Dr. Lance D. Dworkin Department of Medicine Research Symposium

September 28, 2023

Volume 3

COLLEGE OF MEDICINE AND LIFE SCIENCES

THE UNIVERSITY OF TOLEDO

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Dedication to Dr. Lance D. Dworkin

We are honored to dedicate the Department of Medicine Research Symposium to the distinguished and exemplary physician-scientist, Dr. Lance D. Dworkin. This conference stands as a testament to Dr. Dworkin's outstanding contributions to the field of medicine and research, and we are proud to celebrate his lifetime of dedication, innovation, and unwavering commitment to advancing healthcare through prospective, high-quality clinical and translational research.

Dr. Dworkin has been a beacon of inspiration for countless researchers, clinicians, and medical professionals. His commitment to research has not only inspired the way we understand and approach healthcare but has also positively impacted the lives of countless patients. Dr. Dworkin's tireless pursuit of knowledge, innovative thinking, and dedication to improving patient outcomes have set a benchmark for excellence in medical research. While he has conducted a diversity of projects, amongst these Dr. Dworkin has been deeply involved in some of this country's most prominent hypertension studies that now stand as level 1A evidence for how people around the world are treated. This is a clear testament to his lifetime of work.

Throughout his distinguished career, Dr. Dworkin has not only produced important research but has also mentored and guided generations of aspiring healthcare students, residents, fellows and faculty. His generosity in sharing knowledge and nurturing talent has cultivated a community of researchers dedicated to advancing the frontiers of medicine.

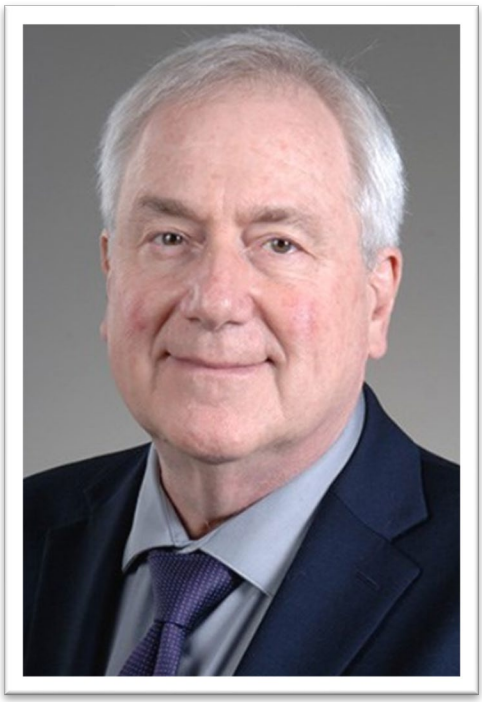
As we convene at this scholarly conference, we acknowledge Dr. Dworkin's profound influence on the medical community and express our heartfelt gratitude for his remarkable contributions. This event is dedicated to celebrating the spirit of inquiry, innovation, and compassion that Dr. Dworkin embodies.

In honoring Dr. Dworkin today, we aspire to carry forward his legacy of excellence and continue the pursuit of knowledge and breakthroughs that will shape the future of healthcare. May this conference be a fitting tribute to a dedicated physician researcher whose work has touched the lives of many and will continue to inspire generations to come.

With deepest respect and gratitude,

Christopher J. Cooper, M.D.
Dean, College of Medicine and Life Sciences
The University of Toledo
September 28, 2023

Message from the Chair



It is my great pleasure to welcome you to the 3rd Annual Department of Medicine Research Symposium. Our program includes welcoming remarks from the Dean of the College of Medicine and Life Sciences, Dr. Christopher J. Cooper, and from Dr. David Kennedy, Associate Professor of Medicine and Director of Student Research This will be followed by a keynote address presented by Dr. Sanjay Rajagopalan, Professor of Medicine, and Director of the Cardiovascular Research Institute at the Case Western Reserve University School of Medicine. The symposium will conclude with an abstract and poster session highlighting ongoing research projects by trainees and investigators working in the Department of Medicine. Abstracts and posters represent every division in the Department of Medicine and cover a wide range of topics such as case reports, quality and outcome studies, metanalyses, clinical translational and laboratory science. The abstract 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, Kennedy, and Rajagopalan for joining us, and to our faculty and trainees for their interest and active support of the symposium.

One of the key missions of our department is to conduct research to increase our knowledge of human biology, health and illness, and medical therapeutics. Trainees and faculty in the Department of Medicine are actively engaged in these endeavors; however, the research that we do may not be well known outside 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 increase the visibility of our research programs, promote collaboration, and energize our students and faculty.

Thank you for your interest, enjoy the symposium, and please obtain a copy of the abstract book and use it to identify areas of overlapping interest and to develop new collaborations.

Sincerely,

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

Keynote Speaker

Sanjay Rajagopalan, MD, FACC, FAHA

Chief, Cardiovascular Medicine
Chief Academic and Scientific Officer
University Hospitals, Harrington Heart and Vascular Institute
Director, Case Cardiovascular Research Institute
Herman Hellerstein, MD, Professor of Cardiovascular Research
Professor, Departments of Medicine and Radiology
Case Western Reserve University

Dr. Rajagopalan completed clinical and research fellowships in cardiovascular medicine and vascular biology at the Emory University School of Medicine, Atlanta, Georgia. Dr. Rajagopalan is among an elite group of physician investigators whose work has help transform perceptions and facilitate understanding of the global impact of chronic diseases including diabetes. He has additionally made seminal contributions towards the development of next generation therapeutic modalities for the treatment of cardiovascular disease and is a leading authority in advancing newer and innovative non-invasive approaches for the diagnosis of complex cardiovascular disorders.

Dr. Rajagopalan's laboratory has been continually funded by the National Institutes of Health (NIH). Dr. Rajagopalan is an elected member of the American Society of Clinical Investigation (ASCI), the Association of University Cardiologists (AUC) and the Association of Professors of Cardiology (APC). Additional honors include the William Keating Award from the American College of Cardiology, the Charles Dana Award and being voted amongst the Best Doctors in America.

Dr. Rajagopalan has published over than 250 original peer reviewed research publications in journals such as JAMA, New England Journal of Medicine, Circulation, Journal of Clinical Investigation and Circulation Research, in addition to more than 300 reviews, book chapters and abstracts. He has served as an editor for at least two textbooks and several monographs on vascular disease and atherosclerosis.

Schedule of Events

3rd Annual Department Of Medicine Research Symposium

Thursday, September 28, 2023

Lloyd A. Jacobs Interprofessional Immersive Simulation Center
The University of Toledo Health Science Campus

Welcome & Introductions

4:00pm	Dr. Lance Dworkin Professor and Chair Department of Medicine
4:05	Dr. Christopher Cooper Professor of Medicine Executive Vice President for Clinical Affairs and Dean College of Medicine and Life Sciences
4:10	Dr. David Kennedy Associate Professor of Medicine Department of Medicine

Keynote Speaker

4:20	Dr. Sanjay Rajagopalan Professor, Departments of Medicine and Radiology Case Western Reserve University School of Medicine
5:15	Awards for Outstanding Abstract Submissions

Reception

5:30	Poster Session

Abstracts

CARDIOLOGY

Mohammad Alqadi, MD

Safety and efficacy of anti-hypertensive medications in patients with heart failure with preserved ejection fraction: A systematic review and meta-analysis

Mohammad Alqadi, MD

Introduction: Hypertension (HTN) is a co-morbidity that is commonly associated with heart failure (HF) with preserved ejection fraction (HFpEF). This meta-analysis aims to evaluate the association of anti-hypertensive medications (AHM) therapy with cardiovascular (CV) outcomes in patients with HFpEF.
Objectives: Treatment of HTN in HFpEF patients is associated with improved CV outcomes.
Methods: Performed a database search (OVID Medline, Web of Science, and Embase) for studies reporting the association of AHM with CV outcomes in patients with HFpEF. The primary endpoint was all-cause mortality. Secondary endpoints include CV mortality, worsening HF, CV hospitalization, and major adverse CV events (MACE).
Results: A total of 15 studies with 17507 HFpEF participants (8732 treated with medical therapy vs 8775 treated with placebo) met inclusion criteria. Use of AHM was not associated with lower all-cause mortality or CV mortality compared to treatment with placebo (OR 1.01, 95% CI 0.80-1.27; p=0.95, OR 0.97, 95% CI 0.86-1.08; p=0.53). Use of AHM was associated with a statistically significant lower risk of MACE and CV hospitalization (OR 0.90, 95% CI 0.83-0.97; p<0.01, OR 0.89, 95% CI 0.81-0.97; p<0=0.04). Subgroup analysis demonstrated this to be primarily driven by studies with mixed HFpEF patients with or without HTN, not HFpEF patients with HTN. There was a non-significant trend toward lower risk of worsening HF in patients treated with AHM and was driven by HFpEF patients with or without HTN, not HFpEF patients with HTN (OR 0.87, 95% CI 0.78-0.97; p=0.02 versus OR 0.57, 95% CI 0.18-1.86; p=0.35).
Conclusion: While treatment with anti-hypertensives was not associated with lower risk of all-cause mortality, their use may be associated with reduced risk of adverse CV outcomes in patients with HFpEF regardless of whether they have HTN. Further studies are needed to clarify this association and determine the effect based classes of medications.

Nahush R. Bansal, MD

Late angina due to anomalous right coronary artery

Nahush R. Bansal, MD, Catalin Dragomirescu, Mona Mahmoud, MD

Introduction: Anomalous origin of the right coronary artery arising from the left coronary sinus and taking an interarterial course between the great vessels is a rare diagnosis, with a reported incidence between 0.026% and 0.250%. While most cases are asymptomatic, the anomalous right coronary artery is typically diagnosed incidentally. However, this abnormal anatomy of the right coronary artery renders it vulnerable to compression between the right ventricular outflow tract or pulmonary artery and the aorta. This compression can potentially manifest as angina, arrhythmias, and sudden cardiac death. We report a case with this rare diagnosis that presented atypically with angina, mainly at rest, and had a late presentation at an older age.
Case Presentation: A 46-year-old female presented to the Emergency department (ED) with a year-long history of intermittent episodes of nocturnal retrosternal chest pain, radiating to the jaw, neck and arm that were severe enough to disrupt her sleep. These episodes worsened progressively over time, leading to multiple office and ED visits for the patient. Notably, the patient did not report any symptoms with exertion or activity. The cardiac

workup, including ECG, troponins, and echocardiogram, yielded benign results. The patient also underwent a nuclear stress test with low-risk result. The coronary CT angiogram revealed an anomalous right coronary artery arising from the left coronary sinus, with compression of the proximal right coronary artery occurring between the right ventricular outflow tract/proximal pulmonary artery and the aorta.
Conclusion: This case adds to the spectrum of atypical presentations occurring from the anomalous right coronary artery. A concrete understanding of the symptomatology and signs will raise the suspicion of this rare diagnosis among physicians. This will eventually help them to make an early diagnosis and intervene early to prevent malignant arrythmias and sudden cardiac death among these patients.

Dhilhani Faleel

Machine learning analysis of identifies polyunsaturated fatty acid metabolites predictive of adverse outcomes in heart failure with preserved ejection fraction patients

Dhilhani Faleel, Ahmed Elzanaty, MD, Vaishnavi Aradhyula, Rohit Vyas, Prabhatchandra Dube, Steven T. Haller, PhD, Rajesh Gupta, PhD, David J. Kennedy, PhD, Samer J. Khouri, MD

Background: Pulmonary hypertension (PH) in heart failure with preserved ejection fraction (HFpEF; PH-HFpEF) is associated with adverse clinical outcomes; however, the pathophysiology of disease is unknown. The development of PH is a continuum of disease processes initiated by HFpEF, where patients initially develop isolated postcapillary PH (ipc-PH) which can transform to combined pre and postcapillary PH (cpc-PH). This transformation of PH does not occur in all patients, is not explained by traditional risk factors alone, and is associated with significant morbidity and mortality suggesting the need to examine novel regulatory mechanisms. Polyunsaturated Fatty Acid (PUFA) metabolites play a vital role in cardiovascular health by regulating balance between anti-inflammatory and pro-resolutory lipid mediators and imbalances have been previously shown to predispose PH.
Objective: We sought to characterize PUFA-derived mediators that can serve in cardiovascular risk stratification in patients with HFpEF.
Methods: Venous serum samples were collected from 88 HFpEF patients without PH (control, n=40), HFpEF with ipc-PH (ipc-PH-HFpEF, n=30), and HFpEF with cpc-PH (cpc-PH-HFpEF, n=18). 143 PUFA metabolized were analyzed using mass spectroscopy with Multiple Reaction Monitoring. A machine learning model (Anaconda v2022.05) was conducted after ANOVA feature selection to assess which molecules were associated with future risk of either all cause death or a combined adverse outcome of death or rehospitalization in the setting of HFpEF.
Results: In patients with HFpEF, increased levels of 9(10)-Epome, 15(R)-PGE1, 17-oxoRvD1, TXB3, RvD3, 5(S),15(S)-DiHETE, and 11dh-2,3-dinor TXB2 at baseline were predictive of all-cause mortality (all $p<0.05$). Increased baseline levels of 8-oxoRvD1, MaR1(n-3DPA), PGE3, and 5,6-DiHETrE were predictive of the combined adverse outcome of death or rehospitalization (all $p<0.05$).
Conclusion: These findings support the hypothesis that distinct PUFA metabolites play a significant role in mediating cardiovascular disease in HFpEF. Our study introduces a novel lipidomics framework for the diagnostic and prognostic assessment of cardiovascular risk in HFpEF patients.

Tahrima Ferdous

Subcutaneous immunoglobulin (SCig) for maintenance therapy in severe POTS: A case report.

Tahrima Ferdous

Introduction: Postural Orthostatic Tachycardia Syndrome (POTS) is a multisystem disorder involving the nervous and cardiovascular systems. POTS diagnosis requires an increase in heart rate of at least 30 beats per minute upon standing, in the absence of orthostatic hypotension.
There have been multiple theories suggesting a possible autoimmune pathogenesis of POTS, as multiple autoantibodies have been identified in patients with POTS such as ganglionic acetylcholine receptor (gAChR)

and voltage-gated potassium channel complex. Moreover, patients with POTS tend to have high prevalence of ANA antibodies and co-occurrence of other autoimmune conditions such as systemic lupus.
The use of immunomodulator therapy such IVIG has been reported in multiple case reports with encouraging results, in this case we report significant improvement POTS symptoms with SCig in a patient with debilitating symptoms.
Case Presentation: A 42-year-old female with a past medical history significant for Ehlers-Danlos Syndrome complicated by multiple vertebral and disc issues was evaluated in the rheumatology clinic for sever debilitating POTS that was refractory to standardized treatment. The patient had repeated hospital admissions for syncopal episodes. The decision was made to start intravenous immunoglobulin and following an initial positive response, she developed aseptic meningitis. Intravenous therapy was discontinued, and the patient was started on subcutaneous immunoglobulin. At the time of this case report, the patient had been on subcutaneous Ig for more than 3 years. She has reported significant improvement in her symptoms with less hospitalization. The patient used an apple watch to measure and record her daily heart rate, summary of average HR reported over 3 years is summarized in the graph below.
Conclusion: This case highlights a case of debilitating POTS that showed a clinical subjective and objective response to subcutaneous immunoglobulin. which suggests a possible autoimmune pathway of disease. Further studies are needed to assess the efficacy and safety of Scig in the treatment of refractory POTS.

Vinicius Guzzoni

Response to aerobic training reveals key differences in cardiovascular adaptation in an adenine diet induced model of chronic kidney disease

Vinicius Guzzoni, Samantha J. McKee, Emma J. Verkley, Nicholas J. Kesler, Prabhatchandra R. Dube, Apurva Lad, Bivek Timalsina, Tatiana Sousa Cunha, Dulce Elena Casarini, Steven T. Haller, David J. Kennedy, Lauren G. Koch

Background: Rat models generated by selective breeding for low (LRT) or high (HRT) response to aerobic training closely embody human phenotypes and can be used to understand the exercise-disease linkages. Aerobic endurance training has been proposed as a model of exercise intervention capable of improving or minimizing the negative consequences of chronic diseases including chronic kidney disease (CKD).
Objectives: We hypothesized that resistance to aerobic training induces kidney damage in CKD settings.
Methods: Male and Female LRT and HRT rats (~ 17 months of age; n = 30) were freely fed with rodent chow supplemented with 0.75% of adenine for the induction of CKD.
Results: At the beginning of the experimental study, LRT rats showed greater body weight and lower arterial blood pressure (systolic, diastolic, and mean pressures) than HRT rats. Following two weeks of adenine diet, body weight of LRT rats remained higher in comparison to HRT rats, consequently both heart and kidney weight / body weight ratio were reduced in LRT (*vs.* HRT) after two weeks of adenine diet. However, after indexing heart weight to tibia length, which avoids biases because of disease-induced body weight changes, we noted that the heart weight / tibia length ratio was significantly increased in LRT vs HRT rats (2.51±0.58 vs 2.13±0.28, $p<0.027$). Kidney weight / tibia length unchanged between the groups.
Conclusion: Our preliminary findings show a better response of HRT rats in terms of cardiovascular adaptations after diet induced CKD. Molecular analyses are being currently performed to further investigate the impact of resistance to exercise induced aerobic training on inflammatory response, renin angiotensin system, pro-inflammatory signaling, and kidney fibrosis.

Marwa Hassan

A case of enterococcus infective endocarditis following parasitic gastroenteritis in a previously healthy 20-year-old male

Marwa Hassan, Vikhyathi Pallerla, MS, Adeel Tausif, Mona Mahmoud, MD

Introduction: Infective endocarditis is a life-threatening condition stemming from various bacterial and viral origins, presenting most commonly in hospital settings. The most common bacterial pathogens contributing to the development of infective endocarditis include staphylococci and streptococci, with Enterococcus faecalis being the third most common cause. Enterococcus faecalis is a part of normal gastrointestinal and genitourinary flora but can sometimes extravasate into the bloodstream following damage to the gut mucosa due to trauma, malignancy, or infection. The resultant Enterococcus bacteremia predisposes patients to infective endocarditis. Enterococcus faecalis contributes to the development of about 5-10% of infective endocarditis cases and presents predominantly in elderly males as a subacute illness.
Case Report: We present a rare case of a 20-year-old male patient with a history of parasitic gastroenteritis six months prior to presenting with symptoms of infective Enterococcus faecalis endocarditis involving the atrial surface of the anterior leaflet of the mitral valve. The gastroenteritis was preceded by a history of travel to Cancun and consumption of octopus, which was suspected to be the source of the gastrointestinal infection.
Conclusion: Enterococcus faecalis tends to lead to infective endocarditis and septicemia primarily in elderly males or patients with in-hospital procedures that can introduce the bacteria into the bloodstream. Our case illustrates an exception in which a previously healthy, young male experienced gut mucosal damage allowing Enterococcus faecalis to invade and spread hematogenously to his heart.

Taryn Hibshman

Dynamics of peripheral artery disease and influencing factors in the United States and the world (1999-2020)

Taryn Hibshman, Sishir Doddi, Oscar Salichs, Rabbia Siddiqi

Introduction: This research explores the evolving epidemiology of Peripheral Artery Disease (PAD) from 1990 to 2019, analyzing trends in global incidence, prevalence, disability-adjusted life years (DALYs), and their variations in the United States (US) and across different socio-demographic contexts. This study provides a comprehensive analysis of PAD's impact on public health, utilizing the Global Burden of Disease (GBD) framework.
Objectives: Our research advances existing knowledge by headlining the unique pattern of PAD trends, as well as emphasizing the higher burden of PAD in high-income countries. Additionally, this study indicates PAD's growing impact on health, irrespective of socio-demographic context, as all countries, regardless of Socio-Demographic Indexes (SDI) status, experience increases in DALYs.
Methods: Data on pancreatic cancer mortality, incidence, prevalence, and DALYs from 1990 to 2019 were sourced from the Global Health Data Exchange (GHDx) database. The Joinpoint Regression Program was used to compute annual percent changes (APC) and overall average annual percent change (AAPC) over the given time period. Confidence intervals for APC were determined using the Grid Search Method with permutation and parametric tests. Identification of significant differences in AAPC trends among groups was conducted through parallel pairwise comparison tests.
Results: Our findings reveal significant upward trends in worldwide PAD prevalence, incidence, and DALYs, paralleling a growing global burden of the disease over this period. In the US, analysis reveals an increase in DALYs, paired with a decrease in both incidence and prevalence. Overall, the US exhibits higher rates of all measured variables attributed to PAD compared to the global population.
Conclusion: In conclusion, our study enhances the understanding of PAD's epidemiology by contextualizing global trends within the US and among different socio-demographic landscapes. By providing a holistic assessment of PAD's advancing burden, this research emphasizes the need for further intervention to address the global challenge posed by PAD.

