infectious diseases-trained physician to identify opportunities for improved antibiotic stewardship.
Results: Overall, opportunities to improve antibiotic utilization were identified in 55.2% of cases, including in (62.9%) cases of community-acquired pneumonia, (51.86%) cases of skin and soft tissue infection, (58.88%) cases of urinary tract infection, (56.8%) cases of hospital-acquired pneumonia, and (72.06%) cases of COPD exacerbation. Patients required transfer to a tertiary care center in 0.73% of circumstances.
Conclusions: When no ID consultant is available, antibiotic courses often deviate from standard-of-care, including for conditions where the benefit of ID consultation has previously been demonstrated. In most circumstances, patients are not transferred to tertiary care centers for their ID-related conditions. Efforts to expand the ID workforce to include coverage at rural hospitals will likely improve antibiotic utilization and patient outcomes.

Joel Kammeyer (F)

COVID-19 Acute Care at Home: A Substitution for Hospitalization in Patients with Mild Symptoms

Kammeyer, JA; Perkins, B; Seegert, S; Caris, D; Hollingshead CM; Brochin, E; Russell, BH

Background: Constraints on resources require healthcare systems to implement alternative and innovative means for delivering care. The COVID-19 pandemic amplified this issue throughout the world, leading to shortages of ventilators, hospital beds, and healthcare personnel. We report the results of an Acute Care at Home Program (ACHP) response to COVID-19, providing in-home hospital-level care to patients with mild symptoms, preserving in-hospital beds for more serious illness.
Methods: Patients with COVID-19 were selected for ACHP after undergoing risk stratification for severe disease, including oxygen evaluation, time course of illness, and evaluation of comorbidities. Patients admitted to ACH met inpatient criteria, required oxygen supplementation of ≤4 liters, and received insurance approval. Services were provided consistent with best practice of inpatient care, including 24/7 provider availability via TeleMedicine, bedside care provided by paramedics and nurses, respiratory therapy, radiology and laboratory services, pulse oximetry monitoring, and administration of medications. Protocols existed for patient transfer to hospital in the event of clinical deterioration.
Results: Our initial cohort included 62 patients enrolled October 1, 2020 – May 31, 2021. Of these, 57 patients were discharged successfully from ACHP. Patients presented with initial oxygen requirements of 0-4 liters. Average length-of-stay in ACHP was 5.4 days.
Five patients required hospitalization after enrollment in ACHP; one subsequently expired, two were discharged home, one returned to ACHP after inpatient hospitalization, and one remains hospitalized. One additional patient that was successfully discharged home from ACHP was later readmitted and expired in a subsequent hospitalization. The patients that expired had significant immunocompromising conditions that may have contributed to their outcomes.
Conclusion: ACHP can provide care equivalent to hospitalization for select COVID-19 patients. Immunocompromised hosts with COVID-19 may represent a subset of patients in which in-house hospitalization must be carefully considered, even with mild oxygen requirements. Health systems should consider ACHP as a substitution for hospitalization for COVID-19 patients with mild symptoms.

Roberta Redfern (GS)

The role of comorbid conditions and social determinants of health on mortality for patients hospitalized with COVID-19

Roberta E. Redfern, PhD; Camelia Arsene, MD, PhD, MHS; Lance Dworkin, MD; Shipra Singh, MBBS, MPH, PhD; Amala Reddy Ambati, MD; Lukken Imel, MD; Sadik Khuder, DDS, MPH, PhD

Introduction: Since the emergence of COVID-19 infection as a global pandemic, is has been clear that in American communities, racial and social factors have been associated with worse outcomes.
Methods: This is a retrospective review of patient data from a single health system. Electronic medical records were queried to obtain information about patients who were admitted to the hospital and had laboratory confirmed COVID-19. Age, gender, Body Mass Index, race, ethnicity, payor status, ventilator use, and comorbid conditions on admission were considered in univariate analyses and Cox proportional hazard regression to investigate their impact on mortality.
Results: In total, there were 3,468 patients admitted between March 11, 2020 and January 26, 2021; 641 expired at the time of investigation, where all-cause mortality rate was 18.5% in the cohort. Mortality rates increased in each of the five increasing age categories ($p < 0.001$). In addition, mortality rates were significantly different by payor status, where the highest mortality rates were observed in the Medicare and "Other" categories. On Cox proportional hazard regression model limited Charlson Comorbidity Index score, race, ventilator use, and payor status continued to be significantly associated with survival.
Conclusions: Considering pre-existing conditions, age, and race in a cohort of COVID-19 positive patients who were admitted for medical treatment reveals that insurance payor is significantly associated with mortality. Those who were mainly self-pay patients demonstrated significantly reduced survival compared to commercially insured patients. Additional research to understand other factors involved in this association are warranted.

Roberta Redfern (GS)

Hyponatremia in COVID-19 Patients

Roberta Redfern, PhD, MPH; Lance Dworkin, MD; Basil Akpunonu, MD; Anand Mutgi, MD; Amala Reddy Ambati, MD; Camelia Arsene, MD, PhD, MHS; Shipra Singh, MBBS, MPH, PhD; Sadik Khuder, DDS, MPH, PhD

Background and Objective: Hyponatremia is the most common electrolyte disorder encountered in clinical practice. Currently, there is not sufficient data to establish the risk of hyponatremia in patient with COVID-19 infection. The prevalence and prognosis of hyponatremia in patients with COVID-19 is not yet known. The purpose of this study was to estimate the prevalence of hyponatremia and assess its impact on mortality among COVID-19 patients.Methods: This is a

retrospective review of electronic medical records of patients who were admitted to the hospital and had laboratory test for COVID-19. Hyponatremia was recorded based on ICD10 code 'E87.1' extracted from one of the five diagnoses on the patient's record. The survival probability for COVID-19 patients with and without hyponatremia was determined using Kaplan-Meier estimates.
Results: There were 8,252 patients 3373 with confirmed COVID-19 diagnosis) admitted between March 11, 2020 and January 26, 2021. The prevalence of hyponatremia was 2.3% and the rate increased in patients with acute kidney failure (AKF) , hypertension, and stroke. No significant difference was found for age, gender, or race. COVID-19 patients without hyponatremia survived longer than those with hyponatremia. However, the difference in mortality between the two groups was not statistically significant ($p = 0.2436$). Hyponatremia was associated with an increase in the length of stay in the hospital.
Conclusions: The prevalence of hyponatremia increases in patients with AKF or hypertension. Hyponatremia may be considered a negative prognostic factor in COVID-19 patients with these comorbidities. It is important to ascertain the precise etiology of this electrolytic disorder so that a targeted treatment strategy can be established in order to avoid serious consequences.

Ryan Shields (MS)
The Multifactorial Sequelae of COVID-19: A Review of Published Autopsy Reports
Ryan Shields (medical student), Stephen Hong (medical student), Karan Chawla (medical student), Lexi Ford (medical student), Fedor Lurie, MD

Introduction: SARS-CoV-2 is responsible for the current global pandemic. SARS-CoV-2 infection underlies the novel viral condition coronavirus disease 2019 (COVID-19). COVID-19 causes significant pulmonary sequelae contributing to serious morbidities. Improved understanding of COVID-19 pathogenesis is necessary for development of preventative and therapeutic strategies. This review of 124 published articles documenting COVID-19 autopsies included 1142 patients.
Methods: A PubMed search was conducted for COVID-19 patient autopsy articles published prior to March 2021 utilizing the query "COVID-19 Autopsy." There was no restriction regarding age, sex, or ethnicity of the patients. Duplicate cases were excluded. Findings were listed by organ system from articles that met selection criteria.
Results: Pulmonary pathology (72% of articles; 866/1142 patients): diffuse alveolar damage (563/866), alveolar edema (251/866), hyaline membrane formation (234/866), type II pneumocyte hyperplasia (165/866), alveolar hemorrhage (164/866), and lymphocytic infiltrate (87/866). Vascular pathology (41% of articles; 771/1142 patients): vascular thrombi (439/771)— microvascular predominance (294/439)—and inflammatory cell infiltrates (116/771). Cardiac pathology (41% of articles; 502/1142 patients): cardiac inflammation (186/502), fibrosis (131/502), cardiomegaly (100/502), hypertrophy (100/502), and dilation (35/502). Hepatic pathology (33% of articles; 407/1142 patients): steatosis (106/402) and congestion (102/402). Renal pathology (30% of articles; 427/1142 patients): renal arteries arteriosclerosis (111/427), sepsis-associated acute kidney injury (81/427) and acute tubular necrosis (77/427).
Conclusions: While this review revealed anticipated pulmonary pathology, these data also demonstrate significant extrapulmonary involvement secondary to COVID-19, indicating widespread viral tropism throughout the human body. These diverse effects require additional comprehensive longitudinal studies to characterize short-term and long-term COVID-19 sequelae and inform COVID-19 treatment.

NEPHROLOGY

Vaishnavi Aradhyula (MS)
Novel Model of Oxalate Diet Induced Chronic Kidney Disease in Dahl-Salt-Sensitive Rats
Prabhatchandra Dube, Vaishnavi Aradhyula, Jacob Connolly, Sophia Soehnlen, Armelle DeRiso, Ayla Cash, Andrew Kleinhenz, Oliver Domenig, Lance D. Dworkin, Deepak Malhotra, Steven T. Haller, David J. Kennedy

Background: Diet induced models of chronic kidney disease (CKD) may offer several advantages vs surgical models in terms of clinical relevance and animal welfare. Oxalate is a plant-based, terminal toxic metabolite and increased load of dietary oxalate leads to renal tubular obstruction and eventually CKD. Dahl-salt-sensitive rats (Dahl-S) are a common strain used to study for hypertensive renal disease, however characterization of other diet induced models on this background would allow comparative studies of CKD within the same strain. We hypothesized that Dahl-S rats on a low-salt, oxalate rich diet would have increased renal injury and will serve as a novel rat model to study CKD.
Methods/Results: Ten week-old male Dahl-S rats were fed either 0.2% salt normal chow (SS-NC) or a 0.2% salt diet containing 0.67% sodium oxalate (SS-OX) for five weeks (n=6-8/group). Real-time PCR demonstrated increased

expression of inflammatory marker IL-6 and fibrotic marker Timp-1 metalloproteinase in the renal cortex of SS-OX rat kidneys compared to SS-NC. Immunohistochemistry of kidney tissue demonstrated increase in CD-68 levels, a marker of macrophage infiltration in SS-OX rats. In addition, SS-OX rats displayed increased 24-hour urinary protein excretion as well as significant elevations of plasma Cystatin C. Furthermore, oxalate diet induced increase in systolic blood pressure and renin-angiotensin-aldosterone system profiling in the SS-OX plasma showed significant increases in angiotensin [1-5] and angiotensin I as well as suppression of the steroid aldosterone.
Conclusion: Oxalate diet induces significant renal injury and CKD in Dahl-S rats and provides a novel diet-induced model to study CKD.

Mingyang Chang (RF)
Melanocortin 5 Receptor (MC5R) Signaling Protects Against Podocyte Injury and Proteinuria
Mingyang Chang, Dworkin Lance, Rujun Gong

Background: Melanocortin therapeutics represented by ACTH has a demonstrable steroidogenic-independent antiproteinuric and glomerular protective effect. It remains unclear which melanocortin receptors (MCR) mediate this renoprotective activity. MC5R was the last MCR to be characterized and has been involved in both biophysiology and pathology. However, the role of MC5R in glomerular disease is unknown and was examined here.
Methods: Adriamycin (ADR) nephropathy was induced in MC5R knockout (KO) and wild-type (WT) mice. Proteinuria and glomerular injury were evaluated. In vitro, ADR-insulted murine podocytes were treated with a highly selective MC5R agonist and cellular injury assessed.
Results: Under physiological condition, KO were no different from WT mice and had normal kidney physiology and histology. Upon ADR injury, KO mice demonstrated an exacerbated glomerular injury, featured by heavier albuminuria and worsened glomerular pathology, including glomerulosclerosis, podocyte apoptosis, loss of podocyte markers and ultrastructural lesions in podocytes like foot process effacement and microvillous transformation. Mechanistically, GSK3β, a transducer downstream of MC5R signaling and key regulator of podocyte injury, was more active in glomeruli of KO mice after ADR injury. This was concomitant with a potentiated activation of NFκB RelA/p65, a cognate substrate of GSK3β, in glomeruli in KO mice, and reinforced de novo expression of NFκB-dependent podocytopathic mediators, including B7-1, cathepsin L and MCP-1, in podocytes. Moreover, paxillin, a focal adhesion-associated adaptor protein and GSK3β substrate, was more activated in glomeruli of KO mice after ADR injury, associated with more disruption of podocyte cytoskeleton, shown by filamentous actin staining. In consistency, in vitro in ADR-insulted podocytes, treatment with a MC5R agonist rectified GSK3β overactivity, suppressed NFκB activation and the consequent de novo expression of B7-1, cathepsin L and MCP-1, and inhibited paxillin phosphorylation, resulting in a protection against podocyte injury, marked by cell shrinkage, hypermotility, cytoskeleton disorganization and apoptosis. This protective activity was blunted by ectopic expression of a constitutively active GSK3β mutant, signifying the mediating role of GSK3β.
Conclusion: MC5R-mediated melanocortinergic signaling protects against podocyte injury and proteinuria.

Bohan Chen (RF)
Regulation of Podocyte Senescence by GSK3β: A Novel Senostatic Target for Delaying Glomerular Aging
Yudong Fang, Bohan Chen, Lance Dworkin, Rujun Gong

Background: Along with worldwide population aging, nephrology practice is challenged by renal aging, which is associated with progression of age-related glomerulosclerosis centrally involving podocyte senescence. Compelling evidence suggests that microdoses of lithium, an inhibitor of GSK3β, alleviated aging in Drosophila and C. elegans. As a multitasking kinase, GSK3β has also lately been implicated in podocyte pathobiology. However, it remains unknown if GSK3β regulates renal aging.
Methods: Renal aging was examined in mice with doxycycline-induced podocyte-specific ablation of GSK3β (KO) or in control littermates at 2, 12 or 24 months. Cultured podocytes were tested for senescence.
Results: Accompanying aging, control mice exhibited evident renal aging, featured by a decline in renal function, persistent albuminuria and typical pathologic changes, including glomerular hypertrophy, focal global glomerulosclerosis, hyaline arteriolosclerosis and renal fibrosis on light microscopy, associated with ultrastructural lesions in podocytes like foot process effacement and deposits of protein aggregates, podocytopenia, and loss of podocyte markers like synaptopodin and podocin. In parallel, senescence-associated β-galactosidase activity and expression of senescence-related p16INK4A, p53 and p21 were progressively increased in glomeruli, correlated with concomitant GSK3β overactivity, as evidenced by linear regression analysis. In the aged KO mice, GSK3β was selectively ablated in podocytes, resulting in a blunted induction of p16INK4A, p53, p21 and β-galactosidase activity in glomeruli, and

alleviation of glomerulosclerosis and other signs of glomerular aging. Mechanistically, in silico analysis revealed that p16INK4A, p53 and p21 are cognate substrates of GSK3β and contain the GSK3β consensus motifs. In vitro, ectopic expression of a constitutively active GSK3β mutant in podocytes promoted phosphorylation of p16INK4A, p53 and p21, incurring a potentiated cellular senescence, marked by an elevated β-galactosidase activity and loss of podocyte differentiation markers like synaptopodin. Conversely, GSK3β knockdown attenuated phosphorylation of p16INK4A, p53 and p21, leading to a diminished cellular senescence.
Conclusions: GSK3β plays a key role in glomerular aging by regulating podocyte senescence, and thus is likely an actionable senostatic target for delaying glomerular aging.

Bohan Chen (RF)
Hematopoietic-Specific Melanocortin 1 Receptor Signaling Protects Against Crescentic Glomerulonephritis and Mediates the Beneficial Effect of Melanocortin Therapy
Xuejing Guan, Bohan Chen, Lance Dworkin, Rujun Gong
Background: Emerging evidence suggests that melanocortin 1 receptor (MC1R) signaling may contribute to the beneficial action of melanocortins in glomerular diseases. However, whether hematopoietic MC1R signaling is implicated is unknown.
Methods: MC1R mutant (e/e) or wild-type (WT) mice were injured with rabbit nephrotoxic serum (NTS) and treated with melanocortins, including the Repository Corticotropin Injection (RCI, Acthar® Gel, Mallinckrodt ARD, LLC), NDP-MSH, and the MC1R selective agonist MS05. Some mice received adoptive transfer of syngeneic bone marrow-derived cells (BMDC) beforehand. Kidney function and injuries were evaluated.
Results: Upon NTS injury, e/e mice developed more severe crescentic glomerulonephritis than WT mice, featured by heavier proteinuria, higher serum creatinine levels and exacerbated renal lesions, including crescent formation, renal inflammatory infiltration and fibrosis as well as podocyte damage, marked by loss of expression of podocyte homeostatic markers in glomeruli. Melanocortin therapy substantially improved renal injury in WT mice and this protective effect was blunted in e/e mice. In contrast, adoptive transfer of BMDC derived from WT mice to e/e mice markedly ameliorated NTS nephritis and reinstated the therapeutic efficacy of melanocortins in e/e mice. Mechanistically, the beneficial action of WT BMDC in e/e mice was associated with diminished glomerular deposition of autologous anti-rabbit IgG and reduced fixation of C5b-9 along glomerular capillary loops, entailing a regulatory effect of BMDC-specific MC1R signaling on humoral immune response to NTS antigens. In addition, melanocortin therapy prominently tilted macrophage polarization towards the anti- inflammatory M2 phenotypes in NTS-injured kidneys in WT mice. MC1R signaling is likely involved in this modulation of macrophage behavior, because MC1R was evidently expressed in bone marrow-derived macrophage (BMM) prepared from WT mice but absent from e/e BMM. Furthermore, MS05 diminished M1 phenotypes and promoted M2 polarization in M1-primed WT BMM but not e/e BMM, thus denoting a pro-M2 skewing effect of MC1R signaling.
Conclusion: Hematopoietic MC1R signaling attenuates NTS nephritis via, at least in part, regulation of humoral immune response and a pro-M2 skewing effect on macrophage polarization.

Bohan Chen (RF)
Delayed treatment with a novel highly selective small-molecule agonist of MC5R attenuates podocyte injury and proteinuria in puromycin aminonucleoside nephrosis
Bohan Chen, Lance Dworkin, Rujun Gong

Backgrounds: Clinical studies indicate that the melanocortin peptide adrenocorticotropic hormone (ACTH) is effective in inducing remission of nephrotic glomerulopathies like MCD and FSGS, even those resistant to steroids, suggesting that a steroid-independent melancortinergic mechanism might contribute. However, the type of melanocortin receptor (MCR) that conveys this beneficial effect as well as the underlying mechanisms remain controversial. Recently, burgeoning evidence suggests that MC5R is likely involved in glomerular pathobiology. This study aims to test the effectiveness of a novel highly selective MC5R agonist (MC5RA) in puromycin aminonucleoside (PAN) nephrosis.
Methods: MC5RA was generated by N-terminal modification of the melanocortin core tetrapeptide His-D-Phe-Arg-Trp-NH2 with an aromatic group, resulting in a triphenylpropionyl melanocortin analog with a 100-fold selective agonistic activity on MC5R. Rats were injured with a tail vein injection of PAN, and 5 days later, were randomized to daily MC5RA or vehicle treatment.
Results: Upon PAN injury, rats developed heavy proteinuria on day 5, entailing an established nephrotic glomerulopathy. Following vehicle treatment, proteinuria continued to progress on day 14 and was sustained till day 21, accompanied by evident histologic signs of podocytopathy, marked by ultrastructural lesions of glomeruli, including extensive effacement

of podocyte foot processes and podocyte microvillus transformation, and concomitant with loss of podocyte homeostatic markers, such as synaptopodin and nephrin, and *de novo* expression of podocyte injury marker desmin. Rescue treatment with MC5RA significantly attenuated urine albumin excretion and mitigated the loss of podocyte marker proteins, resulting in improved podocyte ultrastructural changes. *In vitro* in cultured podocytes, MC5RA prevented the PAN-induced disruption of actin cytoskeleton integrity and apoptosis. Mechanistically, MC5RA treatment reinstated inhibitory phosphorylation and thus averted hyperactivity of GSK3β, a convergent point of multiple podocytopathic pathways, in PAN-injured podocytes *in vitro and in vivo*.
Conclusions: Pharmacologic targeting of MC5R by using the highly selective small-molecule agonist is likely a promising and feasible therapeutic strategy to improve proteinuria and podocyte injury in glomerular disease.