Sara Kazmi, BA

Protocol development for yielding high quality DNA and RNA from archived formalin-fixed paraffin embedded tissues

Sara Kazmi, BA, Bella Khatib-Shahidi, BS, John Najjar, BS, Anish Sharma, BS, Caitlyn Murphy, BS, Humza Bashir, BS, Apurva Lad, PhD, David J. Kennedy, PhD, and Steven T. Haller, PhD

Introduction: While genetic analysis of archived formalin-fixed paraffin embedded (FFPE) tissue specimens would be a significant research resource, extraction of high-quality DNA and RNA from these specimens is a significant challenge. Storage duration, tissue handling and tissue preservation processes as well as their interactions with the nucleic acids could influence the quality and integrity of the DNA or RNA required for genetic analysis.
Objectives: The goal of this study was to establish a protocol to extract high quality DNA and RNA from the FFPE tissues for further use in quantitative PCR analysis.
Methods: For the purposes of this study, human FFPE biopsy tissues from lung, liver, colon and kidney were obtained from a single center biorepository. GeneJET Genomic DNA Purification Kit (Catalog # K0722) obtained from Thermo Fisher Scientific and RecoverAll Total Nucleic Acid Isolation Kit obtained from Life Technologies were modified and used for extraction of DNA and RNA, respectively. Briefly, modifications involved extending reagent incubation times, increasing sample volumes and wash steps, and increased final nucleic acids recovery and concentration steps. Eight sections around 8-10 µm thick were microtomed for each tissue sample and used for extraction. The purity of the nucleic acids obtained was verified using Nanodrop Spectrophotometer.
Results: The average DNA yield from eight sections for each of the tissues was 270±184 ng/µl and for RNA was 296±188 ng/µl. Nucleic acid quality was assessed by measuring the 260nm/280nm absorbance ratio for protein contamination as well as the 260nm/230nm absorbance ratio for salt contamination. Both were found to be within acceptable ranges. RNA was reverse transcribed to cDNA and qPCR was successfully performed on both DNA and cDNA samples.
Conclusion: These results indicate that protocols using the silica-based membrane technology can yield high quality DNA and RNA that can be successfully used for downstream genetic analysis.

Alyssa Lange

Whipple's endocarditis, a blood culture-negative endocarditis

Alyssa Lange, Mona Mahmoud, MD

Introduction: Whipple's disease is rare systemic disease caused by Tropheryma whipplei, a gram-positive rod-shaped bacterium widespread in the general population. The classic course of Whipple's disease includes intermittent arthralgias and fever, weight loss, gastrointestinal symptoms, and neurological symptoms. Blood culture negative endocarditis accounts for 2.5 – 31.0 % of all cases of endocarditis. The incidence rate of T. whipplei among blood culture negative endocarditis cases has not been well established. In this case report, we describe a 63-year-old patient with a past medical history of refractory seronegative rheumatoid arthritis and a newly discovered aortic valve vegetation.
Case Presentation: Our patient presented to the emergency department experiencing increasing non-radiating, sharp, severe abdominal pain with watery diarrhea for a month. After an unremarkable colonoscopy, the pain subsided. An echo showed an aortic vegetation. The TEE showed a 0.7 cm x 0.7 cm vegetation attached to the right coronary cusp of aortic valve.
Two months later, the patient was readmitted after losing thirty pounds since last admission. The EGD showed thickened folds and scalloped mucosa in the duodenum which were biopsied. The results were positive for T. whipplei. A blood culture was performed which was negative. A repeat echo showed a mobile mass on the right side of the interatrial septum, small sessile mass fixed to the right coronary cusp, and now severe atrial valve regurgitation. The patient was treated with six weeks of ceftriaxone and scheduled for a valve replacement.

Conclusion:
We report a typically subacute presentation of infective endocarditis due to *T. whipplei* with a pertinent past medical history of inflammatory, seronegative rheumatoid arthritis and gastrointestinal symptoms. This case highlights the need to consider *T. whipplei* in the differential with infective endocarditis with negative blood cultures especially in the setting of refractory inflammatory arthritis history and recent GI symptoms.

DERMATOLOGY

Shereen G. Yassine

Exposure to microcystin-LR induces differential gene regulation in primary human keratinocytes

Shereen G. Yassine, Benjamin W. French, Steven T. Haller and David J. Kennedy

Introduction: Harmful algal blooms (HABs) are on the rise globally, including in nearby Lake Erie. HABs are composed of blue-green algae, also known as cyanobacteria, which produce cyanotoxins, including microcystins, anatoxins, and saxitoxins, among others. Over 270 congeners of microcystin exist, but microcystin-LR (MC-LR) is most prevalent and potent. Dermal contact represents one of the most common exposure routes to MC-LR and dermal lesions account for a significant majority of HAB exposure symptoms. Despite this, almost no work has been published on the toxicity of microcystins in the skin.
Objectives: Determine potential health impacts in human keratinocytes after exposure to MC-LR, looking at markers of inflammation and structural barrier proteins.
Methods: Primary keratinocytes were cultured in 12 well-plates and exposed to 1 or 10 μM MC-LR for 6, 12, and 24 hours (n=3/group). After the exposure periods, cells were subject to RT-PCR assessing markers of inflammation and key structural barrier proteins.
Results: 1 uM MC-LR exposure caused a time-dependent increase in the expression of structural barrier proteins involucrin (IVL), loricrin (LOR), and filaggrin (FLG), with this trend reaching significance at 24 hours post-exposure (IVL $p = 0.0007$; LOR $p = 0.0276$; FLG $p < 0.0001$). Similarly, the 10 uM MC-LR exposure induced a stepwise increase in the expression of interleukin 1-beta (IL-1B), with significance increases at 12 ($p = 0.0138$) and 24 hours ($p = 0.001$). The 10 uM exposure additionally caused an initial spike in Tumor Necrosis Factor an expression at 6 hours ($p = 0.0286$), followed by a decrease in expression at 24 hours ($p = 0.0072$).
Conclusions: Our results suggest that MC-LR exposure induces significant activation of key proteins involved in inflammation and structural integrity of primary human keratinocytes. These finding suggest that microcystins are capable of inducing genetic changes underlying the skin lesion phenotypes associated with dermal HAB exposure.

ENDOCRINOLOGY

Ahmad Aldasouqi

Natural history of type 1 diabetes in humanized mouse model

Ahmad Aldasouqi, Shafiya Imtiaz Rafiqi DVM, PhD, Shahnawaz Imam DVM, PhD

Type-1-diabetes (T1D) is an autoimmune disease caused by an imbalance in T-regulatory and T-effector cells characterized by the destruction of insulin-producing beta cells by diabetogenic T-effector cells, leading to insulin deficiency and complexities like diabetic nephropathy, retinopathy, and neuropathy. Researchers at The University of Toledo have developed a humanized mice model that spontaneously develops T1D at 3-5 weeks of age and mimics human T1D. This study aims to monitor blood glucose levels before the onset of T1D (pre-weaned stage mice) and track the dynamics of immune cells using flow cytometry throughout the progression of the disease. Our results show that T-regulatory cells constitute 4.773% ± 0.81% cells at preweaning which drops to 2.60± 0.35 (%) in males and 1.78 ± 0.58 (%) in females at the 10th week while CD8+ T cells produce interferon gamma (cytotoxic lymphocytes, CTLs) constitute 3.32 ± 0.60 (%) at preweaning, which increased to

27.625± 1.43 (%) in males and 21.13± 2.87 (%) in females as the disease progresses. This reduction in T-regulatory cells and enrichment of CD8s and CTLs leads to the destruction of beta cells as seen in humans as well. Dysregulation of immune responses can be correlated with the progression of diabetes in terms of blood glucose levels which increased from 147mg/dl (preweaning), peaked at 373mg/dl in 5th week, and was observed in partial remission stage around the 8th week as observed in human T1D 'honeymoon period'. This study will help us to understand the immune dynamics in the progression of T1D as it helps us to present a better picture of the status of immune cells in a human-like immune system and provides benchmark data of the interplay of the immune system.

Rawan Moussa

Role of IQGAP1-estrogen receptorα-AMPK Axis in the sex differences of type 2 diabetes

Rawan Moussa, Alice Lu, Mahasin A. Osman, PhD

Type 2 diabetes (T2D) is a 2-hit chronic metabolic disorder arising from defects in insulin secretion from pancreatic □-cells and insulin sensitivity in peripheral tissues. Population studies indicated that T2D affects more men than women. The mammalian target of rapamycin (mTOR) and its downstream key energy sensor AMPKα have been largely implicated in T2D. Strong evidence suggests that the estrogen receptor α (ERα) influences AMPK activity and T2D sex disparity, but the molecular mechanisms remain unclear. The scaffold signaling protein IQGAP1 binds AMPKα and ERα and regulates insulin secretion in pancreatic □-cells. Here, we aim to test the novel hypothesis that an IQGAP1-ERα-AMPKs signaling axis plays a role in the disparity of T2D and exerts its effects in the pancreas. Preliminary results revealed significant metabolic differences in male and female mice lacking IQGAP1 (KO) and fed a high-fat diet (HFD) compared to control groups. While all KO mice exhibited significant decreases in body weight, the female mice were much leaner and ate less food. Furthermore, metabolic analyses indicated a significant reduction in insulin levels in KO male mice on HFD while the female mice displayed improved glucose homeostasis likely due to enhanced insulin secretion. Insulin, gene expression levels and co-localization of the pathway components in the pancreas are being investigated in treated and control mice groups. Overall, the study likely will provide important new insights into the determinants of sex-differences of T2D and reveal potential diagnostic biomarkers for future therapies.

Shafiya Imtiaz Rafiqi DVM, PhD

Restoration of immune imbalance in type 1 diabetes with simultaneous Notch and eIF5a inhibition

Shafiya Imtiaz Rafiqi DVM, PhD, Ahmad Aldasouqi, BS, Sarah Faisal, BS, Salauddin Qureshi DVM, PhD, Sandesh Dewan, MD, Aneeba Farooqi, MD, Asif Mahmood, MD, FAC, Shahnawaz Imam DVM, PhD

Immune cell plasticity is ability of immune cells to switch between functional states in response to cytokine milieu. In Type 1 diabetes (T1D) Teffector cells attack pancreatic β-cells while T regulatory cells fail to contain this immune attack. The present study explores immune cell plasticity in response to simultaneous treatment with eIF5a (eukaryotic-translation-initiation-factor 5A) inhibitor N1-Guanyl-1-7-diaminoheptane (GC7) and Notch inhibitor anti-DLL4 in human peripheral blood. Delta-like-ligand-4 (DLL4), in the Notch signaling of specific gene expression. PBMCs were isolated from T1D patients (n=3-4) and healthy controls. To evaluate the plasticization of cells into Tregs, Treg deficient CD4 (CD4+CD25-) cells were cultured with GC7(100μM)+anti-DLL4(10μg/ml)+rhGAD65(4μg/ml) for 7 days. Cells were quantified using flow cytometry and compared with conventional stimulation by anti-CD3/CD28 dyna beads. We observed 60-70% of CD4+CD25- plasticized into Tregs (CD4+CD25+). We also investigated the functional stability of plasticized Tregs compared to freshly isolated naïve Tregs from same patient. The plasticized Tregs were co-cultured with Teffector cells in Treg: Teffector ratios of 0:1, 1:1, 1:2 and 1:0 and suppression/proliferation was accessed after 5 days. Flow cytometric revealed that plasticized cells expressed regulatory phenotype (CD4+CD25+FoxP3+)

and suppressed Teffector cells. We further evaluated GC7+anti-DLL4 for adverse effects on cell viability for 7-days. There was no significant difference between control and GC7+anti-DLL4 treated groups in terms of live, dead and apoptotic cells till 48 hrs. However, a significant increase in dead cells post 48 hrs in treated group was observed and cellular signature of cells confirmed increased plasticized Tregs (CD4+CD25+FoxP3+) (2-fold) killing T effectors. This experiment provides a means by which previously committed CD4 T cells or intermediate subsets can be pushed to acquire Treg phenotype to restore immune imbalance in autoimmune disorders, particularly T1D.

Wasef Sayeh, MD

Prophylactic pancreatic stent placement to prevent post-ERCP pancreatitis: A systematic review and meta-analysis

Wasef Sayeh, MD, Sudheer Dhoop, MD, Sahithi Chinnam, DO, Rayna Patel, MD, Azizullah Beran, MD, Sami Ghazaleh, MD, Sara Stanley, DO, Yaseen Alastal, MD

Introduction: Post-ERCP pancreatitis (PEP) is considered a common complication that can sometimes be fatal. Studies showed that the incidence of PEP averages around 9.7% with a 0.7% mortality rate. Many strategies were presumed to prevent PEP including periprocedural aggressive hydration with Intravenous fluids, the periprocedural administration of non-steroidal anti-inflammatory medications (NSAIDS), or pancreatic duct stent placement. We conducted a meta-analysis to study the effectiveness of the prophylactic placement of a stent in the pancreatic duct in the prevention of PEP.
Methods: We performed a comprehensive search of the databases: PubMed/MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials from inception through May 15th, 2023. We considered randomized controlled trials. The primary outcome was the occurrence of PEP. Also, we did a subgroup analysis based on the severity of PEP. The random-effects model was used to calculate the risk ratios (RR) and 95% confidence intervals (CI). A p value <0.05 was considered statistically significant. Heterogeneity was assessed using the Higgins I2 index.

Results: Fifteen randomized controlled trials involving 1,850 patients were included in the meta-analysis. All studies compared the occurrence of PEP which was significantly lower in the pancreatic stent placement group (5.9% vs 16.8%, RR 0.40, 95% CI 0.30-0.54, p<0.001, I2 = 0%) (Figure 1a). Subgroup analysis based on the severity of PEP showed that prophylactic pancreatic stent placement was associated with lower occurrence of mild-moderate PEP (5.6% vs 13.9%, RR 0.46, 95% CI 0.34-.064, p <0.001, I2 = 0%) (Figure 1b). Also, prophylactic pancreatic stent placement significantly lowered the occurrence of severe PEP (0% vs 1.6%, RR 0.26, 95% CI 0.09-0.76, p =0.01, I2 =0%) (Figure 1c).
Discussion: Our meta-analysis demonstrated that the prophylactic placement of a stent in the pancreatic duct decreases the occurrence of PEP. It was especially helpful in significantly lowering the occurrence of severe PEP.

GASTROENTEROLOGY

Zohaib Ahmed, MD

Diagnostic paracentesis within one day of admission is associated with reduced mortality and shorter length of stay in hospitalized patients with cirrhosis and ascites: A systematic review and meta-analysis

Zohaib Ahmed, MD, Andrew Kelly, MD, Joyce Badal, MD, Mohammad Nawras, MD, Wade Lee-Smith, Abdallah Kobeissy, MD

Introduction: Diagnostic paracentesis is recommended by society guidelines for all hospitalized patients with cirrhosis and ascites regardless of reason for admission. 25% of patients with ascites develop SBP, and prompt

identification and treatment of SBP is critical, as mortality approaches 30% in those who develop SBP. Although previous studies have found that provider clinical judgment alone is poorly reliable in recognizing patients with SBP, guideline adherence remains alarmingly low, with only approximately 61% of patients receiving diagnostic paracentesis when indicated. Recent literature has reported that delayed paracentesis is associated with a 2.7 times increased risk of mortality, with a 3.3% increase in mortality for every hour delayed. While there is a clear benefit to early paracentesis, currently no specific time-frame recommendations exist. Therefore, we conducted a systematic review and meta-analysis to evaluate outcomes amongst patients receiving paracentesis within ≤12, ≤24, and >24 hours.
Methods: A systematic review of the literature was performed using Embase, Medline, Cochrane Central Register of Controlled Trials, Web of Science Core Collection, Korean Citation Index, SciELO Citation Index, and Global Index Medicus to identify studies for the meta-analysis. Outcomes of interest included mortality and hospital length of stay between early vs delayed paracentesis in patients admitted to the hospital with cirrhosis and ascites. All statistical analyses were conducted using RevMan meta-analysis software.
Results: Eight retrospective studies including a total of 116,174 patients were included in the final meta-analysis. The pooled risk of in-hospital mortality was significantly lower in patients who underwent early (≤12 hours or ≤1 day) compared to delayed (>12 hours or >1 day) paracentesis (RR: 0.69, 95% CI: 0.64-0.75, p<0.00001, I2=32%). On subgroup analysis, there was a trend towards reduced mortality in patients who underwent paracentesis within ≤12 hours (RR: 0.61, 95% CI: 0.4-0.92, p=0.02, I2=25%) compared to within ≤1 day (RR: 0.70, 95% CI: 0.65-0.75, p<0.00001, I2=48%), although this difference was not statistically significant. The risk of in-hospital mortality was significantly lower in patients who underwent diagnostic paracentesis compared to no paracentesis (RR: 0.73, 95% CI: 0.67-0.80, p<0.00001, I2=27%), and the length of hospital stay was significantly shorter by 5.38 days in patients who underwent early (≤12 hours) compared to delayed (>12 hours) paracentesis (95% CI: 4.24-6.52, p<0.00001, I2=0%).
Conclusion: In conclusion, early diagnostic paracentesis is associated with significantly reduced mortality and shorter length of stay in hospitalized patients with cirrhosis and ascites. Paracentesis should be performed within ≤1 day of admission, with efforts to perform the procedure within ≤12 hours when possible.

Zohaib Ahmed, MD

Efficacy of cap assisted endoscopy for the visualization of major duodenal papilla: A systematic review and meta-analysis

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Background and aims: The current standard of practice is to use a duodenoscope for the evaluation of major duodenal papilla (MDP). Recently, cap-assisted endoscopy (CAE) which uses a transparent cap at the tip of a standard front-viewing endoscope emerged as an alternative.
Methods: A systematic literature search was performed at several databases from inception to January 2023 to identify studies evaluating the efficacy of CAE for the evaluation of MDP.
Results: A total of nine studies including 806 patients met our inclusion criteria. The pooled rate of technical success for CAE was 93.2% [85.6%-96.9%, I2=84.6%]. A subgroup analysis comparing CAE with standard endoscope showed higher odds for the evaluation of MDP with CAE (but not a duodenoscope which was better than CAE) with OR=57.294 [17.767-184.755, I2=45.303%].
Conclusion: CAE offers a significant advantage with high rates of complete MDP evaluation compared to standard forward endoscopy. However, CAE is associated with lower rates of success when compared to side-viewing endoscopes.

Zohaib Ahmed

Fecal microbiota transplant is associated with lower risk of mortality, hepatic encephalopathy, ascites, and infection patients with severe alcohol-associated hepatitis: a systematic review and meta-analysis

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Introduction: Severe alcohol-associated hepatitis (SAH) is an acute, inflammatory liver disease that results in disruptions of the gut microbiome leading to bacterial translocation which drives systemic inflammation and end-organ damage. Despite high risk of mortality, treatment options are limited. Fecal microbiota transplant (FMT) may help restore the balance of healthy bacteria in patients with disrupted gut microbiomes due to SAH, which may decrease systemic inflammation, infection, and mortality. As the role of FMT in the treatment of SAH is not yet established, we conducted a systematic review and meta-analysis to evaluate the currently available literature regarding the impact of FMT on outcomes in patients with SAH.
Methods: A comprehensive search strategy was used to identify studies that reported outcomes of patients with SAH receiving FMT compared to no FMT in Embase, MEDLINE (PubMed), Cochrane Library, Web of Science Core Collection, and Korean Journal Index, and Global Index Medicus. Outcomes of interest included 1-, 3-, and 6- month mortality, overall mortality, and risk of HE, ascites, upper GI bleeding, and infection. RevMan software was used for statistical analysis.
Results: 7 studies with a total of 384 patients were included in the final meta-analysis. Patients who received FMT had significantly lower risk of 1-month mortality (RR: 0.51, 95% CI: 0.29-0.91, p=0.02), 3-month mortality (RR: 0.61, 95% CI: 0.38-0.98, p=0.04), and overall mortality (RR: 0.58, 95% CI: 0.38-0.87, p=0.009) compared to those who did not receive FMT, although the difference in 6-month mortality did not reach statistical significance (RR: 0.73, 95% CI: 0.18-2.89, p=0.65). Patients who received FMT also had significantly lower risk of hepatic encephalopathy (RR: 0.27, 95% CI: 0.16-0.46, p< 0.00001), ascites (RR: 0.47, 95% CI: 0.33-0.67, p< 0.0001), noncritical infections (RR: 0.36, 95% CI: 0.21-0.6, p=0.0001), and critical infections (RR: 0.28, 95% CI: 0.17-0.48, p< 0.00001). There was no significant difference in risk of upper gastrointestinal bleeding (RR: 0.77, 95% CI: 0.48- 1.24, p=0.28).
Discussion: FMT for SAH is associated with significantly lower risk of 1-month, 3-month, and overall mortality, as well as lower risk of hepatic encephalopathy, ascites, and both critical and non-critical infections. Further studies, particularly large randomized controlled trials, are needed to establish the role of FMT in the treatment of patients with SAH.

Audrey Ballard

A prolonged presentation of cyclic vomiting syndrome in an adult

Audrey Ballard, Andrew Campbell, MD

Introduction: Intractable nausea and vomiting are symptoms commonly encountered in the clinical setting. Patients often experience weight loss, nutritional and electrolyte abnormalities, and emotional stress due to inability to eat, work, or socialize. Cyclic vomiting syndrome (CVS) is defined as recurrent episodes of intense nausea and vomiting episodes that can last anywhere from hours or days. It is a diagnosis by exclusion and there is often a negative workup for infectious or functional causes. Most commonly, it is diagnosed in children but occasionally can manifest in the adult population.
Case Summary: A 44-year-old African American male presented with intractable nausea and vomiting and 42 lbs weight loss for several months. Past medical history included GERD, DVT, AVMs and Morbid Obesity. Patient denied use of marijuana and family history included hypertension, diabetes, and migraines. Initial labs showed hypernatremic at 149, hypokalemic at 3.1, chloride at 107, bicarb at 29. Patient was complaining of dizziness and vertigo accompanying the nausea and vomiting. Patient initially improved following intubation

for MRV Brain but returned a few days later. A diagnosis of neuromyelitis optica (NMO) was investigated and the patient was given five days of high dose steroids. However, aquaporin 4 antibody titers were negative and an MRI cervical spine/orbits did not show any signs of NMO. GI workup revealed no obstruction seen on CT enterography and EGD showed grade D esophagitis with erythematous gastric mucosa. No improvement was seen with PPI therapy and primary differential diagnosis was assumed to be intractable nausea and vomiting due to cyclic vomiting syndrome. The patient was started on 25 mg amitriptyline daily which was titrated up to 75 mg daily over a few weeks. With the increasing dose, the patient's nausea and vomiting began to improve and was able to tolerate food by mouth. Patient was discharged after 6 weeks in the hospital with plans for GI follow-up.

Discussion: Cyclic vomiting syndrome is most commonly a pediatric disorder but can occasionally manifest in adults. The cause of CVS is somewhat unknown but is considered to be related to migraines. Other causes have been found to be related to cannabis use, excessive hypothalamic-pituitary-adrenal axis activation, autonomic dysfunction, and mitochondrial DNA mutations. Multiple case reports of CVS in adults suggest patients typically have a family history of migraines and episodes begin in early adulthood. Episodes are often triggered by infections, stress, sleep deprivation, menstrual cycles, food allergies, or cannabis use. CVS has been described as commonly having four phases: interepisodic, prodromal, emetic, and recovery. During the interepisodic phase the patient is often symptom free for weeks to months. The prodromal phase is categorized by the patient sensing the start of an episode. Similar to a migraine aura, symptoms during this period include nausea, sweating, abdominal pain, temperature intolerance, food aversion, and irritability. Once an episode begins patients experience the extreme nausea and vomiting that can last from days to weeks. Finally, during the recovery phase, the patient's nausea diminishes as this slowly increases their tolerance for oral intake. While it is often a diagnosis of exclusion, there are several diagnostic criteria that can be used to consider the diagnosis such as the Rome IV Criteria which includes 1) stereotypical episodes of vomiting that have an acute onset and a set duration, 2) three or more episodes within a year, and 3) absence of vomiting between episodes. The presence of all three criteria supports the diagnosis of CVS. Management of CVS is typically either prophylactic, abortive and/or supportive. Due to the hypothesis of the etiology being related to migraines, standard prophylactic treatment is low-dose amitriptyline. Other studies have shown that topiramate, cyproheptadine, propranolol and erythromycin can also be used as alternative prophylactic treatment. Supportive medication during an episode is typically intravenous fluids and anti-nausea medications like ondansetron or prochlorperazine. Sumatriptan has been shown to be effective as an abortive agent that can be used during the prodromal phase or during an acute episode. Cyclic vomiting syndrome is a minimally understood disorder especially in the adult population and more studies and research are needed to understand the etiology and presentation to hopefully one day minimize the impact on a patient's health and lives.

Bush, M

Differential expression of organic anion transporting polypeptides in the liver and common comorbidities: Implication for toxicity of microcystins and other xenobiotics

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Background: Organic Anion Transporting Polypeptides (OATPs) are a family of transporters found throughout the body and encoded by Solute Carrier Organic Anion Transporter (SLCO) genes. The role of OATP in the transport of xenobiotics has gained increased attention due to harmful algal blooms (HABs) and the subsequent release of cyanotoxins like Microcystin-LR (MC-LR) that can harm humans. Exposure is known to cause acute illness including liver injury, however the extent of illness and susceptibility of individuals with common liver disease comorbidities is unknown.

Objectives: We used a differential expression analysis to determine levels of SLCO expression in both healthy individuals and those with common pre-existing liver diseases to understand how hepatic comorbidities may impact susceptibility to HAB cyanotoxin exposures.

Methods: We examined RNA expression levels of OATP related SLCO genes in hepatic tissue across a variety of comorbidities. Differential gene expression data was obtained from the National Center for Biotechnology Information (NCBI), Gene Expression Omnibus (GEO). Search queries in the GEO browser were formatted as "(Disease) AND tissue." Datasets which did not fulfill "disease vs. healthy" criteria were omitted. Differential Expression Analysis was performed using NCBI's integrated GEO2R software.
Results: Liver tissue exhibited high expression levels of several SLCO isoforms (Figure 1). When compared to non-diseased control liver samples, SLCO expression was decreased in cirrhotic liver, while liver samples obtained from hyperglycemic and diabetic patients as well as patients with hepatocellular carcinoma demonstrated increased expression of SLCO compared with non-diseased controls (Figure 2).
Discussion: This data supports the hypothesis that disease states impact the expression level of SLCOs. Decreased expression in cirrhosis suggests a downregulation of OATP as a response to damaged hepatic tissue. Increased expression in hyperglycemic, diabetic, and hepatocellular carcinoma patients aligns with previous studies from our lab and others indicating that these disease states confer increased susceptibility to cyanotoxin exposure.

Sami Ghazaleh, MD

A rare case of localized colonic amyloidosis identified during a screening colonoscopy

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Introduction: Amyloidosis is an abnormal accumulation of amyloid protein in different organs and tissues, which typically results in nephropathy, cardiomegaly, hepatomegaly, and neuropathy. We report a rare case of localized amyloidosis that was identified during a screening colonoscopy.
Case Presentation: A 73-year-old male patient was referred to the gastroenterology clinic for a screening colonoscopy. Past medical history was significant for essential hypertension, type 2 diabetes mellitus, gastroesophageal reflux disease (GERD), and myasthenia gravis. Screening colonoscopy revealed one 12 mm flat polyp in the ascending colon. The polyp was removed with endoscopic mucosal resection (EMR) and retrieved successfully. Biopsy of the polyp showed amorphous deposits in the submucosa, suggestive of amyloid deposits. Congo red stain was performed, and stain was suggestive of amyloidosis. Liquid chromatography tandem mass spectrometry was later performed on the biopsy, which detected a peptide profile consistent with AL (kappa)-type amyloid deposition. In addition, seven other sub-centimeter tubular adenomas were seen in the transverse and sigmoid colons, which were removed with cold snare and cold biopsy forceps. The patient was referred to hematology to rule out systemic amyloidosis. Workup by hematology was negative for systemic amyloidosis. The only abnormal finding was a slightly elevated kappa/lambda light chain ratio at 1.69. In addition, fat pad biopsy showed no evidence of Congo red/amyloid deposits, cardiac MRI showed no evidence of amyloidosis, and bone marrow biopsy showed no evidence of plasma cell dyscrasia and was negative for amyloid stain. It was concluded that the patient had localized amyloidosis without evidence of systemic disease.
Conclusion: Gastrointestinal amyloidosis is a common finding in systemic amyloidosis, especially AA amyloidosis. However, localized gastrointestinal amyloidosis without evidence of systemic amyloidosis is uncommon. Management consists of observation or removal of the localized deposition. Patients have a good prognosis and they do not typically transition to systemic amyloidosis.

Bella Khatib-Shahidi

Characterization of human colon tissue for harmful algal bloom exposure in cancer and non-cancer patients

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Introduction: Harmful algal blooms (HABs) are occurring more frequently not only in the Great Lakes region but also globally. HABs release cyanotoxins, which present public health concerns and significant health risks. Cyanotoxins may enter humans through water ingestion, aerosol inhalation, or direct skin contact. We have previously demonstrated that cyanotoxins exacerbate pre-existing liver and inflammatory bowel disease in mice. However, the effects of cyanotoxin exposure in humans with colon disease and colon cancer is poorly understood.
Objectives: We sought to identify the presence of cyanobacteria in Formalin-Fixed Paraffin Embedded (FFPE) colon tissue obtained from patients residing in the Great Lakes region. We hypothesized that the levels of cyanobacteria correlate with markers of tumor severity in colon cancer.
Methods: DNA and RNA were extracted using an optimized extraction/purification protocol designed for FFPE colon tissues from invasive adenocarcinoma (n=5) and age and sex matched non-adenocarcinoma controls (n=5). Presence of cyanobacteria and markers of tumor severity were determined using quantitative PCR analysis.
Results: Cyanobacteria levels were elevated in colon cancer tissues compared to non-cancer (1.0±0.27 vs 1.3±.66) although this was not statistically significant. Interestingly, while markers of tissue remodeling were not significantly correlated with cyanobacterial load overall in both cancer and non-cancer samples, within the invasive adenocarcinoma samples, cyanobacterial load was negatively correlated with both Transforming Growth Factor-beta ($r=-0.6121$, $p=0.0334$) and matrix metalloprotease isoform 9 ($r=-0.6272$, $p=0.0261$).
Conclusion: Our results suggest that cyanobacteria may be increased in the setting of invasive adenocarcinoma and may impact the expression of key tissue remodeling genes within these tumors. This data agrees with clinical and experimental evidence suggesting an association between cyanobacteria and cancer progression in other settings and supports the need to investigate the potential role of cyanobacteria in colon cancer progression. Analysis of additional samples is ongoing to establish this relationship in an expanded cohort.

Anas Renno, MD

Acute cerebral edema and hyperammonemia after transjugular intrahepatic portosystemic shunt placement in a patient with chronic liver disease

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Introduction: Transjugular intrahepatic portosystemic shunt (TIPS) in cirrhotic patients results in porto-systemic encephalopathy in approximately 30-35%, usually apparent 2-3 weeks post TIPS. Cerebral edema and intracranial hypertension are known complications of acute liver failure, however, are rarely seen in chronic liver disease. We describe a patient with cirrhosis who had physical exam findings of cerebral edema 24 hours post TIPS.
Case Presentation: A 71-year-old male with newly diagnosed liver cirrhosis who initially presented to the ED with profound hematochezia. He became hypotensive requiring pressor support and massive transfusion protocol. Patient also became altered requiring intubation. Nasogastric tube was placed, and aspirate revealed no evidence of blood. His pH was 6.8 and ammonia level was 43. A flexible sigmoidoscopy revealed an actively bleeding rectal varix. The varix was treated with 6 ml sodium tetradecyl sulfate for varix eradication without success (Fig. 1). Patient required an emergent TIPS for ongoing bleeding with successful embolization of the distal inferior mesenteric vein perirectal varices. The portal pressure gradient was reduced from 20

mmHg to 6 mm Hg. He remained intubated. The following day, the patient developed scleral edema and conjunctival hemorrhage, concern for cerebral edema and brain compression. 24 hours post TIPS the ammonia level 507. The patient was clinically unstable to undergo a CT brain. Hypertonic saline was started, however his clinic status continued to decline, and the patient expired.
Discussion: This case demonstrates the development of acute cerebral edema caused by hyperammonemia as a complication of TIPS in a patient with chronic liver disease. The development of hepatic encephalopathy after TIPS is common, however development of cerebral edema in patients with chronic liver disease undergoing TIPS is rare. Cerebral edema should be recognized as a potential complication of TIPS to avoid permanent neurologic injury. Although elevations in serum ammonia are expected after a TIPS procedure, there is a mistaken impression that cerebral edema is not seen in chronic liver disease. We hypothesize that the serum ammonia level increased after the patient's TIPS because the TIPS shunted ammonia-containing blood to the systemic circulation and away from the liver. Prompt consideration should be given to reversing or downsizing the TIPS as early as possible in the clinical course if warranted.

Wasef Sayeh; MD

The effect of SGLT-2 inhibitors on improving non-alcoholic fatty liver disease: A systematic review and meta-analysis

Wasef Sayeh; MD, Sudheer Dhoop; MD, Sahithi Chinnam; DO, Rayna Patel; MD, Azizullah Beran; MD, Megan Karrick; MD, Anas Renno; MD, Ali Nawras; MD

Introduction: Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease, and its prevalence continues to increase worldwide. Approximately 80% of patients with Type 2 Diabetes Miletus (T2DM) have NAFLD. SGLT-2 inhibitors are novel oral antihyperglycemic medications that showed huge benefits in managing T2DM, Chronic kidney disease and heart failure. Many clinical trials reported that SGLT-2 inhibitors can improve NAFLD.
Methods: We performed a comprehensive search of the databases from inception through May 15th, 2023. The primary outcome was the improvement of liver enzymes (ALT, AST). The secondary outcome was the improvement in the fibrosis index score (FIB-4). The random-effects model was used to calculate the mean differences (MD) and 95% confidence intervals (CI). A p value <0.05 was considered statistically significant. Heterogeneity was assessed using the Higgins I2 index.
Results: Eleven randomized controlled trials involving 589 patients were included in the meta-analysis. All studies compared the levels of ALT between the SGLT-2 inhibitors group and the control group which showed a significant reduction in the enzyme level in the treatment group (MD -5.02, 95% CI -7.89- -2.15, p=0.0006, I2 = 89%) (Figure 1a).Ten studies compared the AST levels which also showed a significant reduction in the enzyme level in the SGLT-2 inhibitors group compared to the control group (MD -2.51, 95% CI -3.37 - -1.65, p <0.00001, I2 = 43%) (Figure 1b). Only, four studies compared the improvement in FIB-4 and the reduction in FIB-4 was significantly lower in the SGLT-2 inhibitors group compared to the control group (MD -0.07, 95% CI -0.08- - 0.05, p <0.00001, I2 =0%) (Figure 1c).
Discussion: Our meta-analysis demonstrated that the use of SGLT-2 inhibitors can be beneficial in patients with NAFLD in terms of lowering the level of liver enzymes (ALT and AST) and lowering the fibrosis index score (FIB-4).

GENERAL INTERNAL MEDICINE

Mohammed Abu-Rumaileh

Into the unknown: Navigating orbital cellulitis to reveal retinal metastasis of a hidden primary tumor

Mohammed Abu-Rumaileh, Kashvi Patel, Fanham Asghar, Anu Garg

Introduction: This is a rare patient presentation of retinal metastasis with an unknown primary tumor.
Case Presentation: A 65-year-old woman with a past medical history of left breast carcinoma stage 1 status post left mastectomy in 2014, iron deficiency anemia, anxiety, and depression presented to the emergency department with 1-2 weeks of worsening lower abdominal pain and left-sided chest pain. She also complained of right eye pain, blurry vision, and painful eye movement. Ocular examination demonstrated edema, mild proptosis, conjunctival chemosis, and conjunctival injection. Patient was started on bacitracin ointment and ceftriaxone due to concerns of orbital cellulitis. Ophthalmology was consulted, and their assessment was suggestive of bilateral metastatic neoplastic lesion in retina of both eyes, more pronounced in the right than the left eye. Left supraclavicular lymph node biopsy showed metastatic adenocarcinoma, likely of gastrointestinal or pancreaticobiliary primary. MRI brain was suspicious for calvarial metastatic disease, MRI abdomen showed multiple nodules in the liver suggesting metastases, and NM bone scan whole body suggested possible metastases in the hemithorax and bilateral femurs. After several goals of care discussions, the decision was made by the patient and her family to pursue comfort measures only and she was discharged home with home hospice.
Conclusion: Retinal metastasis is a rare condition due to the absence of lymphatic system in the eye. The most common primary tumors to metastasize to the eye are from breast (47%), lung (21%), and the gastrointestinal tract (4%). In some cases, patients may have no other symptoms. Thus, retinal metastasis is important to include in the differential diagnosis, especially for patients with a history of treated primary cancer.

Mani Khorsand Askari, MD

Improvement of in-office blood pressure targets in an academic primary care setting

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Background: Accurate blood pressure (BP) measurement in an office-based setting is essential for diagnosis and management of hypertension. Staff education on proper blood pressure measurement technique and recording is a focus of recent hypertension guidelines. Compared with other methods, unattended Automated Office Blood Pressure (AOBP) devices reduce measurement errors and improve BP Management. The addition of AOBP to staff education needs to be assessed objectively.
Objectives: To determine the effect of staff education on proper BP measurement and addition of AOBP devices on BP targets in an academic general internal medicine clinic.
Methods: Education was provided to the medical staff on how to appropriately check BP in general and on the proper use of the AOBP devices. Education was repeated in several intervals to ensure consistency in practice. Six AOBP Hillrom (Welch Allyn spot 4400) devices were deployed for the clinic. Devices allowed for three automated readings 1 minute apart eliminating the first reading and keeping the other 2 readings. Staff were instructed to document two blood pressure readings into the electronic medical record. The number of patients who completed two BP measurements documented in the EMR over time.
Results: Our results showed timely education with refresher, increased BP measurement protocol and improved BP recordings. Adherence to 2 BP checks increased from 40% in Dec-2021 to 99% in Jun-2023. The percentage of patients with improved BP increased from 40% to 76% after staff education and addition of AOBP.

Conclusion: Timely education of medical staff and the addition of AOBP could increase the accuracy of in-office BP measurement.

Mani Khorsand Askari, MD

Effects of reminder systems in reducing no-show rate in an academic general internal medicine clinic

Mani Khorsand Askari, MD, Hoda Shabpiray, MD, Sadik Khuder, PhD, Anand Mutgi MD, Ken Vellequette, MD, Cheryl Growden, Lisa Heyman, Dawn Lennard, Brenda Joyce, Basil Akpunonu, MD

Background: A No-show (NS) is defined as a failure to keep a face-to-face or virtual outpatient appointment without notice. A High no-show rate (NSR) affects continuity of care. The mean NSR in US is 18.8% with the highest rate seen in primary care offices. There are several reasons for NS including transportation issues, concurrent admission on the day of appointment, with the most reported reason being "forgetting the time of appointment." Interventions are designed based on the main reason of NS. Some interventions to decrease NSR include automated reminder systems (ARS) by texts, emails, and staff calls to patients 24hrs before visit. The effect on NSR reduction with these measures in our setting is unclear.
Objectives: This prospective study was conducted to assess the effect of ARS on NSR in an academic general internal medicine (GIM) clinic.
Methods: Data on NSR was collected in the academic GIM clinic after initiating ARS by telephone, text, or email. ARS delivered before the appointment time and was consistent throughout the study. We also collected data on actual reasons for NS by random telephone calls to NS patients. The second intervention was a direct call from staff members to the patients 24 hours before the appointment as a direct reminder.
Results: The total number of visits for the year was 18640. NSR was around 19% at the introduction of ARS, Nov 2022, and over 6 months of using ARS dropped to 15% by end of May 2023 (P=0.001). There was a significant further reduction from June to the end of July with the use of direct staff calls (P=0.0000005).
Conclusion: We conclude the ARS reduces the NSR in this academic GIM clinic. Moreover, the addition of direct staff calls to the patient could further reduce the NSR.

James Bassett

Bridging health gaps in Central America: identifying prevalent diagnoses across medical missions for improving targeting of treatment

James Bassett, Jennida Chan, Jennifer Kim, Richard Paat

Introduction: International medical mission trips commonly have a goal to provide care to underserved populations in developing countries. Despite the recent increase in the number of international medical mission trips and the services they provide, there is limited literature outlining the impact of the mission trips and how it aligns with the needs of the countries they serve.
Objectives: The main objective of this study was to determine the top diagnoses during recent medical mission trips and compare them with the most prevalent health concerns reported within that country. Secondary objectives are to inform preparation for future medical mission trips.
Methods: Volunteers from the medical triage team collected basic patient health information on paper printouts, noting vitals and reason for visit. Care teams updated each patient print-out with diagnose(s), treatment plan, and any relevant prescriptions. Students then uploaded each patient record, removing patient identifiers.
Results: From January 2022 to July 2023, University of Toledo students collected data on two mission trips to Guatemala and one to Honduras. 2,740 patients were treated in total. In Guatemala, top diagnoses included headache (8.8%), dental conditions (7.5%), parasites (7.4%), and arthritis (7.2%). As a result, the top treatments focused on pain and inflammation including ibuprofen (11.6%) and acetaminophen (10.3%). In Honduras, pain

and GERD easily led the group (18.8% and 17.1% respectively) with allergies (11.2%) and headache (10.2%) also common.
Conclusion: Our data indicates a high prevalence of disease in Central America that is treatable and amenable to short-term mission-oriented intervention. However, there was little overlap of the most common diagnoses when compared to the CDC's top five priority health conditions listed for Central America: anemia, Chagas disease, mental health, obesity, and parasite infection. Further studies should explore these differences to address the country's needs more effectively from within and on future medical missions.