Bohan Chen (RF)
MC1R signaling protects against experimental membranous nephropathy and mediates the beneficial effect of melanocortin therapy via regulation of humoral immune responses
Bohan Chen, Xuejing Guan, Lance Dworkin, Rujun Gong

Backgrounds: Clinical evidence suggests that melanocortin therapy by using adrenocorticotropin (ACTH) is effective in inducing remission of proteinuria in patients with idiopathic membranous nephropathy (MN) and even in those resistant to steroids or other immunosuppressants. Likewise, in passive Heymann's nephritis (PHN), a rat model of MN, ACTH and other non-steroidogenic melanocortins are able to ameliorate glomerular injury and proteinuria. However, the type of melanocortin receptor (MCR) mediating this beneficial effect as well as the underlying mechanism remains controversial. To this end, while humoral immune responses, marked by immunological remission of the anti-PLA2R autoantibody, have been noted in most MN patients after ACTH monotherapy, a direct podocyte protective effect of melanocortins possibly conveyed by MC1R has been suggested in animal models. This study aims to define the role of MC1R in the pathogenesis of PHN and in responding to melanocortin therapy.
Methods: MC1R knockout rats ($MC1R^{-/-}$) were generated by the CRISPR/Cas9 gene-editing system, and together with wild-type (WT) rats, received sheep anti-Fx1A antibody injections to develop PHN. Two weeks later, in the autologous phase of PHN, rats were treated with an equal dose (0.7 μmol/kg/d, q.d., s.c.) of NDP-MSH or MS05, or with the Repository Corticotropin Injection (RCI, Acthar® Gel, Mallinckrodt ARD, LLC; 60IU/kg, q.o.d., s.c.) or vehicle.
Results: Four weeks after the anti-Fx1A antibody injection, WT rats developed a constellation of signs of glomerulopathy, as evidenced by massive proteinuria, diminished glomerular expression of podocyte homeostatic markers, including synaptopodin, podocin and WT-1, and *de novo* expression of podocytopathic mediators like B7-1 or desmin. All these signs of glomerular injury were significantly exacerbated in $MC1R^{-/-}$ rats, denoting a protective effect of the constitutive MC1R signaling. Conversely, stimulation of MC1R in WT rats by MS05, an MC1R-specific agonist, or by pan-MCR agonists like RCI or NDP-MSH, substantially attenuated proteinuria in the autologous phase of PHN, and mitigated molecular and pathological signs of glomerulopathy. The therapeutic efficacy of melanocortins was markedly blunted in $MC1R^{-/-}$ rats with PHN. Mechanistically, the worsened PHN in $MC1R^{-/-}$ rats was unlikely due to a sensitized response of the kidney to injury, because on day 7 after anti-Fx1A antibody injection during the heterologous phase, proteinuria was noted to a comparable extent in $MC1R^{-/-}$ and WT rats. Rather, deficiency of an MC1R-mediated extra-renal mechanism may contribute. In support of this, despite granular fixation of the heterologous anti-Fx1A IgG along the glomerular capillary wall to a similar degree in $MC1R^{-/-}$ and WT rats, $MC1R^{-/-}$ rats exhibited much more intense fixation of the autologous anti-sheep IgG and the terminal complement complex C5b-9 along glomerular capillary wall during the autologous phase, denoting an amplified humoral immune response. In contrast, activation of MC1R by MS05 or by RCI or NDP-MSH in WT rats substantially diminished fixation of autologous IgG and C5b-9 along glomerular capillary wall in the autologous phase. This effect of melanocortin therapy was largely abrogated in $MC1R^{-/-}$ rats with PHN.
Conclusions: MC1R signaling protects against the PHN and contributes to the beneficial effects of melanocortin therapy, via at least in part, a regulatory effect on humoral immune responses.
Funding: Mallinckrodt ARD, LLC.

Dhilhani Faleel (GS)
Role of Paraoxanase in regulation of Cardiotonic Steroid
Dhilhani Faleel, Benjamin A. Talbot, Iman Tassavvor, Jacob Connolly, Fatimah K. Khalaf, Sabitri Lamichhane, Shungang Zhang, Prabhatchandra Dube, Deepak Malhotra, Steven T. Haller, David J. Kennedy

Introduction: Cardiotonic steroids (CTS) are significantly elevated in volume expanded conditions such as chronic kidney disease (CKD). CTS binds via their lactone ring and signal through the Na+/K+ATPase, which leads to renal

inflammation. Interestingly, endogenous enzymes Paraoxonases (PON-1, PON-2, and PON-3) are capable of hydrolyzing α-pyrone structures like CTS. In addition, our clinical data demonstrate an association between diminished Paraoxonase activity and CKD severity
Method: LC/MS/MS technique was used to identify the connection between Paraoxanase and CTS. To gain insight into the Paraoxonase - CTS interaction we used molecular modeling techniques. First, to predict binding affinity, we docked the PON-1 protein structure with CTS using Autodock Vina software and compared the simulated binding free energy scores with those of both known PON1 ligands and a random library of >900 small molecules. Next, we conducted a Molecular dynamic simulation study using GROMACS software at the Ohio supercomputer high-performance computing facility. The topology of the protein is defined by AMBER forcefield.
Results: First, our LC/MS/MS data suggest that Paraoxonases hydrolyze and open the CTS α -pyrones. Thus, CTS are unable to bind with Na+/K+-ATPase and stimulate the inflammatory signaling cascades. In our computational study, CTS had more favorable binding free energy scores than both known ligands and random small molecules. In addition, trajectory file analysis using VMD software indicated that CTS stays in the active site of PON-1.
Conclusion: Our Experimental and computational data suggest that PON-1 directly interacts and hydrolyzes CTS, and this may represent a novel regulatory mechanism for CTS.

Yudong Fang (RF)

The role of glycogen synthase kinase 3β in regulation of podocyte senescence: a novel senostatic target for delaying glomerular aging

Yudong Fang, Lance D. Dworkin, Rujun Gong

Backgrounds: Along with the steadily aged population, renal aging or age-related renal impairment has inevitably become a paramount challenge to nephrology practice. Age-associated decline in kidney function is associated with progression of age-related glomerulosclerosis, in which podocyte senescence plays a determinant role. Compelling evidence suggests that microdose of lithium, a typical inhibitor of glycogen synthase kinase 3β (GSK3β), alleviated aging and substantially prolonged lifespan in *Drosophila* and *C. elegans*. Notably, as a convergence point of multiple pivotal pathways, including insulin pathway, energy-sensing pathway and Nrf2 antioxidant response, GSK3β has been involved in podocyte pathobiology. However, it remains unknown how GSK3β regulates renal aging.
Methods: The regulatory effect of GSK3β on glomerular aging was examined in mice with doxycycline-induced podocyte specific ablation of GSK3β (KO) at 2, 12 and 24 months or in control littermates (Con). Cultured podocytes were examined for senescence.
Results: Accompanied with aging in mice, signs of kidney aging were evident in control mice, featured by persistent albuminuria, the relative decline in kidney function, as shown by an elevation in serum creatinine levels, and typical renal pathologic changes, including renal fibrosis, glomerular hypertrophy and focal global glomerulosclerosis on light microscopy, ultrastructural lesions of podocytes like podocyte foot process effacement and **deposits of cytoplasmatic absorption droplets,** podocytopenia marked by diminished WT-1 staining, and loss of podocyte markers like synaptopodin and podocin, as determined by immunohistochemistry staining and immunoblot analysis of isolated glomeruli. In parallel, senescence-associated β-galactosidase activity and the expression of senescence-related $p16^{INK4A}$, p53 and p21 were progressively augmented in glomeruli, concomitant with increased GSK3β activity, as inferred by elevated expression of GSK3β and diminished inhibitory phosphorylation of GSK3β. Linear regression analysis demonstrated that GSK3β activity was positively associated with the expression levels of $p16^{INK4A}$, p53 and p21 in glomeruli. In contrast in the aged KO mice, expression of GSK3β was largely ablated in podocytes in glomeruli, resulting in a blunted induction of $p16^{INK4A}$, p53, and p21 and β-galactosidase activity in glomeruli and a remarkable alleviation of all signs of kidney aging. Mechanistically, in silico analysis revealed that senescence-related $p16^{INK4A}$, p53, and p21 are cognate substrates of GSK3β and contain the GSK3β consensus motifs. Invitro, forced expression of a constitutively active GSK3β mutant in podocytes promoted phosphorylation of $p16^{INK4A}$, p53, and p21, associated with potentiated cellular senescence, marked by a heightened β-galactosidase activity and loss of podocyte differentiation markers like WT-1 and synaptopodin. Conversely, GSK3β knockdown attenuated phosphorylation of $p16^{INK4A}$, p53, and p21, leading to diminished cellular senescence.
Conclusions: GSK3β plays a key role in glomerular aging by regulating podocyte senescence, and thus is likely an actionable senostatic target for delaying glomerular aging.

Xuejing Guan (RF)

Melanocortin 1 Receptor (MC1R) Deficiency Exacerbates Glomerular Injury and Proteinuria in the Autologous Phase of Nephrotoxic Serum (NTS) Nephritis

Xuejing Guan, Rong Zhou, Lance D.Dworkin, Rujun Gong

Introduction: The clinical effectiveness of melanocortin therapy with adrenocorticotropin in inducing remission of steroid-resistant nephrotic syndrome points to a steroidogenic-independent anti-proteinuric activity of melanocortins. However, which melanocortin receptor conveys this beneficial effect is controversial. A growing body of evidence suggests that activation of podocytic MC1R may convey a podocyte protective and anti-proteinuric effect. However, this paradigm seems inconclusive because MC1R agonist was seemingly ineffective in such nephrotoxic glomerulopathies as Adriamycin nephropathy. Moreover, how MC1R signaling is involved in immune-mediated glomerular disease is unknown.
Methods: NTS nephritis was induced in mice with nonfunctional mutation of MC1R (e/e) and in wild-type (WT) mice by injection of rabbit NTS. Kidney function and renal injury were evaluated.
Results: Seven or 14 days after NTS injection during the autologous phase, e/e as compared with WT mice demonstrated an exacerbated kidney dysfunction and injury, as evidenced by higher serum creatinine levels, heavier proteinuria, and aggravated renal pathology, featured by glomerular hypercellularity, crescent formation, mesangial expansion, protein casts,and renal inflammation and fibrosis. Consistent with the worsened proteinuria, e/e mice displayed more severe podocyte injury, characterizedby podocytopenia, marked by diminished WT-1 staining, and loss of podocyte markers like synaptopodin and podocin. Mechanistically, the aggravated renal disease in e/e mice was unlikely due to a sensitized response of the e/e kidney to injury, because 1 day after NTS insult during the heterologous phase, e/e mice developed albuminuria,podocytopathy and glomerular damage to a comparable extent as WT mice.Rather, deficiency of an MC1R-mediated non-kidney-autonomous or extra-renal mechanism may contribute. In support of this, e/e mice exhibited much more glomerular deposition of autologous anti-rabbit IgG together with the terminal complement complex C5b-9 along glomerular capillary loops than WT mice during the same degree of deposition of glomerular basement membrane-reactive rabbit IgG.
Conclusion: MC1R signaling protects against glomerular injury and proteinuria in immune-mediated glomerular disease via, at least in part, an immune modulatory effect.