Titas Bera

Elevated creatine kinase and myoglobin in the setting of worsening restless leg syndrome due to acute blood loss anemia

Titas Bera, Mani Askari, MD, Hoda Shabpiray, MD

Introduction: Restless Leg Syndrome (RLS) is characterized by distressing sensations in the legs and an irresistible urge to move them, typically occurring during rest or at night. This condition has been linked to brain iron deficiency, yet the effectiveness of intravenous (IV) or oral iron replacement for RLS treatment remains unclear.
Case Presentation: An 83-year-old woman presented to the emergency department due to worsening leg cramps, accompanied by mild shortness of breath and muscle cramps. Subsequent examination revealed anemia, with her hemoglobin levels at 6.6 g/dL. Normal creatinine kinase and myoglobin levels ruled out muscle damage as the cause of her symptoms. In addition to receiving packed red blood cells (PRBCs) and intravenous Lasix for suspected vascular congestion and shortness of breath, the patient was found to have elevated creatinine kinase and myoglobin levels on day 2, indicating muscle damage. The treatment approach was adjusted on day 2, with the patient transitioning to intravenous iron and receiving another unit of PRBCs. As a result, her hemoglobin levels improved, and her muscle cramps subsided. The subsequent days showed a decline in myoglobin levels, aligning with their distinct half-lives. The patient's condition continued to improve, with no further complaints of restless legs or leg cramping. By day 5, she was discharged with improved hemoglobin levels and clinical status, accompanied by oral iron supplementation and gabapentin for her restless legs.
Discussion: This case highlights the potential for muscle damage in cases of acute blood loss anemia leading to exacerbated RLS, as evidenced by elevated creatinine kinase and myoglobin levels. Although the connection between RLS and iron deficiency is recognized, addressing iron deficiency to alleviate the discomfort, pain, and clinical deterioration associated with RLS requires further investigation.

Marilee Clemons

The evaluation of a pharmacist-led multidisciplinary quality committee in a general internal medicine outpatient clinic

Marilee Clemons, Sarah Aldrich Renner, William Barnett, MS, MA

Background: Two embedded pharmacists in the outpatient general internal medicine clinics developed and lead a division-wide quality committee. The committee consists of division leadership and select quality champion members including other providers and staff who meet to review and implement clinic-wide processes to improve Accountable Care Organization (ACO) quality measures. Three quality metrics have been the focus of improvement: Hemoglobin A1c < 9%, blood pressure (BP) < 140/90 mmHg, and improved documentation of immunizations.
Objective: To use the perceptions of the clinic team members to evaluate the effectiveness of pharmacist-led quality committee aimed to develop, implement, and facilitate standardized clinic-wide processes to improve ACO quality measures.

Methods: A 32 question survey, including 27 Likert-scale questions and 5 free response questions was created to review the committee members' perspectives on the pharmacist-led committee. The survey was sent to all members of the committee (18 participants). Survey results were evaluated using Winsteps 5.4 Rasch analysis and a variance map was constructed to understand how the items/respondents interacted – this allowed the creation of 4 domains.
Results: Eighteen participants were invited to complete the survey with a 50% response rate. The survey was found to demonstrate high reliability and the Likert scale was appropriate. Based on the variable map, 2 of 9 respondents did not agree with all the questions specifically surrounding effectiveness and engagement of the committee. The results indicate that most committee members agreed with the effectiveness of the pharmacist-led quality committee.
Conclusion: The survey was worded well and appropriate for the study objective. The development of this committee resulted in quality success and the pharmacists are well suited to lead these efforts.

Amna Iqbal

Pre-cut papillotomy versus Endoscopic Ultrasound (EUS) rendezvous for difficult biliary cannulation – A systematic review and meta-analysis

Amna Iqbal, Zohaib Ahmad, Kirubel Zerihun, Manesh Kumar Gangwani, Sara Stanley, Anas Renno, Dushyant Singh Dahiya, Wade Lee Smith, Toseef Javaid, Mona Hassan, Abdallah Kobeissy

Background:
Various endoscopic techniques are employed to achieve biliary cannulation when confronted with difficult biliary access. Every procedure carries its own risk in terms of bleeding, infection, pancreatitis, and cholangitis. Our meta-analysis aims to compare Pre-cut Papillotomy and Endoscopic Ultrasound (EUS)-Rendezvous in terms of technical success rates, and post-procedure pancreatitis and bleeding.
Methods:
We conducted a systematic review and meta-analysis of studies that compared Pre-cut Papillotomy and EUS-Rendezvous. The primary outcome was technical success by achieving biliary cannulation. Secondary outcomes were postoperative pancreatitis and bleeding. A random-effects model was used to calculate the risk ratios (RR), mean differences (MD), and confidence intervals (CI). A P-value <0.05 was considered statistically significant.
Results:
We included 3 studies comparing Pre-cut Papillotomy and EUS Rendezvous. Both procedures were similar in terms of clinical success (RR 0.98, 95%CI 0.94-1.02). No difference was found between rates of post procedure pancreatitis (RR 1.60, 95% CI 0.52, 4.94) and post procedure bleeding (RR 3.94, 95% CI 0.53, 29.39).

Nahshon A. Puente

Association between autoimmune diseases and glioblastoma: results from national inpatient database

Nahshon A. Puente, Mahasin Osman, Sadik A. Khuder, PhD

Background: Glioblastoma multiform (GBM) is the most frequent malignancy among primary brain tumors in adults and has one of the worst 5-year survival rates among all human cancers. Certain autoimmune diseases (AID) and their treatments may increase the risk of cancer. Studies report conflicting data about the effects of AID on the risk of GBM.
Objectives: To evaluate the effect of AID on the risk of GBM.
Methods: Discharge data for 2020 Nationwide Inpatient Sample, Healthcare Cost and Utilization Project (HCUP), which approximates a 20% stratified sample of all US hospitalizations, were analyzed. Cases of AID and GBM were identified using the ICD10 codes. Autoimmune comorbidity index was used for the combined autoimmune diseases. Weighted Multivariable logistic regression was used to examine the association between

GBM and AID and adjusting for sociodemographic characteristics. Adjusted odds ratios (AOR) and 95% confidence intervals (CI) were calculated using SAS survey logistic regression procedure.
Results: Among 6,471,165 admissions, 178,254 patients were identified with AID. The prevalence of GBM in patients with AD was 0.07% compared to 0.12% in patients without AID (AOR = 0.653, CI= 0.546-0.782, p = 0.0016). Significant reduction was found for rheumatoid arthritis (RA), lupus, and scleroderma. The highest reduction in the risk of GBM was for scleroderma. No significant differences were found for Sjogren's syndrome, psoriasis, sarcoidosis, thyroiditis, multiple sclerosis, or other AID.
Conclusion: In the US, among hospitalized adults diagnosed with AID, patients with RA, lupus, and scleroderma are significantly less likely to have GBM. This reduction could be attributed to the effect of anti-AID drugs administered to the patients, or the nature of the activated pathways in AID that naturally antagonize neoplastic activation.

Hoda Shabpiray, MD

The negative consequences of false negative lung cancer screenings

Hoda Shabpiray, MD, Mani Khorsand Askari, MD, FACP, Jerrin George

Introduction: Lung cancer is the leading cause of cancer death in the USA. The USPSTF recommends annual low-dose CT scan (LDCT) for 50- to 80-year-old adults with a 20 pack-year smoking history who are current smokers or have quit smoking within the past 15 years. Although it has been shown to be effective in reducing mortality rate, it also has false-negative rates of up to 15%. We present a patient with a negative lung cancer screening who was diagnosed with stage 4 lung cancer, seven months after negative screening results.
Case Presentation: An LDCT scan for a 61-year-old female with PMH of COPD and 40 pack-year smoking history revealed benign screening and Lung RADS category 2 in October 2021. Seven months later she presented to the hospital with SOB, and productive cough. CXR revealed patchy pneumonia in the left upper lobe. Treatment started and she got discharged. 10 days later following worsening of her symptoms, CT chest obtained which demonstrated a left upper lobe mass suspicious for neoplasm. Lung biopsy revealed small cell carcinoma. Bone scan demonstrated possible osseous metastasis. After further evaluation chemotherapy and radiation therapy started for stage 4 lung cancer.
Conclusion: Lung cancer screening requires a shared decision-making visit. The patient must be educated about false positive results and possible further evaluations. However, almost nothing is mentioned about the false negative results or the possibility of interval diagnosis of lung cancer between annual screenings.
Those with negative tests may be less likely to subsequently present in the event of developing symptoms or may interpret that it is unlikely to have lung cancer later in their life. It may also cause false reassurance for health care workers, causing delayed appropriate testing. Furthermore, a negative test may result in a reluctance to change detrimental health-related behaviors, such as smoking.

Li Wang, MD

There is a "WHAT" in my belly – A rare presentation of abdominal pain

Li Wang, MD, Anu Garg, MD

Introduction: Lithopedion, or stone child in ancient Greek, is a rare medical condition in which the dead fetus from extrauterine pregnancy becomes calcified and retained in the abdominal cavity. We present a case of lithopedion in an elderly lady.
Case Presentation: A 67-year-old woman presented to the emergency room with 2 days of abdominal pain in the middle and right lower quadrant associated with nausea and vomiting. Pain was moderate in intensity and non-radiating. She reported decreased urine output, and denied any fever, chills, or diarrhea. She was nulliparous and denied ever being pregnant. Physical exam was only notable for pain in the abdomen of middle and right upper quadrant on palpation but no rebound tenderness or guarding. Labs were significant for elevated WBC of 28.8 (ref. 4.5-11.0), and urinalysis positive for trace leukocyte esterase and nitrite. A CT abdomen and pelvis showed an irregular uterus with mass which was compressing on the bladder (*figure 1 & 2*). Mass was

identified to be a calcified fetus with a visible head, trunk and limbs and a diagnosis of lithopedion was made. She received IV normal saline, Ondansetron for nausea and vomiting, and ciprofloxacin for urinary tract infection. Patient was discharged home with antibiotics and outpatient follow-up with Obstetrics and Gynecology for further management.
Discussion: Lithopedion is very rare. There are only 18 cases on PubMed where the patients are over the age of 65 at the time of diagnosis, and fewer than 10 were nulliparous. The majority of women have been able to have children or carried subsequent pregnancies without issues. Lithopedion could be asymptomatic, thus many do not find out until decades later, often on incidental X-ray or CT imaging. Most cases are benign, but there are reported complications such as bowel obstruction, abscess, uterine rupture, infertility, fistula formation, etc. Given the rarity of this condition, no definitive treatment is established; however, most have opted for surgical management. As access to prenatal care and imaging use increases, more cases of lithopedion will be reported, studied, and hopefully prevented. It is also a possible albeit rare differential diagnosis in elderly women presenting with abdominal pain.

HEMATOLOGY/ONCOLOGY

Daniel J. Craig, MD

Validation of airway epithelial cell TP53 biomarker for lung cancer risk

Daniel J. Craig, MD, Erin L. Crawford, Heidi Chen, Eric L. Grogan, Steven A. Deppen, Thomas Morrison, Sanja L. Antic, Pierre P. Massion, James C. Willey

Background: There is a need for biomarkers that reliably detect those at highest risk for developing lung cancer, thereby enabling more effective screening by annual low-dose CT. We previously discovered a biomarker for lung cancer risk characterized by an increased prevalence of TP53 somatic mutations in airway epithelial cells (AEC)1. Here we present results from a blinded retrospective case-control validation study.
Methods: AEC genomic (g)DNA specimens were collected at Vanderbilt University in collaboration with the National Cancer Institute (NCI) Early Detection Risk Network (EDRN) according to a University of Toledo IRB-approved protocol. Synthetic DNA internal standards (IS) were prepared for 3 exons in TP53 spanning 193 base pairs and mixed with each AEC genomic DNA specimen prior to competitive multiplex PCR amplicon NGS library preparation. These competitive IS molecules enable the determination of site-specific sequencing error and thus lower the limit of detection for detecting somatic mutations.
Results: TP53 mutation prevalence was significantly associated with cancer status. The lung cancer detection receiver operator characteristic (ROC) area under the curve (AUC) for the TP53 biomarker was 0.845 (0.749-0.942) with sensitivity: 60.0%, and specificity: 96.7%. In contrast, TP53 mutation prevalence was not significantly associated with age or smoking status among non-cancer subjects. The combination of TP53 mutation prevalence and Brock Risk Score significantly improved the association with lung cancer compared with either factor alone.
Conclusion: These results support the validity of the TP53 mutation prevalence biomarker and justify taking additional steps to assess this biomarker in AEC specimens from a prospective cohort and in matched nasal brushing specimens as a potential non-invasive surrogate specimen.

Joseph Dale II

The effects of MC4R activation on behavioral activity in transgenic mice:

Joseph Dale II

Background: Melanocortin receptors are a family of 5 classical GPCRs that activate the adenylyl cyclase pathway in cells leading to a production of the secondary messenger cAMP. Melanocortin are expressed in a

multitude of cell types throughout the body. In humans, the melanocortin 1-receptor is expressed exclusively in melanocytes. Melanocortin 2 receptor is expressed mostly in adrenal glands. The melanocortin 3 and 4 receptors and expressed widely in the brain and central nervous system, with the latter also being expressed in the pelvic ganglia and nerve fibers of the penis also. The focus of this poster will be the melnocortin-4 receptor (MC4R) which is most abundantly expressed in the hypothalamus. The MC4R through its signaling action has been implemented in regulating various physiological processes, including energy homeostasis, cachexia, cardiovascular function, glucose and lipid homeostasis, reproduction, and sexual function. Drugs have been developed to treat eating conditions as well as sexual hypoactivity disorders although the full role of melanocortin signaling in behavior is unknown.
Objectives: The objective of the studies is to characterize the role MC4R receptors play in antagonizing and agonizing specific neuronal subtypes within the PVH and SON of the hypothalamus, both endogenous and exogenous and how those signaling relationships leads to different behavioral changes in mice.
Methods: Treatment of Mc4r agonist in mice and studying behavioral effects in transgenic mice
Tests include mating studies and grooming studies.
Results: Several melanocortin agonist induced some changes in grooming and mating compared to saline treated mice.
Conclusion**:** Although some effects of bremelanotide were observed further studies need to be conducted to further narrow the neurocircuitry responsible for the changes in behavior. A future study will include observing the effects of the neural peptide arginine vasopressin on mating and grooming.

Tatiana B. De Souza

Characterization of a novel IQGAP1-ADRα2 axis as a target of norepinephrine in lung cancer

Tatiana B. De Souza, Yusuf Barudi and Mahasin A. Osman

Lung cancer is a leading cause of cancer death in the US with a few personalized treatment options. IQGAP1 is a signaling scaffold implicated in lung cancer, but its mechanism is poorly defined. We identified the neurotransmitter/hormone norepinephrine (NE) as a specific inhibitor of IQGAP1 in cell proliferation and defined an optimal NE IC50 dose. As the GPCR Adrenergic Receptor α-2a (ADRα-2) is a known NE target, we examined their interaction and found they co-immunoprecipitated and differentially expressed at the protein level in several lung cancer cell lines. We tested the NE effect on IQGAP and ADRα-2 gene expression levels through qRT-PCR. ADRα-2 mRNA was significantly diminished in normal but not cancer cells, suggesting a compensatory mechanism. Furthermore, employing cells lacking IQGAP1 gene, we found that the NE effects require IQGAP1. Using qRT-PCR, we quantified the ADRα-2 and IQGAP1 mRNA levels in wild type (WT) and iqgap1-1- (KO) mouse embryonic fibroblasts (MEFs) in response to NE. In WT, NE significantly reduced IQGAP1 mRNA compared to control, while it insignificantly changed the ADRα-2 mRNA level. By contrast, in KO MEFs, NE treatment appeared to increase the ADRα-2 mRNA, suggesting that IQGAP1 influences ADRα-2 mRNA expression. Next the effect of NE on cell migration, a key function of IQGAP1, was investigated using wound healing assays. NE significantly inhibited cell migration in the KO MEFs compared to WT, suggesting NE likely works through IQGAP1. These findings present the novel ADRα-2-IQGAP1 signaling axis as a potential new target of NE and its analogs in lung cancer personalized medicine.

Alexander J. Didier

Risk factors for thrombosis in a cohort of patients with cancer and COVID-19: a single-institution retrospective cohort study

Alexander J. Didier, Andrew Campbell, MD, Swamroop Nandwani, Alan Fahoury, Camelia Arsene

Introduction: Cancer patients infected with COVID-19 face elevated mortality rates, driving the urgent need to explore contributing factors. Given the shared pro-thrombotic risk between cancer and COVID-19, it has been postulated that co-occurrence may heighten thromboembolic risk, potentially necessitating more intensive

thrombosis prophylaxis. However, existing research on thromboembolic risks in this cohort remains scarce and inconclusive. This study aims to elucidate the incidence and determinants of thromboembolic events in cancer patients with COVID-19.
Methods: Retrospective analysis of cancer patients admitted with COVID-19 at our institution from January 1, 2021, to April 1, 2023, was performed. Eligibility criteria included patients aged above 18 with a recent cancer diagnosis, treatment within the preceding 6 months, and COVID-19-related hospitalization. The occurrence of thromboembolic events during hospitalization was assessed, encompassing various events like extracorporeal circuit thrombosis, deep venous thrombosis (DVT) in the extremities, pulmonary embolism, and more. Patient data on comorbidities and clinical progress were gleaned from records. Statistical analyses, encompassing Chi-squared tests, Fisher Exact tests, t-tests, Mann–Whitney U tests, and multivariate logistic regression, were employed to investigate associations and predictive factors.
Results: We included 456 patients with both cancer and COVID-19. Median age was 69 years, with 55% being male. Most patients where Non-Hispanic White (85%), most patients exhibited lung (19%) or bone marrow (17%) cancer, with 43% undergoing chemotherapy within 6 months pre-hospitalization. Notably, 8.1% experienced thromboembolic events during their hospital stay. Variables like age, race, chemotherapy receipt, and history of hypertension, heart disease, obesity, or stroke didn't emerge as predictive for such events. Patients with thromboembolic events underwent significantly prolonged hospital stays compared to those without (12 days vs. 9 days, $p<0.05$).
Conclusion: The findings underscore the significant impact of thromboembolic events on cancer patients with COVID-19, potentially contributing to escalated mortality rates within this group. Notably, the association between such events and extended hospitalization periods can inflict heightened financial and emotional strains. Consequently, it is imperative to intensify thrombosis prevention strategies encompassing both medical and mechanical interventions among hospitalized cancer patients with COVID-19. Additionally, secondary thrombosis prophylaxis strategies involving early screening detection and treatment of latent thromboses merit emphasis. Future investigations should delve into risk stratification and optimal prophylactic approaches for this distinct patient population.

Sishir Doddi

Liver cancer mortality disparities in the United States

Sishir Doddi, Taryn Hibshman, Oscar Salichs, Rabbia Siddiqi

Background: Liver cancer is a complex disease that presents many challenges in its diagnosis, treatment, and prevention. It’s mortality rate in the United States is a significant and warrants attention.
Objective: To assess the trend of mortality rate due to HCC in the US from 1999 to 2020 by demographic groups for differences in trend of mortality.
Methods: We used the CDC wonder database to collect mortality rate data due to HCC as a multiple cause of death in the US from 1999 to 2020 by sex, race, age, and state of residence. The SEER Joinpoint program was used to calculate trends, defined as average annual percent change (AAPC) and to identify disparities between groups. All age-adjusted rates (AAMR) are reported per 100,000.
Results: From 1999 to 2020, we found that women observed an uptrend (AAPC1.6%) and men observed a slightly higher uptrend in mortality (AAPC 1.8%). In addition, AI/AN population had a significant uptrend (AAPC 2.3%). The AAPI population observed a downtrend (AAPC -2.6%). The Black or African American population observed an uptrend (AAPC 1.8%) The white population also observed an uptrend (AAPC 2.2%). In the 2010 to 2020 time period, Mississippi had the lowest AAMR of any state with 15.2, while Hawaii had with the highest with 38.8.
Conclusion: This investigation assesses mortality rates and trends due to HCC cancer in the US and found significant differences in mortality rates and mortality rate trends due to HCC by demographic status in the US.

Addressing the disparities in HCC incidence and mortality by race, ethnicity, state, and region, as well as improving access to screening, surveillance, and effective treatments, can reduce the burden of HCC and improve outcomes for patients.

Patrick T. Gorman

Comparison of TP53 mutation prevalence in human blood cells from lung cancer patients and control subjects

Patrick T. Gorman, Erin L. Crawford, Daniel J. Craig, James C. Willey

Early detection and diagnosis of lung cancer is a crucial component of treatment and increasing survival odds. Our previous research demonstrated the utility of mutation prevalence of the TP53 gene in bronchial epithelial cells as an indicator of lung cancer risk. The purpose of our research was to determine if TP53 mutation prevalence in peripheral blood cells is a useful marker for determining lung cancer status. We used genomic DNA (gDNA) extracted from blood cells to examine TP53 mutation status and prevalence in lung cancer and non-cancer (control) groups. Samples from cases and controls were selected as pairs based on age, sex, race, smoking status, and smoking history expressed in pack-years. gDNA was extracted from buffy coat samples, target sequences were amplified via PCR, and two sequencing libraries were created. Both libraries have been sequenced: Approximately 28 million reads were obtained from each library with approximately 94.4% %Q30. Bioinformatic analysis is in progress to enable a comparison of TP53 mutation prevalence in cancer and non-cancer groups. If TP53 mutations are more common in the cancer group, it may suggest that mutation prevalence in gDNA collected from peripheral blood can be used as a marker of lung cancer status.

Prajwal Hegde

Pseudo-thrombotic microangiopathy by vitamin B12 deficiency

Prajwal Hegde, Jennifer Kim, Caleb T Spencer

Introduction: Vitamin B12 is a water-soluble vitamin obtained primarily through the consumption of dairy and animal products. It is essential for several key enzymatic processes in the body, including DNA production. Vitamin B12 deficiency can manifest as pseudo-thrombotic microangiopathy (PTMA), which is an unusual clinical presentation of B12 deficiency. PTMA mimics primary thrombotic microangiopathies (such as TTP, DIC, HUS) with features like thrombocytopenia, schistocytes, and hemolytic anemia. In contrast to the aggressive treatment required for primary TMAs, vitamin B12 deficiency-associated PTMA can be effectively treated with B12 supplementation. Here, we present a case of vitamin B12 deficiency PTMA that initially presented with hemolytic anemia.
Case Presentation: A 73-year-old Caucasian male with a history of gout, hypertension, and hyperlipidemia presented with new-onset shortness of breath, bilateral leg pain, dizziness, tinnitus, and peripheral neuropathy. Physical examination revealed bilateral lower extremity edema, scleral icterus, and jaundice. Laboratory findings indicated normal folate levels, decreased vitamin B12 levels, and elevated homocysteine levels. Peripheral blood smear exhibited macrocytic normochromic anemia with schistocytes and hypersegmented neutrophils. Abdominal ultrasound showed normal spleen and liver sizes. ADAMTS-13 activity was low, and positive inhibitor activity was detected. The patient began daily intramuscular vitamin B-12 therapy during admission. Upon discharge, he continued to receive sublingual and intramuscular vitamin B12 treatments. Plasmapheresis was not performed. Substantial improvement in blood counts and reduced hemolytic markers were observed during a one-week follow-up.
Conclusion: Pseudo-thrombotic microangiopathy associated with vitamin B12 deficiency constitutes a crucial aspect of the differential diagnosis for thrombotic microangiopathy. PTMA exhibits an excellent response to B12 supplementation alone, setting the standard for treatment. Physicians must remain vigilant about PTMA, as

it can be easily misdiagnosed. Recognizing this condition could spare patients from unnecessary and risky treatments that might otherwise result in anaphylaxis, hemothorax, and cardiac arrest.

Konrad Katterle

Chemotherapy induced pulmonary fibrosis

Konrad Katterle, Zachary Holtzapple, Abdulmajeed Alharbi, Youngsook Yoon

Background: FOLFOX (Oxaliplatin, 5-Fluorouracil, and Leucovorin) is one of the most commonly used first-line chemotherapies for metastatic colorectal cancer in the USA, and its efficacy has been repeatedly demonstrated by numerous trials. However, it has many side effects that affect numerous organ systems including myelosuppression, neuropathy, hepatotoxicity, and pulmonary toxicity. This case describes an 81-year-old male who developed pulmonary fibrosis after receiving FOLFOX chemotherapy, a late and rarely documented adverse effect.
Case Report: Our patient was an 81-year-old male who underwent 12 cycles of adjuvant FOLFOX chemotherapy for metastatic colon cancer. Patient is a non-smoker, has no industrial exposure to pulmonary toxic agents, no past medical history of autoimmune diseases, and was on medications for hypertension, diabetes mellitus type 2, GERD, Benign Prostatic Hyperplasia, and hypothyroidism, none of which have any known pulmonary toxicity. The patient developed shortness of breath and dyspnea over the next two years, and serial CT scans of the chest showed progressive fibrosis of the lungs. Patient was originally admitted on 2 liters of oxygen via nasal canula with follow up imaging revealing bilateral pneumothoracies secondary to pulmonary fibrosis, five years after initiating FOLFOX treatment.
Discussion: FOLFOX is known to have many adverse effects, including myelotoxicity, neurologic toxicity, diarrhea, and cardiopulmonary toxicity. In this case report, it is our belief that this patient developed bilateral pneumothoraces secondary to pulmonary fibrosis, which in turn was likely to have been caused by the patient's 12 cycles of FOLFOX therapy. Our case report represents an uncommon pulmonary side effect of FOLFOX and a unique manifestation with limited prior documentation.

Swamroop Nandwani

Mortality trends and demographic risk factors in melanoma in the United States

Swamroop Nandwani, Alexander Didier, Alan Fahoury, Daniel Craig, Dean Watkins, Caleb Spencer, Andrew Campbell, Divya Vijendra

Introduction: Melanoma is the deadliest form of skin cancer the United States. This study aimed to look at trends, and demographic risk factors associated with increased melanoma mortality.
Methods: The CDC WONDER database was used to obtain mortality statistics with an underlying cause of death of melanoma. Data were grouped based on demographic and regional variables, and the age-adjusted mortality rates (AAMRs) were calculated. Joinpoint Regression software was used to determine temporal trends in AAMR, and annual percentage change (APC).
Results: Between 1999 and 2020, melanoma led to 184,416 deaths in the US- with an AAMR decrease of -1.3% per year. The APC rose between 1999 and 2013 by 0.2%, then started falling steeply between 2013 and 2017 at a rate of -6.6%.
In 1999, men had an AAMR of 3.8 nearly twice as high as females (1.7). For men, the APC rose until 2009, and after 2014 the APC fell to its steepest rate of -7.3% till 2020. For women, the APC decreased- with the fastest rate of -3.5% occurring from 2011 to 2020.
NH White individuals had the highest AAMR at 3.2 while NH Asian/Pacific Islander had the lowest (0.3). The APC for NH White individuals increased until 2013 and then decreased till 2020. NH Black individuals showed the steepest APC decrease at a rate of -2.3% annually followed by NH Asian/Pacific Islander and Hispanics (-1.2).

The highest AAMR at 12.2 was found in those aged 65+ and was lowest in those 25-44 years (0.8). For those aged 65+, the melanoma death rates rose from 1999 to 2013, after which they fell steeply at a rate of -6.1% annually until 2017.
Conclusion: The decline seen in melanoma mortality was not uniform across all demographics and regions. Understanding these trends can help inform targeted interventions to reduce melanoma mortality.

Swamroop Nandwani

Trends in chronic lymphocytic lymphoma mortality in older adults

Swamroop Nandwani, Alexander Didier, Alan Fahoury, Daniel Craig, Caleb Spencer, Divya Vijendra

Introduction: Chronic lymphocytic leukemia (CLL) accounts for nearly 25% of new adult leukemia cases and commonly affects older adults with a median age of 70 at diagnosis.
Objectives: Currently, no study has assessed demographic trends in CLL mortality in older adults (65+) in the U.S. Our aim was to analyze demographic trends in CLL mortality within the U.S. between 1999-2020.
Methods: The CDC WONDER database was used to determine mortality statistics for patients, 65+, with an underlying cause of death from CLL (ICD-10 C91.1) between 1999-2020. Age-adjusted mortality rates (AAMR) were calculated for groups of interest, and joinpoint regression was used to identify temporal trends and average annual percent change (APC).
Results: Between 1999-2020, CLL accounted for 85,371 deaths in adults 65 years or older with an overall AAMR decrease of 30%. In 1999, men had an AAMR of 16.1, nearly double the female AAMR of 8.1. Both groups experienced a significant drop in overall APC with a drop of –1.7 for men and –2.1 for females. Non-Hispanic Whites had the highest AAMR at 11.9 and a significant decrease in APC. Non-Hispanic Blacks had an AAMR high of 9.6 and had the highest decrease in APC at –2.4 ($p<0.05$). Hispanic individuals had an AAMR high of 4.4 and had the lowest decrease in APC at –1.3 ($p<0.05$). Analysis by population density revealed the highest decrease in APC occurring in urban populations at –2.3 ($p<0.05$), and the lowest decrease in rural populations. All census regions (Northeast, Midwest, South, and West) had significant drops in APC.
Conclusions: Although the mortality rate for CLL in the U.S. has been decreasing, there are differences in the rate of decrease amongst various demographic groups. Demographic background may be a useful factor to identify new cases of CLL and those at higher risk of mortality.

Vikhyathi Pallerla, MS

A case of Nivolumab-induced hypophysitis in a 72-year-old female with metastatic melanoma

Vikhyathi Pallerla, MS, Avish Persaud, MS, Divya Vijendra, MD

Introduction: Hypophysitis is a rare condition in which inflammation in the suprasellar region leads to pituitary gland insufficiency, affecting both its hormonal activity as well as potentially causing mass effect on surrounding structures1. There are various etiologies of this condition including lymphocytic, granulomatous, IgG4-related, and xanthomatous, but it has been commonly confused for other pituitary conditions such as pituitary adenomas due to its similar presentation.
Case Report: We present a case of a 72-year-old female with metastatic melanoma of the lower extremity undergoing Nivolumab immunotherapy. She presented to her oncologist with notable hypotension and one week history of severe fatigue and dizziness, prompting an emergent workup. An MRI was performed and read as a pituitary adenoma, but the high suspicion of immunotherapy-related toxicity led to a CMP showing severe hyponatremia in the 120s, low cortisol, and low ACTH. These findings lead to the rare diagnosis of Nivolumab-induced hypophysitis.
Conclusion: Immunotherapy has revolutionized the treatment of cancer over time, but with its remarkable improvements come immune-mediated side effects. Due to the immune-mediated nature of hypophysitis, it can be reasonably deduced that immunomodulation can predispose to its development. The long-term hormonal and

systemic complications outlined in this case are severe enough to require hospitalization. The severity of complications highlights the importance of developing a high level of suspicion for treatment-related toxicity and in this case, an irreversible effect such as pituitary failure. However, identifying this complication early allowed for our patient to resume her treatment with Nivolumab along with the supplementation of pituitary hormones, effectively treating both her pituitary dysfunction and her melanoma while reducing both morbidity and mortality.

Avish Persaud, MS

A case of a 25-year-old male with pituitary and hypothalamic extension of recurrent anaplastic astrocytoma

Avish Persaud, MS, Vikhyathi Pallerla, MS, Divya Vijendra, MD

Introduction: Although brain tumors are most commonly metastatic, primary brain tumors can present due to various local cellular etiologies. Astrocytoma is a type of glioma comprising of astrocytes, which are cells responsible for assisting various essential neuronal processes but also proliferate in response to cellular insults, occasionally leading to pathologic growth. These gliomas can range from low-grade pilocytic astrocytoma to high-grade, rapidly growing glioblastomas and anaplastic astrocytoma. Anaplastic astrocytoma most commonly present in the 40s, have a dismal prognosis, and can be distinguished from glioblastoma due to lack of endothelial proliferation or surrounding necrosis.
Case Report: We present a unique case of a 25-year-old male with history of recurrent WHO grade three primary CNS anaplastic astrocytoma of the right parietal lobe. The tumor has an IDH1-R132H mutation present, ATRX mutation, unmethylated MGMT promoter, and no deletion of 1p and 19q. Patient had a right frontal craniotomy in 2016, followed by chemoradiation with temozolomide for six months. In 2021, he had a recurrence that presented with seizures, prompting treatment by radiation and temozolomide for 11 months with the seizures being controlled. MRIs done in 2023 showed a new expanding mass at the floor of the anterior third ventricle/prepontine cistern, corpus callosum, pituitary infundibulum and hypothalamus. The extension into the pituitary infundibulum led to a concern for hypopituitarism, prompting testing of pituitary hormone levels which revealed low FSH and LH, testosterone, and cortisol.
Conclusion: Although there have been rare instances of anaplastic astrocytoma coexisting with pituitary macroadenomas, there have not been many reported cases of an anaplastic astrocytoma spreading to the suprasellar region. This case illustrates a novel, important factor to consider in evaluating astrocytoma and other base of skull tumors which includes considering the possibility of pituitary dysfunction.

William Ryan

PAVER: Pathway Analysis Visualization with Embedding Representations

William Ryan, Ali Sajid Imami, Hunter Eby, Robert McCullumsmith, Rammohan Shukla

Interpreting pathway analysis often poses a significant challenge due to the extensive lists of gene ontology (GO) terms that require meticulous manual curation to identify underlying themes. We developed PAVER, a novel R software package, to address this issue by automating theme generation and clustering of GO terms. By utilizing embedding representations and advanced machine learning techniques, PAVER discerns patterns within the GO terms, creating an intuitive visual landscape of clusters for ease of functional interpretation. This method significantly minimizes the time and effort traditionally required for manual curation. We applied PAVER to a previously published dataset, where it demonstrated robustness by generating themes that closely mirrored those produced by manual curation. With PAVER, we present a powerful tool that not only enhances the efficiency of pathway analysis but also broadens its accessibility across various fields, including disease pathway modeling, drug target identification, and comparative genomics. Our work with PAVER marks a significant step towards simplifying the pathway analysis interpretation process in bioinformatics research.

Anish Sharma

Cyanobacterial detection in human kidney formalin-fixed paraffin embedded specimens from cancer and non-cancer populations

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Introduction: Harmful algal blooms (HABs) are uncontrolled outbreaks of cyanobacterial growth that thrive in warm waters. HABs pose a serious health risk to humans due to the release of cyanotoxins produced by cyanobacteria. We and others have demonstrated that the kidney is a key target organ for cyanotoxin induced injury and that these cyanotoxins are capable of activating key oncogenic genes in renal cells in vitro. However, the effects of cyanotoxin exposure in humans with renal cancer is poorly understood.
Objectives: We sought to identify the presence of cyanobacteria in Formalin-Fixed Paraffin Embedded (FFPE) kidney tissue obtained from patients residing in the Great Lakes region. We hypothesized that the levels of cyanobacteria correlate with markers of tumor severity in renal cell carcinoma (RCC).
Methods: DNA and RNA were extracted using an optimized extraction/purification protocol designed for Formalin-fixed paraffin-embedded (FFPE) kidney tissues from RCC (n=13) and age and sex matched non-RCC controls (n=3). Presence of cyanobacteria and markers of tumor severity were determined using quantitative PCR analysis.
Results: Cyanobacteria levels were elevated in RCC compared to non-RCC (1.0±0.34 vs 1.3±.26) although this was not statistically significant. Interestingly, while markers of inflammation and angiogenesis were not significantly correlated with cyanobacterial load overall in both cancer and non-cancer samples, cyanobacterial load was positively correlated with Transforming Growth Factor-beta in all patients (r=0.5452, p=0.0013) as well as within the RCC cohort (r=0.5320, p=0.0052).
Conclusion: Our results suggest that cyanobacteria may be increased in the setting of RCC and impact the expression of key tissue remodeling genes within these tumors. This data is in agreement with clinical and experimental evidence suggesting an association between cyanobacteria and cancer progression in other settings and supports the need to investigate the potential role of cyanobacteria in renal cancer progression. Analysis of additional samples is ongoing to establish this relationship in an expanded cohort.

INFECTIOUS DISEASES

Nora Abdul-Aziz

Multiple Sclerosis anti-CD20 (Ocrelizumab) therapy inducing hypogammaglobulinemia

Nora Abdul-Aziz, Noor Abdulhameed, Amulya Marellapudi, Haroon Shah DO

Introduction: Multiple Sclerosis (MS) is a progressive autoimmune demyelination of the CNS. Therapies typically used in clinical practice encompass anti-CD20 agents such as Ocrelizumab and Rituximab that selectively target CD20+ B-cells to suppress the inflammation of the disease pathway of MS. However, B-cell deficiency contributes to a heightened risk for infection. Anti-CD20 mAb drug-induced hypogammaglobulinemia puts patients at risk for various complications such as reactivation of latent infections, respiratory tract infections, and neutropenia.
Case Presentation: A 58-year old female with past medical history of MS and recurrent sinopulmonary infections on B-cell depleting therapy (Ocrelizumab), presented with persistent fatigue, fevers, and chest discomfort upon inhalation.
Chest CT was notable for ground glass opacities in RUL. Labs were ordered for LDH, viral respiratory panel, histoplasma urine antigen, viral culture, AFB, fungal culture and serum immunoglobulins. Bronchoalveolar lavage was done as work up; mold was isolated from BAL. IV amphotericin B was given for two weeks then

switched to oral voriconazole when isolate identified *Penicillum sp*. fungus. Patient is discontinuing her next infusion due to her chronic immunodeficiency posing an infection risk. Patient may be referred for intravenous immunoglobulin injections.
Conclusion: Hypogammaglobulinemia is normally seen after five years of treatment, but this patient displayed signs after two years. The patient has anti-CD20 mAb drug-induced hypogammaglobulinemia (IgA and IgM deficiencies) that may be contributing to recurrent sinopulmonary infections, including opportunistic molds. Diagnosis of penicilliosis is through microscopy, histology, and culture of the fungus from bone marrow, skin lesions, and blood. Therapy is extrapolated from *Talaromyces marfenii* guidelines. Preferred treatment is induction therapy with amphotericin B for 2 weeks followed by consolidation therapy with itraconazole for 10 weeks. Frequent measurement of immunoglobulin (Ig) levels, Ig transfusions, and immunologist check-ins are vital for immunocompromised individuals on these anti-CD20 therapies.

O. Abdul-Aziz

Persistent skin eruption in a renal transplant patient

O. Abdul-Aziz, S. Habib, A. Sood, M. W. Ellis, MD

Introduction: Renal transplants are the most common transplant surgery performed in the United States and pose a significant challenge in post-operative care due to the need for strict immunosuppression management. These immunosuppressive medications increase the risk of opportunistic infections, including nocardial infections. Nocardia are Gram-positive, partially acid-fast, aerobic, catalase-positive, non-motile branching rod-shaped bacteria. They are considered ubiquitous and are isolated from multiple environmental sources such as soil, decomposing vegetation, and water. Due to its ability to mimic other diseases, nocardial infections pose a diagnostic challenge and often result in a delay in diagnosis and therapy.
Case Presentation: A 72-year-old man with a past medical history for renal transplantation done in 2020 for end stage renal disease secondary to focal segmental glomerulosclerosis (FSGS) presented to the Infectious Diseases clinic with a non-healing left forearm lesion. Three months prior to evaluation, the patient reported that he had cut his forearm while working on a golf cart. Over weeks, the patient developed an ulcerative and crusting wound on his forearm. After topical management with antibacterial and antifungal ointments, and brief courses of cephalexin for common skin and tissue infection he underwent skin biopsy. On physical examination, vital signs were normal as were pulmonary and neurological examination. Skin examination was remarkable for an approximately 5 x 7 cm ulcerated and crusted lesion without surrounding erythema, and slight tenderness. He had no lymphadenopathy. His laboratory studies showed slight lymphopenia and normal renal function with serum creatinine of 1.2 mg/DL. Skin biopsy culture yielded Nocardia abscessus complex. Antibiotic susceptibilities performed at an academic reference lab demonstrated susceptibility to amikacin, doxycycline, tobramycin, imipenem, ceftriaxone, and TMP-MX. To exclude pulmonary or central nervous system involvement, the patient underwent computed tomography (CT) of his chest and magnetic resonance imaging (MRI) of his brain, both of which showed no evidence of infection.
The patient was treated with ceftriaxone during admission along with reduction in mycophenolate sodium. He was discharged on TMP-SMX DS twice daily with a plan for 6 months duration. During follow-up, he was noted to have asymptomatic hyperkalemia and his regimen was changed to doxycycline 100 mg twice daily for a 6-month duration. Within one month of treatment, his arm lesion began to improve.
Conclusion: Cutaneous Nocardiosis usually occurs in immunocompromised individuals who experience bacterial infiltration of the skin via abrasions. Treatment for cutaneous nocardiosis typically involves a single drug regimen based on susceptibilities. This case highlights that opportunistic infections like Nocardia pose a significant challenge to those undergoing immunosuppressive therapy for organ transplantation and that early detection is vital to avoid dissemination.

Noor Abdulhameed

Histoplasmosis of the left wrist in an immunosuppressed host with myasthenia gravis

Noor Abdulhameed, Omar Abdul-Aziz, Meghan Sawyer, Caitlyn Hollingshead, MD, Salman Arif, MD

Introduction: Myasthenia gravis (MG) is an NMJ disorder targeting acetylcholine receptors. Symptomatic treatment inhibits acetylcholinesterase, while long-term therapies target immune system overactivation. Prednisone inhibits antibodies; mycophenolate mofetil decreases T&B lymphocyte proliferation. Immunosuppressants pose opportunistic infection risks, such as histoplasmosis due to Histoplasma capsulatum spores.