Elizabeth Shedroff (GS)

Assessment of Active Kinome Profiles in Peripheral Blood Mononuclear Cells in Renal Transplant Patients

Elizabeth S. Shedroff, , Kunal Yadav, Shobha Ratnam, Khaled Alganem, Hunter M. Eby, Puneet Sindhwani, Lance Dworkin, Robert E. McCullumsmith

End-stage renal disease (ESRD) is a life-threatening condition that is typically managed by dialysis or renal transplant surgery. A renal transplant may offer a patient the most normalcy in managing ESRD, and sometimes requires lifelong dependency on immunosuppressant drugs. We hypothesize that active kinome signatures derived from peripheral blood mononuclear cells (PBMCs) may be used to predict renal transplant rejection, as well as response to immunosuppressant drug therapy. We will prospectively obtain PBMCs from renal transplant candidates before and after transplant. PBMCs will be processed with phosphatase inhibitors and run on the Pamgene kinome array serine/threonine (STK) and phospho-tyrosine (PTK) chips. Samples will be run +/- protein kinase inhibitors to perturb signaling networks. Analysis of the kinome array data will be done via multiple bioinformatic pipelines. Key kinases in the regulatory pathways of the PBMCs will be identified via Upstream Kinase Analysis (UKA) and then classified via PLS-DA machine learning. Classification will sort the subjects into either acceptance or rejection of the kidney transplant, based on kinome profile and how it relates to favorable or unfavorable response to medication. These data will provide a personalized active kinome profile that may be used to guide immunosuppressant treatment for renal transplant patients. Preliminary bioinformatics analyses will be performed on curated data from the iLINCs database and GEO database, with the goal of evaluating drug and disease signatures and their impact of signaling neworks. In summary, this project may provide an important new tool for assessing state- and trait-based signaling networks in peripheral immune cells, allowing prediction of treatment course and drug response in renal transplant patients.

Sophia Soehnlen (MS)

Paraoxonase-3 Regulation of Cardiotonic Steroids Mediates Renal Injury and Dysfunction in a Dahl Salt Sensitive Model of Chronic Kidney Disease

Sophia Soehnlen, Chrysan Mohammed, Sabitri Lamichhane, Prabhatchandra Dube, Jacob Connolly, Andrew Kleinhenz, Dhilhani Faleel, Dragan Isailovic, Deepak Malhotra, Steven Haller, David Kennedy

Background: While the physiologic substrates for the hydrolytic enzyme paraoxonase-3 (Pon-3) are unclear, its lactonase activity is considered central to its native physiological role. Cardiotonic steroids (CTS) are natriuretic hormones that are increased in Chronic Kidney Disease (CKD) and promote renal inflammation and fibrosis via binding of their 17b-lactone ring to the alpha-1 subunit of the Na^+/K^+-ATPase (NKA-α-1). We hypothesized that reduction of Pon3 lactonase activity would lead to increased renal injury and dysfunction in a CTS induced rat model of CKD.
Methods/ Results: First, CTS levels in the urine of Dahl salt-sensitive rats (SS rats) and Pon3 knock-out rats on the Dahl salt-sensitive background (SS-*Pon3* KO) were quantified using mass spectrometry. We found that SS-*Pon3* KO rats had ~59 times greater increase in 24-hour urine CTS levels vs SS rats. Next, to examine the role of Pon3 in mediating CTS induced renal injury, ten-week-old, age-matched male SS control and SS-*Pon3* KO rats were administered the CTS telocinobufagin (TCB, 100 µg/kg/day s.q) for four weeks followed by assessment of blood pressure (tail cuff plethysmography) and renal function. We found that SS-*Pon3* KO rats following TCB administration had significantly increased 24-hour urinary protein excretion (UPE) (50.73 ± 3.59 vs 25.29 ± 2.07, $p<0.0001$), as well as decreased FITC-Sinistrin monitored glomerular filtration rate (GFR) (0.80 ± 0.10 vs 1.16 ± 0.05, $p<0.01$) compared to SS control rats, despite similar degrees of hypertension.
Conclusion: These findings suggest that Pon3 plays a critical role in regulating CTS mediated renal dysfunction in vivo.

Shungang Zhang (GS)

Disruption of CD40 Attenuates Renal Injury Induced by Acute High Salt Intake in Experimental Hypertensive Renal Disease

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Background: We have recently shown that circulating levels of the proinflammatory receptor CD40 predict progression of renal dysfunction in patients with hypertensive renal disease and the soluble ligand for CD40 (sCD40L) is significantly elevated in this setting. In our CD40 knockout (KO) model developed on a background prone to hypertensive renal disease (Dahl S rat), we demonstrated significantly reduced renal fibrosis and improved renal function following a chronic high salt diet. To test the hypothesis that disruption of CD40 attenuates early indicators of renal injury and reduces inflammation, we performed the following acute high salt study.
Methods: Seven-week old Dahl S wild-type and Dahl S CD40KO male rats (n=8 per group) were given a high salt diet (2% NaCl) for 1 week. Blood pressure, urinary protein excretion (UPE), and plasma creatinine were measured. Kidneys were assessed for evidence of inflammation and injury.
Results: After acute high salt diet, blood pressure and plasma creatinine between wild-type Dahl S rats and Dahl S CD40KO rats were similar. UPE was significantly reduced in the Dahl S CD40KO compared to Dahl S rats (33.7 ± 6.8 mg/24h vs. 106.9 ± 28.6 mg/24h, $p<0.05$). Renal cortex gene expression of kidney injury molecule-one (KIM-1) ($p<0.05$), monocyte chemoattractant protein-1 (MCP-1) ($p<0.001$), and chemokine (C-X-C motif) ligand 2 (CXCL-2) ($p<0.05$) were significantly lower in Dahl S CD40KO rats compared to Dah S rats as assessed by quantitative PCR.
Conclusion: Disruption of CD40 significantly reduced proteinuria, KIM-1, and markers of inflammation following acute high salt induced renal injury. Our results indicated that CD40 may serve as a therapeutic target to inhibit acute renal injury and prevent the progression of hypertensive renal disease.

PULMONOLOGY

Erin Crawford (S)

Low frequency TP53 mutations in airway epithelial cells serve as lung cancer risk biomarker

Daniel J. Craig, Erin L. Crawford, Pierre P. Massion, Thomas Morrison, James C. Willey

Background: Lung cancer is the leading cause of cancer-related death in men and women in the United States. Based on evidence from controlled trials in the United States and Europe that low dose CT (LDCT) screening significantly reduces lung cancer mortality, the United States Preventative Services Tasks Force (USPSTF) recommends LDCT screening for

individuals with high demographic risk based on age and smoking history. However, alarge fraction of lung cancers occur in individuals who do not meet LDCT screening threshold criteria. Thus, there is a need for biomarkers that supplement demographic factors to more accurately detect those at highest lung cancer risk and include additional individuals who will benefit from LDCT screening. An initial study from this lab demonstrated that TP53 mutations with 0.05-1.0% variant allele fraction (VAF) were significantly more prevalent ($p<0.005$) in grossly normal airway epithelial cell (AEC) specimens from lung cancer cases compared to non-cancer controls matched for smoking and age. Here, we present an expanded follow-up study aimed at testing this biomarker according to PRospective-specimen-collection, retrospective-Blinded-Evaluation (PRoBE) design.
Methods: AEC specimens were prospectively collected through the National Cancer Institute Early Detection Research Network (EDRN) program from 60 subjects at high demographic risk for lung cancer by bronchoscopic brush biopsy at Vanderbilt University Medical Center. Genomic (g)DNA was extracted from each AEC specimen and stored at -80 degrees Celcius. Subjects matched for age and smoking history who subsequently did or did not develop lung cancer were identified and gDNA specimens, blinded with respect to cancer status, were shipped to the University of Toledo. gDNA specimens were quantified and 50,000 gDNA copies were included in each NGS library preparation. Synthetic DNA internal standards (IS) were prepared for multiple lung cancer driver mutations within the TP53 gene and mixed with each AEC gDNA specimen prior to competitive multiplex PCR NGS library preparation. By controlling for technical error, this approach enables reliable detection of mutations with VAF as low as 5 x 10-4 (0.05%) (Craig et al, BMC Cancer, 2019).
Results: Following library preparation and sequencing on Illumina Novaseq, there was sufficient library complexity to detect TP53 VAF <0.05% in >90% of AEC specimens. The data are currently in pipeline analysis. After analysis is complete, VCF files will be sent to Vanderbilt for unblinding and validation of the biomarker.
Conclusions: Based on preliminary data, we expect that sufficient AEC gDNA is available from most subjects enrolled in the EDRN program for TP53low VAF biomarker analysis, and the previously reported method (Craig et al, BMC Cancer, 2019) is reliable and feasible. The current study should provide additional information regarding validity of the biomarker.

Erin Crawford (S)

Use of a synthetic spike-in ladder to measure NGS library complexity

Erin L. Crawford, Tian Chen, Daniel J. Craig, James C. Willey

Background: Detection of rare variants in traditional and liquid biopsies is becoming increasingly important for cancer diagnosis, monitoring and treatment. Next Generation Sequencing (NGS) has the capacity to detect known and novel variants in small biological samples with a high level of sensitivity. However, the limit of detection is affected by sample DNA concentration and integrity, technical error and number of unique molecules captured and sequenced (library complexity). Unique molecular identifiers (UMl) and random fragment end analysis commonly are used to measure complexity yet both are reported to have systematic biases leading to a non-random read distribution when measured, altering interpretation of results and potentially skewing data. Here we describe the use of a spike in complexity calibration ladder comprising synthetic DNA internal standard competitors (IS) as an orthogonal measure of library complexity.
Methods: An Endogenous Complexity Calibration Ladder (ECCL) comprising multiple unique synthetic IS at different concentrations was created. All ECCL IS share homology with each other and endogenous human SCGB1A1 sequence but each contain nucleotide changes at different positions along the sequence string so that they can be distinguished. The ECCL was mixed with several IS targeting different TP53 exons in a fixed proportion. The ECCL/TP53 IS mixture is designed to be used in either amplicon or hybrid-capture library preparation. Here, amplicon libraries were generated. Molecule numbers and ratios between IS were determined using deep sequencing of multiple replicates. The ECCL/TP53 IS mix was spiked into a commercial human gDNA prior to NGS library preparation. Serial dilutions (1.5-, 3-, 6-, 12- and 24-fold) and intentional addition of inhibitors were conducted to stress and test the system. The ECCL/TP53 IS mixture also was spiked into gDNA from 60 primary airway epithelial cell (AEC) specimens prior to library preparation and NGS to measure TP53 variant fraction while controlling for complexity.
Results: Observed complexity measured using the ECCL was close to expected for each serially diluted mixture of gDNA and ECCL/TP53 IS. The precision of complexity measurement for less dilute and less inhibited samples was limited by absence of finer titration of the least concentrated IS in ECCL. Use of ECCL enabled measurement of inter-sample variation in complexity among the 60 AEC specimens.
Conclusions: The ECCL controls for both sample and library specific variation in complexity, and enables better estimation of the lower limit of detection for variant allele fraction (VAF). Additionally, it is compatible with the use of target specific IS which allow for improved measurement of technical sequencing error. The variation in complexity

observed in primary AEC gDNA samples demonstrates the need to account for this when assessing rare variant allele fraction.