Case Presentation: A 55-year-old male with MG on prednisone 40mg/daily and mycophenolate mofetil 1,500mg/daily presented with left wrist pain and forearm swelling one month prior, following a gardening injury. Cellulitis treated with trimethoprim-sulfamethoxazole and doxycycline without improvement and started on IV vancomycin. CT revealed olecranon bursitis and soft tissue inflammation. Patient underwent debridement; serous fluid was cultured. Patient discharged after 5 days on trimethoprim-sulfamethoxazole 800mg-160mg twice/daily. Fluid histoplasma antibodies tested positive. CXR unremarkable for pulmonary histoplasmosis.

Patient was prescribed itraconazole 100mg/twice daily for 9 months. After 6 weeks, patient reported open left foot wound, without underlying trauma. MRI revealed soft tissue swelling consistent with cellulitis. The patient underwent debridement due to cutaneous histoplasmosis history. Cultures revealed Streptococcus agalactiae. Patient prescribed amoxicillin- clavulanate 875-125mg BID and foot healed. 16 months post-itraconazole therapy, patient revealed no cyanosis nor edema with a left sporotrichoid scar along the ulnar lymphatics from resolved infection.

Conclusion: Corticosteroids are vital for rheumatological therapies but involve diabetes, avascular necrosis, osteoporosis, and CVD. Their anti-inflammatory properties contribute to lymphocytopenia and pose dose-dependent infectious risks. Opportunistic pathogens should be evaluated in MG patients including VZV, tuberculosis, PJP, aspergillosis, candidiasis, and cryptococcosis. This case is a rare example of isolated extrapulmonary histoplasmosis in an immunocompromised patient. Immunosuppressed MG patients should be educated on risk of infections. Lower corticosteroid dosages decrease infection risk. PJP prophylaxis should be offered in appropriate patients. Vaccinations and lifestyle modifications reduce infectious complications. This case highlights the importance of early detection, and the challenges opportunistic infections pose to patients undergoing immunosuppressive therapy.

Katherine Esser

Current legislative status of pharmacy-driven PEP in the US

Katherine Esser, Joan Duggan, MD, Kaylee Scarnati, Eric Sahloff, Pharm D

Introduction: Non-occupational post-exposure prophylaxis (nPEP) to prevent HIV infection is highly effective and consists of initiation of antiretroviral medications (ART) ideally within 2 – 24 hours after HIV exposure and continued for 28 days: it is a medical emergency requiring rapid ART access. Rapid access problems have hindered its widespread usage. Pharmacy-initiated PEP access was first trialed in New York City in 2017, allowing pharmacists to prescribe a seven-day supply of PEP without a prescription for consumers at high risk for HIV infection. The provision of PEP by pharmacists – ie, pharmacy-driven PEP (PDP) – may improve access to this time-sensitive HIV prevention strategy in the US but the current status of PDP nationwide is not known. We assessed the current legal status of PDP nationally since its initiation in 2017.

Objective: To assess the current legislative status of pharmacy-driven PEP in the US.

Methods: A review of the status of current state legislation/guidance related to PDP was performed.

Results: As of July 31, 2023, 12 states allow pharmacists to furnish HIV PEP through specific legislative initiatives. The authority for pharmacist prescribing or furnishing nPEP is defined primarily through state

government-defined protocols, standing orders, prescriptive authority or collaborative practice agreements (California, Colorado, Illinois, Maine, Missouri, New Mexico, New York, Nevada, North Carolina, Oregon, Utah, Virginia). Multiple states have legislation pending specifically for nPEP (Massachusetts, New Jersey, Florida, and Maryland).
Conclusion: The lifetime risk of contracting HIV among Black MSM (men who have sex with men) is 1 in 2. nPEP is currently rapidly accessible through pharmacies for patients at risk in 12 states but is accessible only through physicians and physician extenders in 38 states. Analysis of barriers to widespread implementation of pharmacy-driven PEP nationwide should be undertaken to improve rapid access to nPEP for communities at risk.

Justin Franco

Recurrent salmonellosis complicating ofatumumab therapy for Multiple Sclerosis

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Introduction: Multiple Sclerosis (MS) is an autoimmune disease characterized by destruction of neural myelin sheaths. Treatment involves anti-CD20 monoclonal antibodies, such as Ofatumumab. Anti-CD20 therapeutics function by reducing autoreactive B-cell populations. Although anti-CD20 therapeutics are associated with infection risk, the occurrence of recurrent Salmonella infection is novel.
Case Presentation: A 41-year-old male presents with watery diarrhea occurring over 10-days. Past medical history includes depression, MS, and Salmonella infection. Initial Salmonella infection was reported 12-weeks prior, while the patient was taking Ofatumumab for MS. Salmonella infection was resolved following 2-weeks of IV-ceftriaxone. Ofatumumab was discontinued 7-weeks prior to hospital admission due to leukopenia. Physical exam was unremarkable, with mild abdominal tenderness. Laboratory findings revealed decreased antibody titers and positive Salmonella cultures.
Patient underwent EGD and colonoscopy, with biopsies indicating infectious colitis. He was diagnosed with recurrent non-Typhi Salmonella (NTS) infection. For treatment, the patient underwent a cholecystectomy and was discharged on a 14-day course of Azithromycin.
Discussion: Anti-CD20 therapies are mainstays of MS treatment. However, anti-CD20 medications are associated with increased risk for moderate infection (e.g., respiratory tract infection or UTIs). Rare infections associated with anti-CD20 therapeutics include HBV reactivation and progressive multifocal leukoencephalopathy.
The development of recurrent NTS in response to anti-CD20 therapy has not been reported in the literature. Gastroenteritis caused by NTS is self-limiting in immunocompetent patients. Major risk factors for recurrent NTS include young/old age, contaminated food, and immunosuppression. Although our patient discontinued Ofatumumab 7-weeks prior to admission, he presented with reduced antibody titers (i.e., hypogammaglobulinemia). B-cell reconstitution following termination of Ofatumumab takes 24 to 36-weeks, during which time patients are immunosuppressed. One of the side effects of anti-CD20 therapy is reduced antibody titers, which can increase the patient's risk for NTS. This case highlights anti-CD20 therapy as a novel risk factor for recurrent NTS.

Safa Habib

Pulmonary tuberculosis infection in the setting of interstitial lung disease

Safa Habib, Rebecca Asher, Salman Arif, Hend Elsaghir

Introduction: Tuberculosis (TB) is a contagious airborne infection with many undiagnosed cases. Here we present a case of pulmonary tuberculosis that was treated in a 9-month course in a patient with a history of ILD.
Case Presentation: A 78-year-old man has a past medical history significant for idiopathic pulmonary fibrosis, hypothyroidism, coronary artery disease, hypertension, and obstructive sleep apnea. The patient was diagnosed with progressive idiopathic pulmonary fibrosis in 2013 and developed hypoxic respiratory failure. He was

intolerant to Nintedanib and deemed unfit for a lung transplant. Therefore, the patient was instructed to use the albuterol inhaler and attend pulmonary rehab. In July 2021, he presented with cough, fatigue, dyspnea, and a decreased appetite. Treatment with amoxicillin-clavulanate was ineffective and his COVID-19 test was negative. Imaging showed a left upper lobe infiltrate and his chest CT (Computed Tomography) displayed left upper lobe consolidation with necrotic changes concerning for severe pneumonia. He was treated with IV ceftriaxone, oral azithromycin, and discharged with a 5-day course of cefdinir. After no improvement, he returned, and Tuberculosis was diagnosed with bronchoscopy with positive acid-fast staining and TB PCR (Polymerase Chain Reaction). The patient completed a 9-month treatment course with infectious disease follow-ups afterward. He had a negative acid-fast bacilli since September 2021.
Conclusions: Diagnosing a TB infection in ILD patients can be difficult due to the presence of interstitial processes and fibrosis masking the infection. In this case, atypical radiological patterns initially led to a misdiagnosis of pneumonia. Once TB was confirmed, the treatment regimen was successful. Clinicians managing ILD patients must rule out mycobacterial infections, such as TB, through a comprehensive diagnostic approach.

Zachary Holtzapple

Newly-diagnosed severe AIDS with recovery of CMV retinitis with concurrent Cryptococcal Meningitis

Zachary Holtzapple, Ayman Salih, Cassidy Eby, Mitchell Salke

Background: With modern medicine, human immunodeficiency virus (HIV) has become easily manageable for patients and the feared complication of acquired immunodeficiency syndrome (AIDS) has become relatively uncommon. This condition leads as a pathway to multiple illness not commonly seen in healthy individuals, including but not limited to pneumocystis pneumonia, disseminated histoplasmosis, cytomegalovirus infections, and extrapulmonary cryptococcosis. When these patients are critically ill, communication can be limited by pain, delirium, and intubation, which severely limits our ability to evaluate patients.
Case Report: Our patient presented to the hospital with generalized fatigue and shortness of breath. Further workup revealed severe HIV with CD4 count being < 50. Follow up CT Chest was initially concerning for pneumocystis pneumonia which was later ruled out with a bronchoscopy lavage. Lumbar puncture revealed cryptococcus meningitis and fundoscopic exam revealed findings consistent with CMV retinitis. In our patient, intubation for repeat lumbar punctures provided a barrier to the patient's communication and led to progressing CMV retinitis that briefly led to full loss of vision. Patient was appropriately treated with antifungals and antivirals throughout the hospital course.
Conclusions: Our patient presented to the hospital with generalized fatigue and shortness of breath. Further workup revealed severe HIV with CD4 count being < 50. Follow up CT Chest was initially concerning for pneumocystis pneumonia which was later ruled out with a bronchoscopy lavage. Lumbar puncture revealed cryptococcus meningitis and fundoscopic exam revealed findings consistent with CMV retinitis. In our patient, intubation for repeat lumbar punctures provided a barrier to the patient's communication and led to progressing CMV retinitis that briefly led to full loss of vision. Patient was appropriately treated with antifungals and antivirals throughout the hospital course.

Victoria Soewarna

Perihepatic abscess secondary to sphingobacterium spiritivorum

Victoria Soewarna, Kada Williams, Salman Arif, Hend Elsaghir

Introduction: *Sphingobacterium spiritivorum* is a gram-negative rod belonging to the *Sphingobacterium* species, previously classified as *Flavobacterium* species. The genus is comprised of *S. spiritivorum* and *S. multivorum*. It is commonly found in nature, primarily in water and soil. Human infections are rare and predominantly

impact immunocompromised or elderly individuals. We present a case of a perihepatic abscess secondary to *Sphingobacterium spiritivorum*.
Case Report: A 65-year-old male with a history of pulmonary embolism on Eliquis, hyperlipidemia, anxiety, depression, and thyroid disease presented to the hospital as a level 1 trauma due to motor vehicle accident with multiple orthopedic fractures. On admission, computed tomography (CT) of the abdomen and pelvis revealed mild degree of diffuse hepatic steatosis with no gross focal hepatic lesion. On hospital day two, CT of the abdomen and pelvis revealed a subcapsular lesion in the right liver, concerning for hemangioma or cyst. On day eleven, hospitalization was complicated by a lower extremity wound infection positive for Bacillus species and Acinetobacter baumannii complex. The patient was treated with Vancomycin and Unasyn for 7 days with resolution of symptoms. On hospital day sixteen, CT abdomen/pelvis revealed an increase in subcapsular fluid accumulation along the right hepatic lobe now measuring 7 cm by 5 cm. The perihepatic abscess was drained by interventional radiology on hospital day 17 and sent for cultures. Cultures were positive for Sphingobacterium spiritivorum. The patient completed a course of IV ceftriaxone 2 grams daily for 6 weeks via PICC line, metronidazole 500 mg every 8 hours for 14 days, and repeated imaging of the liver in 4 weeks.
Discussion: Currently, there are no standard treatments for Sphingobacterium spp. Based on previously reported cases and antibiotic susceptibility, Sphingobacterium spiritivorum is susceptible to carbapenems, quinolones, trimethoprim-sulfamethoxazole, and ceftazidime. This patient was successfully treated with ceftriaxone and metronidazole, which supports these susceptibilities.

A. Sood

Mycobacterium goodii associated with breast tissue expanders

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Introduction: *Mycobacterium goodii*, a non-tuberculous mycobacterium (NTM), is associated with implanted medical devices. Due to the rise of nosocomial infections, *M. goodii* presents a challenge due to unique resistance patterns. We present a case of bilateral breast tissue expanders infected with *Mycobacterium goodii*.
Case Description: A 52-year-old woman with a history of hypertension, type 2 diabetes mellitus, infiltrating ductal carcinoma of the left breast, and a history of previous Group B Strep (GBS) infection associated with breast tissue expanders. The patient underwent a delayed bilateral breast reconstruction due to the breast expanders needing removal. There was also a placement of tissue expanders and bilateral biosynthetic mesh along with a left periprosthetic capsulectomy and excision of right chest subcutaneous cyst in December 2021. She was noted to have increased drain output post-operatively, which prompted aspiration from her bilateral breast expander ports and initiation of empiric doxycycline. Due to doxycycline being a broad-spectrum antibiotic and typically being used in skin, mucosa, and similar infections, it was chosen as initial treatment. Three days after initiating doxycycline, the patient was in a high-speed motor vehicle collision and presented at our hospital. The patient had severe injuries such as a right orbital blow out fracture, dental avulsion, cervical fracture, rib fracture, and left wrist fracture which required surgical intervention with orthopedics. Following surgery, the patient remained afebrile without leukocytosis but continued to have 10-15mL of drain output bilaterally. Infectious diseases were consulted to specifically investigate and understand which bacteria was inflicting the patient. Cultures drawn from her bilateral breast expander ports became positive for a beaded, gram-positive rod that was modified acid-fast positive which signified a nosocomial, opportunistic infection. Meropenem and trimethoprim-sulfamethoxazole (TMP-SMX) were initiated due to concern for rapidly growing mycobacterial infection. She was discharged after about two weeks after the MVC with a PICC line and a follow-up with ID. The organism was found to be positive for M. *goodii*. The organism was found to be sensitive to TMP-SMX, and meropenem was discontinued. She tolerated therapy with TMP-SMX well and had no allergic reactions or other adverse side effects. About two weeks after being discharged, her breast expanders were removed, and cultures at this juncture were negative. On follow-up, she had completed 3 months of TMP-

SMX post-removal of implants and had a delayed bilateral deep inferior epigastric perforator (DIEP) free flap procedure without any signs of recurrence of infection.
Discussion: Mycobacterium goodii is a rapidly growing non-tuberculous mycobacterium (NTM) that was originally associated with traumatic wound infections, particularly osteomyelitis following open fractures. Since its original description, M. goodii has emerged as a challenging infectious pathogen of implantable medical devices. M. goodii is naturally resistant to rifampin and macrolides, which are often the empiric treatment of choice in NTM infections. If the infection involves a medical implant, removal of the device is usually pursued, though there have been cases of successful cure with retention of the implant. As with other mycobacterial infections, duration of antibiotics is prolonged, ranging from 1-12 months. We found in our review that there has been one other documented case of M. goodii infection due to a breast implant, in which the patient required reoperation and a prolonged course of antibiotics. Therapy should ultimately be targeted based on culture sensitivities and patient tolerance with likely explanation of the infected hardware and prolonged duration of antimicrobials.

Victoria Starnes

Fungal prosthetic joint infection: A case series and review of the literature

Victoria Starnes, Caitlyn Hollingshead, MD, Joan Duggan, MD

Background: The most effective treatment for fungal prosthetic joint infections remains unclear. Most cases are treated with two-stage revisions combined with systemic antifungal medications. To date, the largest studies of total hip arthroplasty and total knee arthroplasty fungal infections have included 37 and 45 patients, respectively.
Objective: The goal of this study is to examine reported cases to determine trends in management and outcomes.
Methods: A retrospective record review of patients admitted in 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 as well as a review of the literature. A PubMed and Embase search of the English-language literature from Jan 1, 1980, to Jan 1, 2023, was performed with review of the pertinent references for cases meeting the following case definition: individual with prosthetic joint and positive deep tissue culture for fungus.
Results: 159 patients fit criteria. 73 patients had knee replacements, 62 patients had hip replacements, and 5 had other joint involvement. 52% were female. 137 patients had yeast involvement, with Candida species being predominant, while 11 had mold and 11 with dimorphic infections. 55 patients were treated with two-stage revisions, 44 received one-stage revisions, 32 received debridement only or Girdlestone procedure, and 1 required amputation. 141 reported details on antifungal therapy. After performing multivariate analysis, polyene treatment was found to be associated with higher rate of recovery, $p=0.042$. However, there was a trend towards recurrence requiring surgical intervention in patients treated with polyenes, $p=0.067$. 22.6% had a poor outcome, including recurrence, amputation, or death.
Conclusion: Surprisingly, polyenes did not underperform when compared to other antifungal therapy. Prospective research assessing optimal surgical treatment modality and antifungal therapy is needed as this infection is associated with high morbidity and mortality.

NEPHROLOGY

Margo Bush

Differential expression of organic anion transporting polypeptides in the kidney: Implication for cyanotoxins toxicity

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Background: Organic Anion Transporting Polypeptides (OATPs) are a family of transporters found throughout the body and encoded by Solute Carrier Organic Anion Transporter (SLCO) genes. The role of OATP's has gained increased attention due to harmful algal blooms (HABs). We have previously demonstrated the kidney is a major target organ of HAB cyanotoxins, however the impact of common kidney comorbidities on OATP transporters is unknown.
Objectives: We used a differential expression analysis to determine levels of SLCO expression in both healthy individuals and those with common pre-existing kidney disease to understand how renal comorbidities may impact susceptibility to HAB cyanotoxin exposures.
Methods: We examined expression levels of OATP related SLCO genes in renal tissue from 230 participants across a variety of comorbidities. Differential gene expression data was obtained and analyzed through the National Center for Biotechnology Information (NCBI), Gene Expression Omnibus (GEO). Search queries in the GEO browser were formatted as "(Disease) AND tissue." Datasets which did not fulfill "disease vs. healthy" criteria were omitted.
Results: Renal tissue exhibited a similar pattern of expression of SLCO isoforms to other major organs with the highest level of expression for SLCO isoforms 2A1, 2B1, and 4C1 (Figure 1). When compared to non-diseased controls, patients with diabetic nephropathy demonstrated significant ($p<0.01$) increases in glomerular expression of SLCO isoforms 1B1, 2B1, and 4C1 as well as tubulointerstitial increases in expression of SLCO3A1 (Figure 2). There was also mild downregulation of SLCOs 1A2, 1C1, 2B1, and 5A1.
Conclusion: This data supports the hypothesis that disease states impact the expression level of key transporters for cyanotoxins in the kidney. Increased expression in both the glomerular and tubulointerstitial expression of OATP transporters in patients with diabetic nephropathy agrees with experimental evidence suggesting an increased susceptibility to renal injury after cyanotoxin exposure in diabetic models.

Bohan Chen

Deficiency of melanocortin 5 receptor exacerbates proteinuria and podocytopathy after glomerular injury

Bohan Chen, Yan Ge, Lance D. Dworkin, Rujun Gong

Background: Converging evidence suggests that therapeutic targeting of nonsteroidogenic melanocortinergic pathways represents a novel strategy for treating proteinuric glomerulopathies. However, the type of melanocortin receptor (MCR) mediating this beneficial effect remains controversial and uncertain. MC5R is one such receptor that is expressed in glomerular cells. This study examined the possible effect of MC5R knockout (KO) in nephrotoxic serum (NTS)-elicited podocytopathy.
Methods: NTS nephritis was induced in MC5R KO mice and wild-type (WT) littermates. Additional WT mice received treatment with a highly selective MC5R agonist or vehicle before NTS injury. Proteinuria, podocyte injury and glomerular damage were evaluated.
Results: Despite no discernible phenotype under physiological conditions, KO mice sustained exacerbated glomerulopathy early in the heterologous phase of NTS nephritis, as shown by heavier albuminuria. This was associated with worsened glomerular pathology, which was characterized by glomerular hypercellularity, swelling of glomerular endothelial cells, and fibrinoid necrosis of glomerular capillary tufts. In parallel, KO mice exhibited more severe podocytopenia than WT mice after NTS injury, as evidenced by reduced numbers of WT-1 positive cells in glomeruli, as well as worsened podocyte injury, marked by loss of glomerular expression of podocyte homeostatic proteins such as podocin and synaptopodin. Conversely, to test if activation

of MC5R signaling is sufficient to protect against NTS-elicited podocytopathy, WT mice with NTS nephritis were subjected to MC5R agonism by using a peptidomimetic selective agonist. This resulted in an attenuated proteinuria and an improved podocyte injury, shown by preserved expression of podocyte marker proteins. However, glomerular depositions of the glomerular basement membrane-reactive heterologous rabbit IgG and the C5b-9 membrane attack complex along the glomerular capillary loops were found to be comparable in the WT and KO groups after NTS insult.
Conclusions: MC5R-mediated melanocortinergic signaling protects against proteinuria and podocytopathy upon glomerular injury and may be harnessed as an actionable target for treating proteinuric glomerulopathies.