Colette Gaba (F)

Increasing racial diversity in GELCC high-risk lung cancer families

Diptasri Mandal, Colette Gaba, James C. Willey, Erin Crawford, Ann Schwartz, Joan E. Bailey-Wilson

Introduction: Lung cancer (LC) is the leading cause of cancer related deaths for both men and women in the United States and is the second most commonly diagnosed cancer. The age-adjusted LC incidence rate is ~32% higher in African Americans (AA) compared to European-Americans (EAs). Previous multipoint linkage analyses of high-risk LC families (≥4 affected LC cases/family) collected by the Genetic Epidemiology of Lung Cancer Consortium (GELCC) detected significant linkage to the 6q23-25 regions in 52 families (including 14 families recruited by the University of Toledo). Targeted sequencing analyses in the region have identified susceptibility genes including RGS17, PARK2 and other loci in the 9 linked families. Families with >4 lung cancers, for our purposes, represent familial lung cancer (FLC).
Methods: Karmanos Cancer Institute (KCI), in Detroit, MI serves a clinical population that is 40% AA and identifies AA lung cancer families via identification in the clinic and through previous lung cancer case-control studies. KCI also partners with the Detroit Research on Cancer Survivors (ROCS) study, a U01 infrastructure grant supporting the population-based enrollment of AA cancer survivors and their caregivers in studies of cancer outcomes. KCI has accrued 68 AA lung cancer families for GELCC, supported by community partnerships to increase involvement of AA in cancer research.
In Louisiana, having a 35% statewide AA populace and only 9.1% of the state population with a college degree, Louisiana State University (LSU), has recruited 17 AA families with 3 or more lung cancer cases and 16 AA families with 2 lung cancer cases in the family for GELCC. Outreach efforts are underway to involve and provide incentives for increasing AA participation.
Toledo, Ohio, serves a 27% AA populace, nearly double the US average, of 14%. City-wide disparities include a 25% are uninsured rate, versus 15% county-wide rate. University of Toledo contributed an African American family for linkage to GELCC, and nearly 10 families submitted samples overall. To increase AA involvement and retention, we are connecting with local partners and thought leaders for the benefit of AA families and the positive.
Results: Recruitment and retention of AA individuals into research studies is known to be complex and may be difficult due to multiple reasons including distrust of the scientific community, previous unethical research involving AA individuals, and concerns over discrimination and marginalization as a result of genetic studies1. In an analysis of study participation at the New Orleans site of the Genetic Epidemiology of Lung Cancer Consortium (GELCC) project, requiring a screening telephone interview on smoking history and familial cancer history, Harris (2004) reported only 46% of eligible African-Americans but 57% of Caucasians agreed to participate (unpublished data). The main reason given by African-Americans who declined participation was that they were too sick, while Caucasians declined participation primarily due to disinterest. The authors concluded that the disparity in participation may be reduced by culturally-sensitive recruitment strategies, which address unique concerns and barriers to participation.
Discussion: The GELCC's long-term collection of 169 well-phenotyped, highly aggregated HRFLC families with multiple biospecimens and our very large collection of additional FLC cases with a family history of LC make this study unique. The work planned in these ongoing projects will strengthen this resource by increasing the number of AA families in the study.
Fully developed pedigrees for linkage analysis of African-American families may identify rare risk and protective variants specific to their race and will improve the generalizability of our findings to those with AA heritage

Lukken Imel (CF)

Comparison of Comorbidities between Sarcoidosis and Sjogren's Syndrome

R. Lukken Imel, Yasmin Khader, Ragheb Assaly, Nezam Altorok, Sadik Khuder

Background and Objective: Sarcoidosis and Sjögren's syndrome share common features in terms of their autoimmune nature involving host white blood cells targeting various organs. The purpose of this study was to further characterize comorbidities associated with these diseases as well as identify characteristics of those affected based on ethnicity, gender, socioeconomic factors, and healthy lifestyle.
Methods: The HCUP data from 2017 and 2018 were analyzed with Statistical Analysis Software (SAS). ICD10 codes was used to identify Sarcoidosis and Sjögren's syndrome. Prevalence of chronic lung disease, depression, obesity, tobacco

abuse was calculated for both disease states and compared using Chi square test. Prevalence amongst different races and median household income were also compared.
Results: Chronic lung disease, COPD, obesity, tobacco abuse was significantly higher in sarcoidosis compared to Sjogren's syndrome. Depression was more prevalent in Sjögren's syndrome. Females were more likely to be affected in both diseases, however, Sjögren's syndrome was significantly higher with 91.5% compared to 56% of Sarcoid patients. Sarcoidosis was highest amongst blacks and lowest amongst Asians whereas Sjogren's was highest amongst whites and lowest amongst blacks and Hispanics. Sarcoidosis was highest amongst low-income groups whereas Sjögren's syndrome was highest amongst those in the high-income groups.
Conclusions**:** Sjögren's syndrome and sarcoidosis share common features in their predisposition to respiratory diseases. An interdisciplinary approach between pulmonary medicine and rheumatology is important for optimal care and treatment in such patients.

Nithin Kessireddy (R)
Efficacy of Exercise Program on Asthma Control Questionnaire: A systematic review and meta-analysis
N. Kesireddy, MD; W. Khokher, MD; P. Mudiyansselage, MD; S. Vukanti (Undergraduate Student)
Background: Recent studies have highlighted possible linkage between obesity and inflammatory response of asthma. Helping control asthma symptoms in obese patients can be particularly difficult. Few studies have explored the efficacy of exercise in controlling asthma symptoms in the obese.
Patients and methods: We performed a comprehensive search in the databases. We considered randomized controlled trials, cohort studies, case-control studies, and case series. We excluded abstracts, animal studies, case reports, reviews, editorials, and letters to editors. From each study, we collected the number of patients who had exercise intervention program. The primary outcome was control of symptoms per asthma control questionnaire. Secondary outcomes were not calculated due to studies having different parameters. The control group underwent weigh loss measures but did not have any exercise intervention. The random-effects model was used to calculate mean differences in asthma control questionnaire, and confidence intervals (CI). A p value <0.05 was considered statistically significant. Heterogeneity was assessed using the Higgins I^2 index.
Results: Three randomized controlled trials involving 379 patients were included in the meta-analysis. The exercise program population did have significantly lower ACQ scores compared to those patients just receiving standard treatment along with weigh loss intervention (MD -0.67, 95% CI -1.27 – 0.07, $p < 0.01$, $I^2 = 77\%$).
Conclusion: Our meta-analysis demonstrated that exercise program can help reduced scores for ACQ which might help in overall asthma symptom control in obese patients.

Nithin Kessireddy (R)
CPAP Effects on Recurrent Atrial Fibrillation After Ablation: A Systematic Review and Meta Analysis
N. Kesireddy, MD; W. Khokher, MD; P. Mudiyansselage, MD; M. T. Awad, MD; S. Ghazaleh, MD; S. Iftikhar, MD

Introduction: Atrial fibrillation (AF) is associated with higher rates of obstructive sleep apnea. There are limited studies indicating if patients with obstructive sleep apnea (OSA) carry higher risk of recurrent AF after successful catheter ablation. Our metanalysis looks to compare recurrence rate of atrial fibrillation in treated vs untreated OSA patients who underwent successful catheter ablation.
Methods: We performed a comprehensive search in the databases. We considered randomized controlled trials, cohort studies, case-control studies, and case series. From each study, we collected the number of patients who received CPAP for their OSA and those who had No CPAP. The events recorded were the recurrence of atrial fibrillation. The random-effects model was used to calculate the risk ratios (RR), and confidence intervals (CI). A p value <0.05 was considered statistically significant. Heterogeneity was assessed using the Higgins I^2 index
Results: 13 studies were examined which fit the search criteria with 2336 patients. OSA patients with AF after catheter ablation who had CPAP intervention decreased risk of recurrent AF with pooled risk ratio of 0.66 (CI 0.50-0.87, I^2=77). Most of the patients in the study were free of recurrent of atrial fibrillation for minimum of three months.
Conclusions: Our meta-analysis demonstrated that patients with OSA and had CPAP intervention with significantly reduced the rate of recurrent atrial fibrillation compared to those with untreated OSA.

Nithin Kessireddy (R)
Efficacy of Proton Pump Inhibitors in the Prevention of Upper Gastrointestinal Bleeds in the Intensive Care Unit - A Systematic Review and Meta-Analysis
N. Kesireddy, MD; W. Khokher, MD; P. Mudiyansselage, MD; S. Vukanti (Undergraduate Student)

Introduction: Upper gastrointestinal bleeds (UGIB) can occur secondary to stress ulcers, especially in intensive care unit ICU patients who are undergoing increased physiological stress. We assessed the occurrence of UGIB in ICU patients with proton pump inhibitor (PPI) compared to placebo.
Methods: We conducted a systematic review and meta-analysis of studies that investigated the efficacy of PPI prophylaxis in preventing UGIB in ICU patients. We performed a comprehensive search in the databases of PubMed/MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials. We considered randomized controlled trials, cohort studies, case-control studies, and case series. We excluded abstracts, animal studies, case reports, reviews, editorials, and letters to editors. From each study, we collected the number of patients who received PPI prophylaxis vs placebo (saline) daily. The primary outcome was the occurrence of UGIB. Secondary endpoints were difficult to assess due to studies reporting data inconsistently for secondary endpoints. The random-effects model was used to calculate the risk ratios (RR), and confidence intervals (CI). A p value <0.05 was considered statistically significant. Heterogeneity was assessed using the Higgins I^2 index.
Results: Six trials involving 693 patients were included in the meta-analysis. The occurrence of UGIB was similar between the experimental and placebo group (RR 1.07, 95% CI 0.37 – 3.10, $p < 0.90$ $I^2 = 0\%$).

James Willey (F)
University of Toledo Licensee Accugenomics, Inc. Develops Synthetic Internal Standards for Pharmaceutical and Diagnostics Industry.
Tom Morrison, Bradley Austermiller, Nick Lazaridis, Chris Holshouser, Caroline Smith-Moore, Karen O'Connell, Peter Bernhardt, Veronica Fowler, Melissa Scott, Peggy Thomas, Nicole Hoover

Companies that prepare commercial passive antibodies for protection against COVID-19 work with large cell banks. Adventitious agent (AA) testing of Master and Working cell banks is one critical aspect of purity testing as it minimizes risk of upstream contamination. Adventitious agent testing is moving away from the use of animal models to more in vitro tests such as cell culture and PCR-based methods. Targeted next generation sequencing (NGS) panels promise multiplex detection of AA but are highly complex which may lead to unpredictable testing failures. In this project, funded by National Institute for Innovation in Manufacturing Biopharmaceuticals, AccuGenomics developed a test kit—AccuKit—that streamlines adventitious agent screening (to one day) while directly ensuring every target is measured with the required sensitivity of RT-PCR and the specificity of NGS. The SNAQ sensitivity controls are compatible with efforts to produce non-biased AA detection, as it ensures that known agents would be detected if present. The project had a budget to create 22 AA NGS panel. Celgene, Merck and NCSU could not agree upon the 22 AA, so AccuGenomics took their >100 target wish list and created a ranked of order AA list to select the top 24. The literature searches identified at least 3 validated primer pairs for each AA. Synthetic dsDNA templates were created and diluted to 10 copies to identify pairs capable of detecting template by SYBR GREEN realtime PCR. The resulting primer pairs were tested in multiplex PCR the mimic the first PCR step of the NGS library preparation (PCR1) and end point yields estimated by real-time PCR. Based on endpoint yields, primer pairs were divided into three PCR pools. The IS sensitivity controls indicated 13 of 19 assays achieved the desired test sensitivity. Root cause analysis for the 6 poorly performing samples were the result of switching nucleic acid extraction from a "mega" scale to a method designed for a cell pellet affected some primer pairs during the multiplex PC step. Based on these preliminary results, Accugenomics is now funded by NIIMBL and the USAF for a total of >$2 million to develop internal standards for NGS measurement of critical targets, including Sars-COVID-19.