Mengxuan Chen

GSK3β: a key regulator of glomerular podocyte injury in diabetic kidney disease

Mengxuan Chen, Yan Ge, Lance D. Dworkin, Rujun Gong

Background: Emerging evidence suggests that glycogen synthase kinase (GSK)3β, a critical transducer downstream of the insulin signaling pathway, acts as a convergent point for myriad pathways implicated in kidney injury, repair, and regeneration. However, its role in the pathogenesis of diabetic kidney disease remains highly controversial and was examined here.
Methods: Conditionally immortalized mouse podocytes were cultured under nonpermissive conditions and exposed to a diabetic milieu containing high ambient glucose and insulin as well as proinflammatory conditions, following GSK3β silencing, ectopic expression of a constitutively active GSK3β mutant (S9A), or treatment with tideglusib, a highly-selective small molecule inhibitor of GSK3β. Podocyte injury was assessed and signaling pathways examined.
Results: Upon diabetic insult, podocytes demonstrated prominent signs of cytopathic changes, marked by loss of homeostatic marker proteins like synaptopodin, increased oxidative stress and apoptosis, and stress-induced premature senescence, as evidenced by increased staining for the acidic senescence-associated-β-galactosidase activity, amplified formation of γH2AX foci, and elevated expression of mediators of senescence signaling, like p21 and $p16^{INK4a}$. Podocyte injury was associated with a reduction in inhibitory phosphorylation of GSK3β, denoting GSK3β hyperactivity. In podocytes overexpressing S9A, diabetic podocytopathy was worsened, concomitant with a desensitized insulin signaling activity, enhanced senescence response, impaired Nrf2 antioxidant response and the ensued exacerbation of oxidative damages. Conversely, GSK3β knockdown potentiated the insulin signaling, reinforced Nrf2 antioxidant response, and suppressed senescence, resulting in an improvement in podocyte injury. This protective effect was mimicked by tideglusib co-treatment, suggesting that GSK3β hyperactivity plays a key role in mediating diabetic podocytopathy.
Conclusions: Our findings suggest that GSK3β hyperactivity contributes to glomerular podocyte injury in diabetic kidney disease.

Mengxuan Chen

Hyperinsulinemia milieu elicits glomerular podocyte impairment and dysfunction via inducing GSK3β hyperactivity

Mengxuan Chen, Yan Ge, Lance D. Dworkin, MD, Rujun Gong

Background: Epidemiological evidence suggests that hyperinsulinemia or insulin resistance is a significant risk factor for the development of diabetic complications such as DKD. However, whether hyperinsulinemia per se plays a causative role in the development of diabetic kidney injury is unknown and was explored here.
Methods: Pre-diabetic db/db mice were examined for serum insulin levels, urinary albumin to creatinine ratios and renal histology. Conditionally immortalized mouse podocytes were cultured under non-permissive conditions and exposed to high ambient insulin conditions, following GSK3β silencing, ectopic expression of a constitutively active GSK3β mutant (S9A), or treatment with a small molecule GSK3β inhibitor tideglusib. Podocyte injury was assessed and signaling pathways examined.

Results: In pre-diabetic db/db mice, hyperinsulinemia was evident and associated with microalbuminuria and early signs of podocyte impairment, including diminished expression of homeostatic marker proteins like synaptopodin, as compared with db/m littermates. In vitro, prolonged exposure of differentiated podocytes to high ambient insulin induced podocytopathic changes, including cellular hypertrophy, loss of synaptopodin, and disruption of actin cytoskeleton integrity. This was associated with a desensitized insulin signaling and diminished inhibitory phosphorylation of GSK3β, denoting GSK3β hyperactivity. In pre-diabetic db/db mice, GSK3β hyperactivity was confirmed in glomerular podocytes, correlating with the level of hyperinsulinemia or microalbuminuria. In cultured podocytes, ectopic expression of S9A caused podocyte hypertrophy and podocytopathic changes, reminiscent of the harmful effect of the hyperinsulinemic milieu. Conversely, GSK3β knockdown mitigates podocyte injury elicited by hyperinsulinemic milieu. This protective effect was mimicked by the small molecule inhibitor tideglusib.
Conclusion: GSK3β hyperactivity is required and sufficient for Hyperinsulinemic milieu-elicited glomerular podocyte impairment and dysfunction.

Zachary Holtzapple, MD

Prolonged diabetic ketoacidosis with hyperammoniemia in the setting of normal liver function

Zachary Holtzapple, MD, Mohammad Al Azzawi, MD, Harith Al-Ataby, MD, Rayna Patel, MD, Ayman Salih, MD, Andrew Abrahamian, MD, Fadi Safi, MD

Background: Acute encephalopathy in the setting of diabetic ketoacidosis is typically metabolic in origin, but less pursued are other causes including hepatic encephalopathy, namely hyperammonemia. These cases are less common in the setting of diabetic ketoacidosis and more so associated with cirrhotic pathology, however they should not be excluded in the differential diagnosis of patients with altered mentation in the setting of normal liver function.
Case Report: 37-year-old female patient presented to the emergency department with a chief complaint of confusion and nausea/vomiting over the past few days prior to admission. She has past medical history of type 1 diabetes mellitus, and she had intermittently taken her insulin over the past year. On initial presentation, patient was found to be in acute respiratory distress and ill-appearing. She was oriented to person but not place nor time.
On initial lab works, the patient had severe metabolic acidosis with pH less than 7 on venous blood gas and bicarb of 2 with anion gap of 30 and glucose elevated 581. Beta hydroxybutyrate was elevated on admission. Patient required emergent intubation given her severe respiratory distress. Surprisingly, her ammonium was elevated at 138 with normal liver function test.
Throughout her hospital course diabetic ketoacidosis protocol was followed and patient's anion gap closed within the three days. Patient was safely transitioned to subcutaneous long-acting insulin along with close follow-up with outpatient endocrinology. Liver function tests continue to remain stable throughout the hospital course.
Conclusion: This case highlights a rare manifestation of hyperammonemia in the setting of a young patient with normal liver and kidney function. It also highlights the molecular mechanisms behind diabetic ketoacidosis along with how they applied a clinical practice. Often overlooked are the protein catabolic reactions and their bioproducts that are underlying patients with prolonged ketosis, as seen in this case.

Madhavaram, Anvitha R

Rituximab in kidney-limited microscopic polyangiitis: A case report

Madhavaram, Anvitha R; Nezam, Altorok MD

Background: Microscopic polyangiitis (MPA) is an immune complex mediated necrotizing vasculitis. The diagnosis is based on symptoms, including rapidly progressive glomerulonephritis, peripheral nerve disorder, lung abnormalities, and positive MPO-ANCA findings. The pathophysiology involves formation of neutrophil

extracellular traps in the kidneys, which correlate with ANCA affinity for MPO and disease activity. Rituximab has been used in cases where conventional cyclophosphamide therapy may not be suitable.
Case Presentation: A 78-year-old white male with a past medical history of gout and type 2 diabetes mellitus, presented with general weakness. Laboratory testing revealed serum creatinine of 5.2 mg/dl (normal <1.3 mg/dl) on presentation. He underwent kidney biopsy which demonstrated crescentic pauci-immune glomerulonephritis. He was treated with two doses of rituximab 1 gram, two weeks apart every 6 months for the past year. Upon presentation, he underwent dialysis for 2 months. After two years of treatment, laboratory evaluations reveal a stable creatinine of 1.77 and MPO antibody titers persistently elevated above 8. The patient responds well to Rituximab treatment, with stable renal function and no signs of extrarenal organ involvement. The plan is to continue treatment for a minimum of five years due to his consistently elevated MPO titer.
Discussion: Rituximab, a monoclonal antibody against CD20, is used as monotherapy for MPA to induce remission or alongside prednisone in severe MPA [4]. Given the patient's age, his remarkably kidney-limited disease, and favorable side effect profile, rituximab infusions were initiated over conventional chronic corticosteroids and cyclophosphamide therapy.
This case report highlights the kidney-limited form of MPA and aims to underscore the utility of rituximab as a treatment option for kidney-limited MPA. Further research is needed to understand long-term outcomes, optimize management, and establish guidelines for management of similar cases.

John Najjar

Characterization of human liver tissue for harmful algal bloom exposure in cancer and non-cancer patients

John Najjar, Bella Khatib-Shahidi, Anish Sharma, Sara Kazmi, Bella Khatib-Shahidi, Caitlin Murphy, Humza Bashir, Julissa Vargas, Bivek Timalsina, Apurva Lad, David Kennedy, Steven Haller

Introduction: Harmful algal blooms (HABs) are occurring more frequently not only in the Great Lakes region but also globally. HABs release cyanotoxins, which present public health concerns and significant health risks including associations with hepatocellular carcinoma. Cyanotoxins may enter humans through water ingestion, aerosol inhalation, or direct skin contact. We have previously demonstrated that cyanotoxins exacerbate pre-existing liver and inflammatory bowel disease in mice. However, the effects of cyanotoxin producing cyanobacteria in humans with liver cancer is unknown.
Objectives: We sought to identify the presence of cyanobacteria in Formalin-Fixed Paraffin Embedded (FFPE) liver tissue obtained from patients residing in the Great Lakes region. We hypothesized that the levels of cyanobacteria correlate with markers of tumor severity in hepatocellular carcinoma (HCC).
Methods: DNA and RNA were extracted using an optimized extraction/purification protocol designed for Formalin-fixed paraffin-embedded (FFPE) liver tissues from HCC (n=4) and age and sex matched non-HCC controls (n=4). Presence of cyanobacteria and markers of tumor severity were determined using quantitative PCR analysis.
Results: Cyanobacteria levels were elevated in liver cancer tissues compared to non-cancer (1.0±0.23 vs 2.8±1.0, p=0.06) although this was not statistically significant. Interestingly, while markers of tissue remodeling were not significantly correlated with cyanobacterial load overall in both cancer and non-cancer samples, within the HCC samples, cyanobacterial load was positively correlated with tissue inhibitor of metalloproteinases isoform 1 (TIMP-1, r=0.9103, p=0.0008).
Conclusion: Our results suggest that cyanobacteria may be increased in the setting of hepatocellular carcinoma and may impact the expression of key tissue remodeling genes within these tumors. This data is in agreement with clinical and experimental evidence suggesting an association between cyanobacteria and cancer progression in other settings and supports the need to investigate the potential role of cyanobacteria in liver

cancer progression. Analysis of additional samples is ongoing to establish this relationship in an expanded cohort.

Oscar Salichs

Trends of renal failure mortality from 1999 to 2020 in the United States by demographics

Oscar Salichs, Sishir Doddi, Taryn Hibshman, Puneet Sindhwani, Rabba Siddiqi

Introduction: This study scrutinizes the mortality rates of renal failure in the United States spanning 1999 to 2020. It aims to unravel influencing factors, including healthcare policies, advancements in treatments, demographic disparities, and challenges associated with renal failure outcomes.
Methods: Utilizing CDC WONDER's multi-cause mortality data, we assessed mortality due to renal failure (ICD-10 Codes: N17-N19). Age-adjusted mortality rates (AAMR) were collected, stratified by sex and race. The Joinpoint Regression Program analyzed trends, calculating annual percent change (APC) and significant average annual percent change (AAPC) from 1999 to 2020. Segmented line regression models were employed for parallel pairwise comparisons.
Results: Renal failure mortality rates decreased for both sexes during the late 2000s. The ACA's enactment in 2010 coincided with improved access to healthcare, possibly contributing to the decline. Demographic disparities highlighted variations in mortality rates across racial and gender groups. Advancements in renal care practices were evident, driven by innovations in treatment modalities and disease management. Significant temporal trends were observed by race, with varying periods of decrease or uptrend.
Conclusion: The decline in renal failure mortality rates during the late 2000s was potentially influenced by the ACA and advances in renal care practices. Demographic disparities emphasize the need for equitable healthcare access and interventions. These findings underscore the significance of healthcare policies and medical advancements in reducing renal failure mortality rates and addressing disparities. Persistent efforts to mitigate challenges such as healthcare access, cost barriers, and disparities remain crucial to enhancing renal failure outcomes.

PULMONOLOGY

Abdulmajeed Alharbi, MD

The Impact of Sickle Cell Disease on acute coronary syndrome outcomes: A retrospective observational study in the United States for the year 2020

Abdulmajeed Alharbi, MD, Clarissa Pena, MD, Caleb Spencer, MD, Masharib Bashar, MD, Michelle Cherian, Mohammed Siddique, MD, Ragheb Assaly, MD

Introduction: Sickle cell disease (SCD), a multisystem disorder resulting from a single gene mutation, has been recognized as a global health issue, affecting more than 300,000 infants every year with an expected rise to 400,000 by the year 2050. The influence of Sickle Cell Disease (SCD) on Acute Coronary Syndrome (ACS) outcomes have been the focus of a number of previous studies.
Objective: In this current study, we investigated the clinical characteristics and outcomes of SCD patients admitted with ACS and assessed the impact of SCD on ACS patient outcomes.
Methods: This was a retrospective observational study of a large cohort of adult patients who died with a primary diagnosis of SCD and a secondary diagnosis of ACS within the United States in the year 2020. The focus of our study was on in-hospital mortality, length of stay, and total hospital charges which were compared between the two cohorts. Procedure Classification System (ICD-10-CM) codes were used to identify codes for diagnosis with the final study sample of patients admitted with ACS comprising 779,895. Of the patients admitted with ACS, 23085 also had established diagnosis of SCD.

Results: Our findings revealed that firstly, SCD patients admitted with ACS demonstrated a heightened prevalence of hypertension, drug abuse, and chronic lung diseases, further highlighting the association between SCD and these co-morbidities. Secondly, among patients admitted with STEMI, SCD patients exhibited higher inpatient mortality rates, although this disparity did not reach statistical significance. Lastly, among SCD patients admitted for ACS who underwent PCI, the study revealed a statistically significant elevation in the risk of coronary dissection. Additionally, there were notable increases in the occurrences of atrial fibrillation and acute heart failure in this group; however, these associations did not reach statistical significance.
Conclusion: These findings provide valuable insights into the outcomes of SCD patients in the context of ACS and PCI, particularly in regard to the increased risk of coronary dissection posed to these patients. However, future studies are warranted to explore the underlying mechanisms and potential implications between SCD and ACS.

Muzdah Anwar

Recurrent bilateral pleural effusion secondary to idiopathic pleuritis in a young female patient

Muzdah Anwar, Sree Jambunathan, Kashvi Patel, Zaid Zakaria, Faraz Badar MD, Amna Al-Tkrit MD, Fadi Safi MD, Mohamed Omballi MD

Introduction: We present a rare case of a 38-year-old female patient with recurrent bilateral pleural and pericardial effusion and Primary Raynaud phenomenon.
Case Presentation: A 38-year-old female presents with bilateral recurrent exudative pleural effusions requiring drainage six times in the past five months. She has complaints of discoloration of the fingers (Raynaud phenomenon), dry cough, and bilateral leg swelling. She denies joint pain, upper extremity swelling, fever, or chills. She has no history of cancer and no new medications. She had extensive rheumatology work-up due to primary Raynaud's phenomenon. Work-up revealed negative cyclic citrullinated peptide, antinuclear antibody, rheumatoid factor, anticentromere, and anti-scl 70. Her TSH was elevated at 6.7 being controlled with levothyroxine 88 mcg daily. She does not have other clinical features of connective tissue disease or autoimmune inflammatory disease such as Familial Mediterranean Fever. CT abdomen revealed bilateral pleural effusion, pericardial effusion, ascites, and no ovarian masses. Liver ultrasound showed normal echotexture and no cirrhosis. Urinalysis showed no proteinuria. Cardiac MRI showed no infiltrative disease. No pulmonary hypertension. Cytology from the pleural fluid has been negative. Patient underwent fluoroscopy with pleural biopsy and PleurX catheter placement. Pleural biopsy showed pleuritis. She received empiric prednisone with plan for right-sided heart catheterization to rule out constrictive pericarditis or restrictive cardiomyopathy.
Conclusion: There are many causes of pleural effusions including congestive heart failure, malignancy, pneumonia, pulmonary emboli, and liver or renal failure. Non-specific pleuritis, defined as fibrinous or inflammatory pleuritis without a specific etiology, can also cause recurrent pleural effusions. Thoracoscopic pleural biopsy is valuable in investigating patients with exudative pleural effusions, especially when pleural fluid analysis is uninformative. Thus, with pleural effusions of unknown etiology, it is important to include pleuritis, constrictive pericarditis, and restrictive cardiomyopathy.

Anas Alsughayer

The association between myocardial bridging and hypertrophic cardiomyopathy and their implications on percutaneous coronary intervention outcomes - A retrospective study

Anas Alsughayer, Abdulmajeed Alharbi, Momin Shah, Michelle Cherian, Ragheb Assaly

Introduction: Hypertrophic Cardiomyopathy (HCM) is a heterogeneous cardiac disorder associated with diverse clinical outcomes, including sudden cardiac death. Myocardial bridging (MB), characterized by a coronary artery segment traversing intramurally within the myocardium, adds complexity to coronary blood flow

dynamics. This retrospective study aims to explore the connection between MB and HCM and their potential influence on outcomes following percutaneous coronary intervention (PCI).
Methods: This study employed data from the National Inpatient Sample (NIS) of 2019, encompassing approximately 20% of U.S. hospitalizations. Patients with concurrent MB and HCM undergoing PCI were identified and analyzed. The study investigated key inpatient outcomes, including mortality, length of stay, hospital cost, and post-PCI complications such as atrial fibrillation, acute kidney injury, bleeding, and coronary dissection.
Results: Patients with HCM and MB displayed distinctive demographic characteristics. The study did not establish significant associations between HCM/MB and inpatient mortality, length of stay, or hospital cost. However, a higher occurrence of atrial fibrillation and acute kidney injury was noted in HCM patients following PCI (aOR 2.33, 95% CI 1.46 to 3.71, p ? 0.001). Furthermore, myocardial bridging was linked to increased incidences of acute heart failure (aOR 0.62, 95% CI 0.42-0.92, p=0.02) and post-procedural bleeding (aOR 4.88, 95% CI 1.17-20.2, p=0.03) after PCI.
Conclusion: The study unveiled unique demographic profiles for HCM and MB patients. Notably, HCM patients exhibited elevated rates of post-PCI complications, including atrial fibrillation and acute kidney injury. This nationwide investigation provides fresh insights into the relationship between MB and HCM, as well as their influence on PCI outcomes. These findings hold implications for enhanced patient management and tailored interventions in cases of HCM and MB.

Benjamin French

Short-term exposure to nanoplastic – containing aerosol causes immunomodulation in healthy human primary airway epithelium

Benjamin French, Joshua Breidenbach, PhD, Shereen Yassine, James Willey, Jeffery R. Hammersley, MD, Erin Crawford, Deepak Malhotra, Steve Haller, PhD, David Kennedy, PhD

Introduction: As an environmental pollutant, nano-plastics (NP) have been detected in ocean and freshwater ecosystems. NPs are used in a variety of commercial and industrial processes, and larger plastics released into the environment will inevitably break down into NPs. Recent evidence suggests that NP particles become airborne in aerosols generated by natural water body motion. Occupational exposure to various NPs suggest airway irritation, neutrophilic inflammation, translocation, increased risk of lung carcinoma and chronic respiratory disease such as asthma, and even respiratory failure.
Objectives: Determine how a 3-dimensional cell culture model of airway epithelial cells responds to aerosolized NP particles.
Methods: A 3-dimensional cell culture model was constructed using cells pooled from 14 donor patients using a 24 well plate transwell insert format. Each set of cells was exposed to nanoplastic aerosol (2.5% w/v, 0.05 µm mean diameter) or vehicle for 3 minutes per exposure, 3 exposures per day, for 3 days total. Tissue integrity, mucociliary clearance, protein secretion, and chemoattractant potential were all measured post exposure.
Results: No changes to tissue integrity or mucociliary clearance were detected after exposure. However, protein secretion of IL-21, IL-2, IL-15, CXCL10, and TGFß were all significantly decreased after exposure to NP-containing aerosol vs. control (all $p<0.05$)l, while MIP-1a showed a significantly higher secretion from the NP-containing aerosol exposed cells vs. control ($p<0.05$). Additionally, a Boyden Chamber assay revealed that aerosol exposed cells caused a significantly higher migration of neutrophils.
Conclusion: Aerosolized micro- and nanoplastics are a potential threat to human health, inducing immunomodulatory effects even after short term exposures in healthy human airway epithelium. Those living in areas with high levels of pollution, and those with pre-existing conditions may be at higher risk for inhalation toxicity, which warrants further study.