RHEUMATOLOGY

Aya Abugharbyeh (CF)
Decreased incidence of Scleroderma in Type 1 and Type 2 diabetes and reduced frequency of Scleroderma lung disease in patients with Type 2 diabetes
Aya Abugharbyeh, Shadia Nada, Sadik Khuder and Bashar Kahaleh

Introduction: Limited evidence suggest that autoimmune diseases tend to coexist at a higher rate than expected, reflecting common pathogenetic pathway. Here we investigate the co-occurrence of scleroderma (SSc) and diabetes (DM).
Methods: HCUP-US data for the years 2017 and 2018 were searched using ICD10 codes. We identified 79,980 patients with type 1 DM, 1,574,262 patients with type 2 DM, and 6335 SSc patients (SSc I) and 442 SSc patients with lung involvement (SSc II). We used weighted logistic regression to examine the association between diabetes and SSc adjusting for demographics and other confounding variables.

Results: The prevalence of SSc I among patients with type 1 DM (0.06%) was significantly lower than that for the non-DM control group, (0.09%) with p-value = 0.0026. Similarly, lower prevalence was noted among patients with type 2 DM (0.07%) that was significantly lower than that for the control group (0.10%) with p-value < 0.0001, with a 43.9% reduction in the odds of scleroderma among patients with type 2 DM.
The prevalence of SSc II among patients with type 1 DM was lower than that in the control. However, the difference was not statistically significant (p = 0.0731). While the prevalence of SSc II among patients with type 2 DM (0.001%) was significantly lower than the control group (0.01%) with p-value < 0.0001.
Conclusions: The data suggest an inverse relation between SSc and DM suggesting that SSc and DM may have different immune-pathogenesis or that DM environment influence the incidence of SSc and SSc organ complications.

Abdulaziz Aldhafeeri (R)
Leflunomide induced pancytopenia in a patient with rheumatoid arthritis
Abdulaziz Aldhafeeri, Kirubel Zerihun, Yasmin Khader, Nezam Altorok

Background**:** Leflunomide arrests the growth of activated lymphocytes by inhibiting the enzyme dihydroorotate dehydrogenase, thus inhibiting de novo pyrimidine synthesis.
Case presentation: A 69-year-old male with past medical history of rheumatoid arthritis on leflunomide presented with worsening diarrhea, fatigue and diffuse abdominal pain. Physical examination was remarkable for pale conjunctiva and oral mucositis. CBC with differential show pancytopenia with WBC = 1.1 x10E9/L, RBC = 2.76 x10E12/L, Platelet= 16 x10E9/L, absolute neutrophil count of 0.1 x10E9/L and absolute lymphocyte count within normal limit at 1 x10E9/L. At time of admission, leflunomide was discontinued and cholestyramine was started. Bone marrow aspiration show mildly hypercellular marrow for age comprised of maturing trilineage hematopoiesis with relative erythroid and megakaryocytic hyperplasia. The findings were consistent with myelodysplastic syndrome with multilineage dysplasia. Over the course of 9 days, CBC with differential was obtained on a daily basis and it clearly show improvement of pancytopenia in the setting of discontinuation of leflunomide and administration of cholestyramine. At time of discharge, CBC with differential show WBC =2.4 x10E9/L, RBC= 3.08 x10E12/L, PLT= 204 x10E9/L, absolute neutrophil= 1 x10E9/L, and absolute lymphocyte= 1. 1 x10E9/L. Six days after discharge, CBC with differential show WBC=7.8 x10E9/L, RBC= 3.81, Platelet= 186 x10E9/L, absolute neutrophil= 6.6 x10E9/L and absolute lymphocyte= 1.1 x10E9/L.
Conclusions: Incidence of pancytopenia in patients taking leflunomide dramatically increases with concomitant use of methotrexate. However, our case show pancytopenia associated with leflunomide with recent use of methotrexate and uncovered underlying myelodysplastic syndrome.

Abdulaziz Aldhafeeri (R)
Sjogren's Syndrome patient presented with Organizing Pneumonia
Abdulaziz Aldhafeeri, Raied Hufdhai, Nezam Altorok

Background: Secondary organizing pneumonia is a challenging diagnosis and rarely associated with Sjogren's syndrome.
Case presentation: A 64-year-old female with history of Sjogren syndrome, proven by minor salivary gland biopsy, and hypothyroidism presented with progressively worsening shortness of breath over six weeks. Initial labs show WBC at 5.8x10E9/L, CRP at 15mg/dL, and Procalcitonin at 0.20ng/mL. CT scan of the chest show extensive bilateral multi-lobar regions of bandlike confluent regions of groundglass and consolidative opacity with basal predominance, consistent with organizing pneumonia. On day 3, intravenous (IV) methylprednisolone 30 mg every 8 hours was added due to lack of improvement. On day 4, patient was intubated due to increased oxygen requirement. Bronchoalveolar lavage was done at time of intubation, but the culture came back negative. On day 7, repeat CT scan of the chest show significant progression of chest findings. Therefore, mycophenolate mofetil was added. On day 10, mycophenolate mofetil was discontinued and rituximab 1000 mg was initiated in addition to IV methylprednisolone 250 mg daily for three days due to lack of improvement. Her respiratory status subsequently improved, and she was extubated on day 13 of admission. Eventually, patient condition improved and did not require oxygen at time of discharge. Four weeks after discharge, she did not require oxygen support.
Conclusion: Secondary organizing pneumonia is a challenging diagnosis and usually requires collaboration of rheumatology to recognize connective tissue disease associated lung disease, as it may have a dramatic impact on outcome of treatment as highlighted in this case.

Azizullah Beran (R)

Colchicine Treatment in SARS-CoV-2 Infection: A Systematic Review and Meta-Analysis

Azizullah Beran, Mohammed Mhanna, Sami Ghazaleh, Omar Sajdeya, Muhamad Kalifa, Hazem Ayesh, Omar Srour, Asmaa S. Mhanna, Nezam Altorok, Ragheb Assaly

Introduction: Several studies have investigated the use of colchicine in COVID-19 due to its anti-inflammatory effects. However, the data regarding its efficacy is still limited and conflicting. This meta-analysis aimed to evaluate the impact of colchicine on mortality and risk of mechanical ventilation in patients with COVID-19.
Methods: We performed a comprehensive literature search of electronic databases from inception through April 10, 2021, for all peer-reviewed studies that evaluated the clinical benefits of colchicine COVID-19 patients. The primary outcome was the mortality rate. The secondary outcome was the risk of mechanical ventilation. Pooled risk ratio (RR) and 95% confidence intervals (CIs) were obtained by the Mantel-Haenszel method within a random-effect model.
Results: A total of eight studies involving 926 COVID-19 patients (406 patients received colchicine along with standard-of-care (SOC) therapy and 520 received SOC therapy alone) were included. The mean age was 63.7±14.7 years, and males represented 63.3%. Mortality rate was significantly lower in the colchicine treatment group compared to SOC (RR 0.49 (95% CI: 0.34-0.72, P = 0.0002). However, there was no statistically significant difference in the risk of mechanical ventilation (RR 0.69, 95% CI: 0.31-1.57, P = 0.38).
Conclusions: Colchicine showed improvement in mortality in COVID-19 patients. However, there was no significant improvement in the risk of mechanical ventilation. Colchicine may be a potential therapeutic option for COVID-19. Even though the results are encouraging, we need more large-scale randomized controlled trials to better characterize the clinical benefits of colchicine in COVID-19 patients.

Brad Brickman (MS)

Spondyloarthropathies that Mimic Ankylosing Spondylitis

Brad Brickman; M. Tanios, MD; Sreeram Ravi

Study Design: Narrative Review.
Introduction: To highlight the epidemiology, pathophysiology, presentation and management of spondyloarthropathies as they affect the axial skeleton and mimic ankylosing spondylitis.
Methods: Search of electronic databases such as Google Scholar, PubMed, and Ovid for publications including ankylosing spondylitis, psoriatic arthritis, inflammatory bowel disease related spondyloarthropathy, and alkaptonuria.
Results: Ankylosing spondylitis is the most common type of seronegative inflammatory spondyloarthropathies. It presents with low back or neck pain, stiffness, kyphosis, and fractures that are commonly missed on initial presentation. Other types of seronegative inflammatory spondyloarthropathies such as psoriasis, reactive arthritis and metabolic spondyloarthropathies such as alkaptonuria affect the spine and have similar presentation to ankylosing spondylitis. However, there are characteristic radiographic findings and laboratory tests that may help in the differential diagnosis.
Conclusions: Axial presentations of seronegative inflammatory and metabolic spondyloarthropathies occur more often than previously thought. Identification of their associated symptoms and radiographic findings are imperative to effectively manage patients with these diseases.

Nicholas Delcimmuto (MS)

Nontraumatic subarachnoid hemorrhage in a patient with sarcoidosis.

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Introduction: Granulomatous inflammation involving the meninges is a rare manifestation of sarcoidosis that may disrupt the blood-brain-barrier. We present a case of sarcoidosis presenting with a chief complaint of thunderclap headache.
Case presentation: A 28-year-old African American male with essential hypertension and recent sinus biopsy-proven sarcoidosis presented with thunderclap headache associated with hiccups and confusion. Patient's family history is remarkable for intracranial aneurysm. Vital signs were significant for hypertension. Physical examination was remarkable for neck stiffness. Routine labs were unremarkable. Computed tomography scan of the head showed subarachnoid blood product in the interhemispheric fissure anteriorly. Cerebral angiogram was negative for aneurysm, arteriovenous malformation, fistula or any structural abnormality. Magnetic resonance image (MRI) with contrast of the brain showed extensive cortical signal abnormality and diffusely enhancing leptomeninges, most consistent with neuro-sarcoidosis. Lumbar puncture (LP) showed lymphocytosis with elevated protein, normal glucose, and elevated angiotensin converting

enzyme level in the cerebrospinal fluid. Patient was started on intravenous methylprednisolone 1000 milligram (mg) daily. After three days of treatment and clinical improvement, IV methylprednisolone was gradually decreased over the course of admission. Patient was eventually discharged to inpatient rehabilitation with prednisone 60 mg daily and Azathioprine 100 mg daily.
Conclusion: Subarachnoid hemorrhage is a potential rare complication of neuro-sarcoidosis. As there is no neurodiagnostic test pathognomonic for neuro-sarcoidosis, MRI brain with contrast and LP are helpful to rule out other differential diagnoses. The mainstay of treatment for neuro-sarcoidosis is immunosuppression with steroids.

Raied Hufdhi (R)
Successful treatment of Rheumatoid Arthritis Associated Interstitial Lung Disease with Rituximab; A case series
Raied T Hufdhi MD; Nezam Altorok MD

Rheumatoid arthritis (RA) is a chronic autoimmune disease affecting nearly 1% of the population. RA associated interstitial lung disease (RA-ILD) is one of the extra-articular manifestations of RA associated with a significant increase in morbidity and mortality. Existing literature is scarce on best approach to treatment of RA-ILD. This report describes three RA-ILD patients who experienced significant improvement of RA-ILD after treatment with Rituximab, an anti-CD20 monoclonal antibody. All patients initially received two 1000 mg doses of Rituximab two weeks apart. Repeated every six months.
Patient #1: 61 years old African American male with seropositive (RA) and ILD, RA manifested by inflammatory arthritis and synovitis of hands small joints bilaterally associated with synovial thickening of interphalangeal joints, (ILD) has been worsening despite multiple courses of Prednisone, Hydroxychloroquine and continuous O2, Pulmonary function test (PFT) was strikingly diminished FEV1 42%, FVC 38% and DLCO 23%, was being evaluated for lung transplant. Rituximab initiated, after first dose PFT improved, FEV1 47.18%, FVC 43.88, more improvement in PFT was achieved, O2 sat is 94% on ambient air (off the O2 for the first time in two years), significant improvement reported in joint pain, PFT is FEV1 69%, FVC 65%. Our patient is able to walk 2.3 mile, maintain normal O2 sat, lung transplant plans were held off.
Patient #2: 65 years old female patient with seropositive RA and ILD, ILD related arthritis, Rituximab led to significant improvement in respiratory function, over the course of treatment he received two cycles of rituximab, in the meantime she was on small dose prednisone, leflunomide 20 mg and hydroxychloroquine. FVC improved significantly from 50% to 64% with significant improvement in DLCO. After resuming the full dose of rituximab her symptoms improved significantly.
Patient #3: a 74 years old male patient with seropositive RA and ILD since 2004 on Infliximab, methotrexate and prednisone, rituximab started early 2015 for lack of symptoms control and worsening lung function, within few months of initiating the rituximab infusion, he reported significant improvement in hands pain, breathing and exercise tolerance. The PFT significantly improved FVC of 99% and DLCO on 60%, to FVC 107% and DLCO 62%.
Conclusion: In conclusion, we report a favorable outcome in patients with RA-ILD after treatment with Ritixumab. Our findings suggest a potential role for rituximab in treatment of RA-ILD.

Raied Hufdhi (R)
Shrinking lung syndrome a rare complication of connective tissue disease, case presentation
Raied T. Hufdhi MD, Hadeel I. Rushdi MD, Abdulaziz Aldhafeeri MD, Nezam Altorok MD

Introduction: Shrinking lung syndrome (SLS) is a relatively rare respiratory complication of systemic lupus erythematosus (SLE), the prevalence is around 1% in SLE patients, however, (SLE prevalence in the US is ranging between 20-150 in 100,000 population). Pathophysiology is likely due to phrenic nerve neuropathy, diaphragm muscle involvement and pleural tissue inflammation, unexplained dyspnea and/or pleuritic chest pain should raise suspicion. In this case presentation we will discuss the respiratory function decline in a patient with SLE.
Case presentation: Our case is a 62 year-old lady former smoker for 38 years (quit 10 years ago) who was diagnosed with SLE in 2015 based on positive ANA, malar rash and polyarthropathy. She was maintained on treatment with hydroxychloroquine. In February 2020 she started complaining of pleuritic chest pain on the left side. She had PFT done, which show significant decrease in her FVC (52% predicted), FEV1 (53% predicted), TLC (69% predicted) and significantly reduced DLCO (74% predicted), chest CT scan (figure 2) showed linear scarring on the left lung base, ventilation/perfusion scan showed small unmatched but non segmental perfusion defect consistent with linear atelectasis seen on the CT scan, echocardiogram was not remarkable. Restrictive lung disease was initially entertained with possible obstructive airway pattern at the small airway level. PFT showed significant decline in lung volumes and diffusion lung

capacity (figure1). NSAIDs and muscle relaxants did not improve her chest pain, Prednisone was started however, she stopped taking it after two days due to uncontrolled hyperglycemia.
Conclusion: SLS is a rare complication of SLE, SLS tends to affect more patients with less active SLE disease on the SLE disease activity index, the most reported presentation is fatigue, dyspnea on exertion, chest pain pleuritic in nature (our patient presented also with restrictive respiratory pattern) and diaphragmatic elevation with limited or no parenchymal involvement, diagnosis` preferred modality is imaging (chest X-ray and high resolution chest CT in addition to pulmonary function test, SLS can be debilitating in certain patients with difficult to control chest pain, and the treatment is not widely standardized however, steroid is the mainstay ranging between medium and high dose, in addition to immunosuppressive agent if low or no response with steroid alone, bronchodilators can also be added to the treatment regimen. Overall prognosis is favorable.

Raied Hufdhi (R)
The Burden of Neuro-Psychiatric Symptoms in a Large Cohort of Patients with Non-Clonal MCAS
Raied T Hufdhi MD, Matthew P Giannetti MD, Matthew Hamilton MD; Mariana Castells MD, PhD

Background: Non-clonal mast cell activation syndrome (MCAS) is defined by episodic and/or chronic multisystem symptoms, response to medications and increased MC mediators. The burden of neuro-psychiatric symptoms in this population has not been characterized.
Aim of the study: To assess the frequency and severity of neuro-psychiatric symptoms in patients with MCAS along with the impact on quality of life and productivity.
Materials and methods: We retrospectively reviewed the charts of 169 patients referred to the Brigham and Women`s Hospital Mastocytosis Center with mast cell activation symptoms and at least one elevated MC mediator.
Results: All patients had MC-related symptoms, response to anti-MC medications, and at least one positive laboratory testing of MC mediator. Extensive testing was performed to exclude clonal MC disorders including KIT mutation in peripheral blood and, in some cases, bone marrow examination. 139 (82%) were females. Many patients had multiple system involvement. 130 (77%) with neuro-psychiatric symptoms. 145 (85%) had GI involvement, 148 (87%) cutaneous, 98 (58%) respiratory, 87 (51%) constitutional, and 92 (54%) skeletal, 67 (39%) had anaphylaxis and 58 (34%) required an ED visit. The neuro-psychiatric symptoms were prominent and were further analyzed. In this subset, the following were reported: headache 74 (43%), anxiety 61 (36%), depression 51 (30%), 50 (29%) poor concentration, and 47 (27%) memory loss. Interestingly, we found that 76 (23%) of the patients with MCAS were unable to work and more than half of these had applied for disability.
Conclusion: Neuro-psychiatric symptoms are prevalent in patients with MCAS and likely have a significant impact on quality of life and productivity.

Logan Roebke (MS)
Recognition and Treatment of Seymour-Type Fractures in Adults: Case Report and Review of the Literature
Logan Roebke, J. Bowman MD, P. Chapman MD, N, Ebraheim MD

Introduction: Seymour fractures are caused by a hyperflexion injury to the distal phalanx in the pediatric population leading to an open extra-articular fracture with physeal separation. These complex pediatric fractures have been described thoroughly in the literature; however, there is a paucity of literature concerning adult Seymour-type fractures. These fractures are extra-articular fractures at the base of the distal phalanx between the extensor and flexor tendons' insertion points with associated nail bed injury after a hyperflexion injury.
Methods: This case report regards an adult Seymour-type fracture that presented to clinic and was subsequently taken for operative fixation and irrigation and debridement. Thorough literature review was obtained investigating the current literature regarding adult Seymour-type fractures.
Results: A 20 year-old female came in for a follow-up after going to an urgent care center with a finger-tip injury following a hyperflexion injury from getting her finger caught in a car door. On exam, a hematoma around the nail root was seen with the nail appearing longer compared to the contralateral finger. After prompt recognition of this open fracture, treatment with antibiotics, irrigation and debridement, and k-wire fixation through head of the distal phalanx were carried out.
Conclusion: Prompt recognition of this Seymour-type fracture lead to successful management. There should be elevated clinical suspicion and subsequent diagnosis of adult Seymour-type fracture using this institution's proposed methodology of identifying a transverse distal phalanx fracture, hyperflexion injury, hematoma around the root of the nail, and the nail appearing long in comparison with the contralateral finger.

Logan Roebke (MS)

Periprosthetic Humeral Fractures: A Systematic Review

Logan J. Roebke; Josh W. Vander Maten; Liu J MD

Introduction: Periprosthetic humeral fractures (PHFs) provide a unique complication after total shoulder arthroplasty (TSA), reverse shoulder arthroplasty (RSA), or hemiarthroplasty surgeries. Presented here is a systematic review of the outcomes associated with different treatment options as well as outcomes to each of these fractures at different classifications.
Materials/Methods: The database PubMed was used to search for English literature on periprosthetic humeral fractures before May 2019. Studies presenting human subjects with TSA, RSA, or hemiarthroplasty with subsequent periprosthetic humeral fractures either intraoperatively or postoperatively were analyzed. Clinical outcomes, treatments for periprosthetic humerus fractures, classifications of periprosthetic humeral fracture, and patient demographics were recorded and analyzed.
Results: There was a total of 411 PHFs gathered from these studies. The most common nerve complication associated with these studies was a radial nerve injury. This complication was reported in 20 cases. The vast majority of postoperative PHFs' mechanism of injury was by fall. Analysis of surgical vs conservative treatment, revision surgery vs. other surgical techniques had t-test values of .86 and .44 respectively.
Conclusion: In the terms of union time, conservative treatment may be a viable option for all of the classifications of PHFs; however, due to limited sample size no definitive conclusion can be made. Revision surgery vs surgical techniques like locking plate provided similar results in healing time.

Maya Shumyatcher (MS)

Lessons from autoimmune disease management: TNFα inhibitors as novel Alzheimer's disease treatment approach, an umbrella review of meta-analyses and systematic reviews

Maya Shumyatcher, Dr. Mehmood Rashid

Introduction: TNFα inhibitors have revolutionized management of autoimmune conditions such as rheumatoid arthritis, psoriasis, and inflammatory bowel disease. Autoimmunity is notably associated with increased incidence of Alzheimer's disease (AD) and other dementias. Treatment with TNFα inhibitors decreases rates of these autoimmune disease complications, with AD risk in particular falling below that of the general population, which may hold promise for AD treatment more broadly. AD drug development has been a major undertaking, with no medication successfully altering clinical disease progression. Elucidating the role of TNFα in AD may change the paradigm. This umbrella review examines systematic reviews and meta-analyses to discuss the role of TNFα in AD and the potential of anti-TNF agents as AD treatment.
Methods: The PubMed, Embase, and Cochrane databases were queried for meta-analyses and systematic reviews using search criteria: (Alzheimer's) AND (TNF OR tumor necrosis factor OR DMARD OR Etanercept OR Infliximab OR Adalimumab OR Golimumab OR Certolizumab OR biologics). This study was conducted according to the Joanna Briggs Institute guidelines for umbrella reviews.
Results: 4 meta-analyses and 1 systematic review were included in this study. 11 additional reviews lacked the rigorous methodology for inclusion in the formal review. TNFα inhibitors substantially decreased AD risk in human patients and animal models. Additionally, certain TNFα polymorphisms were associated with increased AD risk.
Conclusions: AD drug development has been fraught with challenges. With insights from autoimmune disease treatment and an emerging consensus regarding neuroinflammation in AD, the TNFα pathway poses a compelling and under-explored treatment targe

Yongqing Wang (F)

Epigenetic down-regulation of microRNA-126 in scleroderma microvascular endothelial cells is associated with impaired responses to VEGF and defective angiogenesis

Yongqing Wang, John Sun, Bashar Kahaleh

Introduction: Impaired angiogenesis in scleroderma (Systemic Sclerosis, SSc) appears in spite of upregulation of VEGF and other proangiogenic factors. MicroRNA-126 (miR-126) is expressed mainly in MVECs. It regulates angiogenic signaling and responses to VEGF by direct repression of negative regulators of VEGF, including Spred1, and PIK3R2.
Methods: MVECs were isolated from SSc-skin and matched subjects. MiR-126 expression was measured by qPCR and in situ hybridization. SPRED1 and PIK3R2 expression were examined by qPCR and western blot. Matrigel-based tube

assembly was used to test angiogenic potentials of MVECs. MiR-126 levels were inhibited by hsa-miR-126 inhibitor and enhanced by hsa-miR-126 Mimic. Epigenetic regulation of miR-126 expression was examined by the addition of epigenetic inhibitors (Aza and TSA) to MVECs and by bisulfite genomic sequencing of DNA methylation pattern of the miR-126 promotor region.
Results: MiR-126 expression, as well as EGFL-7 (miR-126 host gene), in SSc-MVECs and skin were significantly down regulated in association with increased expression of SPRED1 and PIK3R2 and diminished response to VEGF. Inhibition of miR-126 in NL-MVECs resulted in reduced angiogenic capacity. Whereas overexpression of miR-126 in SSc-MVECs resulted in enhanced tube assembly. Addition of Aza and TSA normalized miR-126, and EGFL-7 expression levels in SSc-MVECs. Heavy methylation in miR-126/EGFL7 gene were noted.
Conclusion: The results demonstrate that downregulation of miR-126 is related to DNA hypermethylation of miR-126/EGFL7 promoter, resulting in impaired angiogenesis of SSc-MVECs by upregulation of the endogenous angiogenesis inhibitors.

Yongqing Wang (F)
Epigenetic regulation mediated repression of Prostacyclin Receptor (IP) and Prostacyclin Synthase (PTGIS) in Scleroderma skin, Vascular Smooth Muscle Cells (vSMCs), and Microvascular Endothelial cells (MVECs)
Yongqing Wang, Bashar Kahaleh

Introduction: Diffuse vascular dysfunction with defective vasodilatation and enhanced vasospasm and intimal hyperplasia is one of the hallmarks of scleroderma (systemic sclerosis, SSc). The dysfunction results from an imbalance in endothelial signals with increase vasoconstrictors and defective release of vasodilators. In this study, we examined the expression levels of PTGIS and IP in normal and SSc skin, MVECs and vSMCs and the effects of DNA methyltransferase inhibitor Aza, and the histone deacetylase inhibiter TSA on PTGIS and IP gene expression.
Methods: The expression levels of IP and PTGIS were measured by qPCR and WB in SSc and control MVECs and vSMCs before and after addition of epigenetic inhibitors
Results: The mRNA expression levels of PTGIS and IP were significantly downregulated in SSc-skin by 0.183-fold ± 0.03 for PTGIS ($P < 0.01$) and 0.54-fold ± 0.06 for IP ($P < 0.01$), compared to control skin. The mRNA expression levels of PTGIS and IP were also decreased in SSc-vSMCs, compared to control (0.29-fold ± 0.04, $P< 0.01$ for PTGIS; 0.46-fold ± 0.06 for IP, $P<0.01$). WB analysis demonstrated similar reduction on the protein levels in SSc -vSMCs. Addition of Aza and TSA resulted in increased expression levels of IP and PTGIS in SSc-vSMCs to almost normal levels.
Conclusion: The data demonstrate defective PGI2-IP pathway in SSc-MVECs and vSMCs. The addition of Aza and TSA corrected the reduced expression levels of PTGIS and IP in SSc cells suggesting that epigenetic regulation influence IP and PTGIS gene expression in SSc.

RHEUMATOLOGY/GERONTOLOGY

Matt McCracken (MS)
Syndesmosis Screw Breakage: What Variables Predict Breakage Location?
Josh W Vander Maten, Matthew McCracken, Jiayong Liu

Introduction/Purpose: Concerns have been raised about screw breakage within the tibia or fibula, referred to as intraosseous breakage. The purpose of this investigation is to assess variables that may predict location of syndesmosis screw breakage.
Materials: A retrospective analysis of over 1,000 patients who underwent syndesmosis fixation was completed. Demographics, screw length, width, number, height above the tibial plafond, angle, breakage location, and breakage location on the screw were collected and analyzed.
Results: Intraosseous (IO) screw breakage (91 screws, 68 patients) was more common than clear space (CS) breakage (28 screws, 18 patients) ($P = < 0.001$). Within the IO group, screw breakage within the tibia (60 screws, 52 patients) more common compared to fibula breakage (29 screws, 24 patients) ($P = < 0.001$). Increased BMI and use of multiple screws were associated with IO breakage ($P = .007$) and CS breakage ($P = .012$), respectively. Increased screw angle and age were associated with fibular IO breakage ($P = .021$, $P = .036$). Screw angle and placement had no other significant effects ($P = .629$, $P = .570$).
Conclusion: Increased BMI, increased age, increased screw number, and screw angle relative to the tibial plafond were significantly associated with locations of syndesmosis screw breakage.

Josh Vander Maten (MS)

Does Surgical Placement of Syndesmosis Screws Affect Breakage Rate? A Retrospective Comparative Study

Josh W Vander Maten, Matthew McCracken, Logan Roebke, Jiayong Liu

Abstract Background: Screw fixation remains the gold standard treatment for syndesmotic disruption. Screw breakage remains a complication seen in many patients following metal fixation. Recently breakage location within an intraosseous location has been associated with increased pain. To date, no study has compared patients with syndesmosis screw breakage and patients with intact screws based on surgical placement variables in conjunction with screw characteristics.
Questions/Purpose: The purpose of this study is to compare patients with syndesmosis screw breakage versus those with intact screws based surgically controlled variables assess effects breakage rate and location. Does height of placement above the tibiotalar joint affect syndesmosis screw breakage? Does angle of placement relative to the tibia plafond affect syndesmosis screw breakage? When comparing patients with broken syndesmosis screws versus those with intact screw, do any patient characteristics differ? When comparing screws of patients with broken syndesmosis screws versus those with intact screw, do any screw characteristics differ?
Methods: A retrospective analysis of patients who underwent syndesmotic screw fixation was performed. Patients with syndesmosis screw breakage were compared to those with intact screws. The number of screws used, width, length, fracture type and number of cortices were all collected. Further analysis included radiographic measurement syndesmosis screw angle, height of placement above the tibial plafond.
Results: A total of 176 patients and 260 syndesmosis screws were included in the study, 88 patients each with and without broken syndesmosis screws. Decreased screw width, increasing numbers of screws used, and younger age were all associated with increased rates of screw breakage. ($p < .001$, $p = .019$, $p = 0.020$). No statistical difference was appreciated between groups based on screw length, number of cortices used, or angle relative to the tibial plafond ($p = .2432$, $p = .4699$, $p = .9233$). Height of screw placement group differences remained following stratification analysis ($p = .022$). No difference was appreciated between groups based on screw angle ($p = .099$) or fracture type ($p = .272$). Regression analysis revealed a decreased screw width, increased height of screw placement, and increased screw angle relative to the tibial plafond were associated with the breakage group (OR = .096 $p < .001$, OR = 1.053 $p = .007$, OR .1.039 $p = .017$). No difference was appreciated based on screw length, number of cortices, number of screws, of ankle position during surgery. Comparing intact screws against broken screws in patients with at least one broken screw revealed no statistically significant differences in any measured variable.
Conclusion: Higher placement of syndesmosis screws above the tibiotalar joint increases screw breakage rate. No difference was appreciated based on screw angle relative to the tibial plafond. Decreased screw width, increasing numbers of screws used, and younger age were all associated with increased rates of screw breakage.

Josh Vander Maten (MS)

Does the Location of Syndesmosis Screw Breakage Affect Patient Outcomes?

Josh W Vander Maten MS, Matthew McCracken MS, Jiayong Liu MD

Introduction/Purpose: Breakage of syndesmosis screws is believed to have few consequences. Recently it has been suggested screw breakage may lead to significant pain depending on the location of the breakage. The purpose of this investigation is to assess patient outcomes and removal secondary to pain based on syndesmosis screw breakage location.
Materials: From January 1, 2008 to December 17, 2020 a retrospective analysis of all patients receiving syndesmosis fixation was performed. Data collected included BMI, comorbidities, pain scores, complication rate, revision rate and reason for removal.
Results: Intraosseous (IO) screw breakage is associated with increased pain scores, screw removal rate, and removal due to pain when compared to clear space (CS) breakage ($P = .0026$, $P = .008$). Breakage location closer to the CS within the tibia was associated with increased pain leading to removal ($P < .001$). Patients reported higher pain scores if more than one screw was used within the tibia ($P = .025$, $P = .005$). IO screw removal was associated with improved ROM ($P = .0096$).
Conclusion: Intraosseous breakage is associated with increased pain, rates of screw removal, and removal due to pain. Breakage location within the tibia closer to the clear space is associated with higher pain scores and removal rate. Broken screw removal improves range of motion. More revisions and complications led to increased removal due to pain.

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