Zachary Holtzapple

Carfilzomib induced pulmonary fibrosis

Zachary Holtzapple, Ayman Salih, Cassidy Eby, Mitchell Salke

Background: Multiple myeloma is a malignancy characterized by an abnormal accumulation of clonal plasma cells in bone marrow. Carfilzomib is commonly used as a medication for relapsed and refractory multiple myeloma. It is well known to cause a myriad of side effects including pulmonary toxicity.
Case Report: Our patient presented with severe shortness of breath, nausea, diarrhea without signs of hemoptysis that started the evening after chemotherapy infusion 3 days prior to admission, which included carfilzomib, pomalidomide, and dexamethasone. She was found to be severely hypoxemic and required high flow oxygen in the emergency room. Computerized tomography (CT) scan of the patient's chest showed findings concerning for pulmonary hemorrhage.
Conclusion: Carfilzomib has multiple known side effects including peripheral neuropathy, herpes zoster reactivation, hepatotoxicity, thrombocytopenia, neutropenia, pulmonary toxicity, and heart failure. In our case, we suspect carfilzomib induced alveolar hemorrhage in the setting of ongoing multiple myeloma resulted in this patient's severe anemia and acute hypoxic respiratory failure on admission. Our case report represents an uncommon pulmonary side effect of carfilzomib with limited prior documentation.

Rachel Ko

Effects of fentanyl exposure during mechanical ventilation: A retrospective study

Rachel Ko, Dan Wright, Jonathan Irvin, Anna Guo, Saira Khan, Zachary Holtzapple, MD, Andrew Abrahamian, MD, William Barnett, MS, Brian Kaminski, DO, Ragheb Assaly, MD

Background: Analgesics and sedation are often administered to ensure the comfort and safety of patients receiving mechanical ventilation (1). Patients are commonly treated with fentanyl, an opioid, to provide both pain control and sedation while mechanically ventilated. As opposed to benzodiazepines or propofol, fentanyl results in better pain control but is associated with risks such as chest wall rigidity, that may negatively impact outcomes of patients placed on mechanical ventilation (1, 2).
Objective: To assess the impact of fentanyl exposure on the outcomes of patients who undergo mechanical ventilation.
Methods: This study was a retrospective cohort study of 1191 patients from a tertiary care center. Data was gathered for all mechanically ventilated patients that survived to discharge from 2019-2022. The cumulative dose of fentanyl was quantified throughout the patient's hospital stay. Outcomes including ICU and total length of stay were ascertained upon review of the patient's medical record.
Results: Greater fentanyl exposure was associated with a longer duration of ICU and total hospital length of stay. ICU length of stay increased by 1.09 days when exposed to low doses of fentanyl and 8.78 days with higher exposure. High-dose fentanyl exposure increased total hospital length of stay by 9.71 days.
Conclusions: Higher levels of fentanyl exposure while on ventilator support significantly increased ICU and total hospital length of stay. Longer length of stay is associated with negative health outcomes such as hospital-acquired infection and cardiac arrythmias. High doses of fentanyl in critically ill patients predisposes them to serious and life-threatening medical complications.

Matthew Orchard

GELCC phenotype database: familial lung cancer data across families

Matthew Orchard, Colette Gaba, Erin L. Crawford, Christopher I. Amos, and James C. Willey

The Genetic Epidemiology of Lung Cancer Consortium (GELCC) is a collective study that has been gathering data and biosamples from individuals in families with a strong record of lung cancer and compiling this information into a phenotype database. GELCC features 10 different participating sites with [n = 10,624]

database entries: the University of Toledo accounts for [n = 1,951] entries. Lung cancer in the US is the leading cancer in mortality and has the second highest incidence of cancers. Often presenting with aggressive development and rapid lethality, lung cancer is influenced by several environmental factors, including tobacco and arsenic. Furthermore, prior studies illustrate the genetic influences in lung cancer linked to specific genes, such as TP53, RB1, and PARK2. Prior comparison between sequenced data and pedigrees from the GELCC database (e.g., multipoint linkage analysis) found significant linkages on 6q, which uncovered susceptible genes, such as RGS17, through targeted sequencing analysis. Subsequently, it is probable that other genes impacting the incidence of familial lung cancer have yet to be discovered, and this is what GELCC aims to achieve. In order to enable this aim with the latest and most accurate information, a wide variety of data and records were validated and updated in the GELCC database. Five UToledo families, including [n = 729] individuals and 3 new lung cancer cases, were updated, or added into the database. Furthermore, family pedigrees were generated for each of these families, and multisite linkage analysis will be completed at Baylor College of Medicine. Overall, these pertinent updates alongside performing further linkage analysis can help elucidate and characterize the underlying causes, pathways, and mechanisms influencing familial lung cancer incidence. Moreover, this characterization can potentially aid in screening at-risk individuals with the goal of increasing early diagnoses that corresponds with better clinical outcomes.

Kashvi Patel

Acute exacerbation of bronchiectasis secondary to achromobacter xylosoxidans in a patient with mycobacterium-avium intracellulare infection

Kashvi Patel, Sree Jambunathan, Faraz Badar MD, Muzdah Anwar, Zaid Zakaria, Amna Al-Tkrit MD, Fadi Safi MD

Introduction: We report the rare case of a patient with known history of Mycobacterium-avium intracellulare (MAI) presenting with bronchiectasis exacerbation due to multidrug resistant organism (MDRO) Achromobacter xylosoxidans.

Case Presentation: A 79-year-old female with history of acquired bronchiectasis secondary to MAI infection presented with worsening dyspnea and pleuritic chest pain for 1 month duration. Chest auscultation revealed coarse breath sounds bilaterally and CT chest showed diffuse bronchiectasis with multifocal bronchial opacification bilaterally and diffuse bronchial wall thickening.

Laboratory testing showed normal immunoglobulins, cyclic citrullinated peptide, antinuclear antibody and alpha-1-antitrypsin levels. Flexible fiberoptic bronchoscopy with bronchoalveolar lavage showed copious amounts of mucopurulent secretions. Respiratory culture was negative for acid fast bacilli and fungal smear but positive for Achromobacter xylosoxidans. Sensitivity testing showed resistance to multiple antibiotics including cephalosporins, penicillin, fluroquinolones, aztreonam, and aminoglycosides. Patient received trimethoprim/sulfamethoxazole for 1 week and reported improvement in symptoms.

Conclusion: Achromobacter xylosoxidans is a rare MDRO that closely resembles the ubiquitous gram-negative bacillus Pseudomonas but is distinguishable due to its peritrichous flagella. It is most commonly colonized in bronchiectatic lung from conditions such as cystic fibrosis and MAI as a result of repeated antibiotic courses leading to antimicrobial resistance. Our case demonstrates the importance of investigating the cause of bronchiectasis exacerbation in a timely manner by screening sputum cultures or bronchoscopy. Specific treatment guidelines for Achromobacter xylosoxidans are yet to be established; clinical management and antibiotic choice is mostly based on general treatment of bronchiectasis and Pseudomonas infection.

RHEUMATOLOGY

Halah Alfatlawi

The Impact of Libman-Sacks Endocarditis on Inpatient Outcomes of Patients with Systemic Lupus Erythematosus: A Retrospective Study

Halah Alfatlawi

Introduction: Libman-Sacks endocarditis (LSE) is recognized as the hallmark cardiac manifestation in individuals with the autoimmune disease of systemic lupus erythematosus (SLE). The existing literature offers limited insights into the influence of LSE on inpatient outcomes in individuals with SLE. This study was conducted to explore the characteristics and prognosis of SLE patients with LSE and the impact of LSE in patients with SLE on inpatient outcomes including inpatient mortality, length of stay, acute heart failure, atrial fibrillation, and cerebrovascular accidents (CVA).

Methods: This study followed a retrospective observational design and included adult patients who were hospitalized with SLE between the years 2019 and 2020, using the National Inpatient Sample (NIS) database. The total number of patients with a diagnosis of SLE in the 2019 and 2020 in the NIS database was 150,411. Of those, 349 had a diagnosis of LSE.

The study population was divided into two groups: one group with SLE and LSE, and another group with SLE but without LSE.

Results: Caucasians made up 54.9% of the patients with a diagnosis of SLE in our patient population, while African Americans made up 26.9% and the Hispanics accounted for 12.2%. Of patients with LSE, Caucasians and African Americans made up 42.9% each.

Patients with a diagnosis of LSE had a higher inpatient mortality than those with SLE without LSE (aOR: 9.74 CI 1.12-84.79, p 0.04). Patients with SLE with LSE were more likely to have acute heart failure than those without LSE, although this was not statistically significant (aOR 1.18 CI 0.13-11.07, p 0.88). Similarly, patients with SLE with LSE were more likely to have atrial fibrillation than those without LSE (aOR 4.45 CI: 0.77-25.57, p 0.10). CVAs were significantly higher in SLE patients with LSE than those without LSE (aOR 141.43 CI 16.59-1205.52, p <0.01).

Discussion: Findings from this study underscore the significance of conducting further studies to explore the relationship between systemic lupus erythematosus and Libman-Sacks endocarditis. Particularly, patients who develop LSE were found to have significantly higher risks of inpatient mortality and cerebrovascular accidents. Early and precise detection of LSE in such patients may ensure timely intervention and prevention of the associated adverse outcomes. Further studies may attempt to develop screening methods for detection of LSE to effectively reduce morbidity and mortality associated with SLE.

Masharib Bashar

Durvulumab-induced rheumatoid arthritis

Masharib Bashar, Aqsa Farooqui, and Divya Vijendra

Introduction: Durvulumab is a type of checkpoint inhibitor used in cancer immunotherapy and approved to treat different types of cancers including lung, bladder, and biliary tract cancers. It inhibits a human immunoglobin monoclonal antibody which blocks the interaction between programmed cell death ligand (PD-L1) with the PD-1 (CD279).

Case Presentation: Our patient was a 70-year-old female patient who was diagnosed with biopsy-proven Stage 3A (T1N2M0) non-small cell lung cancer of left upper lobe who underwent radiation therapy as well as chemotherapy with combination of cisplatin and premetrexed. Patient then received single dose of durvulumab during her course of treatment and developed incapacitating joint pains after just single dose. After review of

symptoms and lab findings and evaluation by rheumatologist, she was diagnosed as case of rheumatoid arthritis, secondary to durvulumab.
Discussion: As per our literature review, this is the first-ever reported case of rheumatoid arthritis caused by durvulumab.

Masharib Bashar

Hypocomplementemic-Urticarial Vasculitis Syndrome (HVUS), an extremely rare, debilitating condition, starting as trivial episodic urticarial symptoms. discussion about diagnostic strategies and latest management options: A case report

Masharib Bashar, Aqsa Farooqui, and Halah Al-Fatlawi

Introduction: Hypocomplementemic urticarial vasculitis syndrome (HVUS) Is an extremely rare debilitating condition whose exact pathophysiology remains unknown. This article serves to create more awareness about this rare condition among clinicians and specifically highlights the appropriate diagnostic strategies and treatment options available, with special emphasis on the latest advancements in management as well as ongoing or recent clinical trials regarding treatment of this condition.
Case Presentation: Our patient was a 47-year-old Caucasian female whose initial symptoms started with episodic urticarial which gradually progressed to respiratory symptoms. She became increasingly resistant to conventional treatment with antihistamines and steroids and had multiple failed treatments with medications targeting complement and bradykinin-mediated pathways. She suffered immense stress along with delayed diagnosis and multiple failed treatments before finally a skin biopsy, clinched the above diagnosis.
Conclusion: We hope that the comprehensive and condensed summary of the salient features, diagnostic strategies, and discussion of latest treatment options, will serve to better aid the specialists in treating patients suffering from this rare but highly morbid disease.

Sahithi Chinnam

A Case of bullous systemic lupus erythematosus

Sahithi Chinnam, Alborz Sherafati, Matthew Niedoba

Introduction: Bullous systemic lupus erythematosus (BSLE) is a rare manifestation of systemic lupus erythematosus (SLE) with an incidence of 3.4 cases per million per year. (1) BSLE manifests with vesicles and bullae that affect the trunk, head, neck, extremities, and mucosal membranes (2). Most lesions resolve leaving pigmentation without scarring or milia, but milia and scarring occurs in a minority of cases. The criteria for diagnosis of BSLE include acute onset of vesicles/bullae, histopathology of subepidermal blistering with neutrophil-dominant infiltrate in superficial dermis, direct immunofluorescence of linear or granular immunoglobulin at basement membrane, elevated ANA, and excluding other causes.
Case Description: A 19-year-old female with a history of SLE, lupus nephritis, chronic impetigo, and recent septic shock secondary to Streptococcus pyogenes presents with one week of worsening bilateral lower extremity swelling with bullous lesions that scarred with resolution. Skin punch biopsies were performed on the left anterior thigh. Histopathology shows vacuolar interface dermatitis with subepidermal splitting with lymphocyte infiltrate in superficial dermis. Direct immunofluorescence was negative for IgG, IgG4, IgM, and IgA and showed discontinuous weak granular deposits of C3 at the basement membrane and non-specific deposits of fibrinogen in connective tissue. Patient was treated with dapsone, which provided significant improvement in skin lesions.
Discussion: BSLE is a rare manifestation of SLE with multi-organ involvement that should be considered as a differential diagnosis for vesiculobullous lesions in patients that must be differentiated from other cutaneous bullous skin lesions, including bullous pemphigoid, linear IgA dermatosis, and epidermolysis bullosa acquisita.

Although rare, scarring should not rule out BSLE. Histopathology is also similar to other conditions, and immunofluorescence cannot solely diagnose this condition. In this case presentation, a diagnosis of BSLE was made based on patient history, clinical presentation, antibodies, and histopathology in the setting of negative direct immunofluorescence.

Dharmindra Dulal, MS

A case of palindromic rheumatism and literature review

Dharmindra Dulal, MS, and Bashar Kahaleh, MD

Introduction: Palindromic rheumatism (PR) is an autoimmune condition characterized by transient migratory arthritic attacks involving one or multiple joints. Although any joints are vulnerable to attack, the wrist, knee, and fingers are commonly involved. PR attacks are debilitating pain with joint stiffness, swelling, and warmth, but without residual damage. PR is a commonly misdiagnosed condition due to the lack of established diagnostic guidelines, and it often presents with standard inflammatory and autoimmune markers.
Case presentation: The patient is a 36-year-old white female who was first presented to the rheumatology clinic on November 8th, 2022, complaining of migratory joint pain over multiple days. However, the patient denied any swelling, erythema, or morning stiffness. The patient was noted to have an elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) over the past two years. All other inflammatory and autoimmune markers were found to be in the normal range. Evaluation of the sacroiliac joint and cervical spine via X-rays was unremarkable. The trial of 5mg prednisone for two weeks failed to show improvement in symptoms.
Conclusion: After multiple follow-ups over a year, the patient was diagnosed with PR based on recommendations proposed by Pasero and Barbieri, which include: 1) six months history of brief, sudden, and recurrent episodes of mono-arthritis or polyarthritis; 2) the physician must observe at least one attack; 3) PR must involve three or more joints; 4) radiographic findings are normal; 5) diagnosis of exclusion. Although there haven't been any FDA-approved medications to treat PR, the clinician has been using conventional therapy to treat other rheumatic conditions as a mainstay treatment. Among traditional treatments, hydroxychloroquine (HCQ), corticosteroid, methotrexate (MTX), and biologics (such as rituximab) have shown the most significant therapeutic benefits in limited case studies. Therefore, our patient was offered HCQ, MTX, and biologics as treatment options.

Rawish Fatima, MD

Secukinumab induced bullous pemphigoid in a patient with psoriatic arthritis

Rawish Fatima, MD, Sabeen Sidiki, MD, Julianna Mae Sim, Nezam Altorok, MD

Abstract: The use of biologics is a common practice in Rheumatology and physicians need to be cognizant of the possible implications and side effects of these medications. We present the case of a 62 year old male who developed bullous pemphigoid after using Seckinumab.
Introduction: Secukinumab is a human anti-interleukin (IL) 17A monoclonal antibody which is widely used for the treatment of Psoriatic arthritis and psoriasis. It is preferred in patients with peripheral arthritis who do not respond adequately to two different TNF inhibitors.
Case Presentation: A 62-year-old male with history of skin psoriasis and psoriatic arthritis (PsA) who had previously failed Adalimumab and Apremilast. He was started on Secukinumab, and he responded well to it for a year. His treatment had to be interrupted for almost a year while he was getting treated for a Methicillin-Sensitive Staphylococcus infection of olecranon bursa, which developed into osteomyelitis. Secukinumab was resumed after his infection was appropriately treated. He experienced improvement in his joint pain and skin psoriasis. A month after resuming the medication, he started to notice bullous lesions with clear discharge on

his lower extremities (Picture 1 and 2). He felt they were increasing in size and number despite using Neosporin. He was prescribed oral Doxycycline for 2 weeks which did not help with the lesions. In a few months, he started to develop lesions on his upper extremities and buccal mucosa as well. Secukinumab was immediately stopped, and he was referred to Dermatology. His pemphigus antibody panel came back negative, and the skin biopsy showed subepidermal blister with neutrophils and eosinophils with a dense superficial and deep inflammatory infiltrate. The immunofluorescence was negative for immunoglobulin or complement deposition. Given the subepidermal split he was diagnosed with bullous pemphigoid. After stopping his medication, the bullous lesions started to heal, and significant improvement was noticed. His Naranjo score was estimated to be +5 out of maximum +13 which translates to him having a probable adverse drug reaction.
Discussion: Secukinumab is a selective binder of interleukin (IL) 17A which prevents its interaction with the IL-17 receptor and activation of the IL-17 receptor signaling pathway associated with inflammatory processes. A multi-center study done in Southern Italy showed that it has excellent safety profile and efficacy. A randomized, double-blind, placebo-controlled, phase 3 study in patients with active PsA named FUTURE 5 showed long-term achievement of low disease activity or remission. The study also showed that young age, low body mass index at baseline, low disease activity and pain at week 16 are predictors for sustained low disease activity. It was also found to have protective effect on radiographic progression in patients with PsA. Some of the commonly reported side effects of secukinumab include infection, nasopharyngitis and soreness at the injection site reactions. However, there have also been reports of rare manifestation of eczematous dermatitis, IgA vasculitis and lymphocytic colitis after its use. Bullous pemphigoid is an autoimmune blistering disease which classically presents as tense, fluid-filled bullae on skin. The pathogenesis of bullous pemphigoid is very broad and can include factors like central neurological disorders, old age, infections, and medications. The most common medications that are considered the culprit are immune check point inhibitors, calcium channel blockers, beta blockers, NSAIDs, salicylates, angiotensin converting enzyme Inhibitors and antibiotics. There have also been cases where bullous pemphigoid was attributed to biologic use. The commonly involved biologic culprits are tumor necrosis factor alpha (TNF-α) blockers and interleukin-23 inhibitors. From our literature search there has only been a single case reported for secukinumab induced bullous pemphigoid. Psoriasis by itself has been associated with a higher incidence of bullous pemphigoid which may play some role in the incidence in this particular population. Bullous pemphigoid is usually treated with high-potency topical corticosteroid, oral corticosteroid and doxycycline. Corticosteroid-sparing agents like dapsone, methotrexate, mycophenolate, azathioprine can be added to the regimen to limit steroid use. In patients who have refractory disease medications like rituximab, omalizumab, dupilumab, and intravenous immune globulin (IVIG) are initiated.
Conclusion: Unfortunately, there are no optimal therapeutic recommendations for biologics induced bullous pemphigoid so physicians should be mindful of this side effects and promptly consider skin biopsy and stopping the medication.

Jerrin George

Polyarteritis Nodosa presenting with abdominal pain and mesenteric stenosis

Jerrin George, Avish Persaud, Nezam Altorok, MD, Nathaniel Gilbert, MD

Introduction: Polyarteritis nodosa (PAN) is a rare medium-vessel vasculitis that occurs in about 0.003% in the United States annually. Mesenteric vasculitis due to PAN presents as an atypical but life-threatening cause of bowel ischemia and acute abdomen. We present a unique case of PAN with several complications and unusual findings on imaging.
Case Presentation: Our patient is a 43-year-old female who presented to the emergency department with abdominal pain. She had persistently elevated blood pressures in the range of 200/100. Computerized tomography (CT) of the abdomen demonstrated segmental occlusion of the proximal celiac artery, small intimal

dissection flap of the superior mesenteric artery (SMA), a 6mm focal pseudoaneurysm that had enlarged in size over 3 months, high-grade luminal narrowing of the SMA, right hepatic artery occlusion, right renal artery occlusion, and a small infrarenal aortic dissection. Laboratory workup was negative for antineutrophilic cytoplasmic antibody. In addition, she had an elevated C-reactive protein of 2.8 (units), an erythrocyte sedimentation rate of 50 (units), and proteinuria of 0.5 grams daily. PET CT scan confirmed metabolic activity in the vasculature described above. She was started on a prednisone taper at 20 mg for 15 days for concerns of PAN with reduction in her pain that was previously refractory to opioids. The patient was treated successfully with a tapering dose of dexamethasone starting at 6 mg twice daily and azathioprine 150 mg daily.
Conclusions: Treated PAN has a five-year survival of 80%, while untreated PAN has a survival of 13%, making the workup and diagnosis of PAN urgent to reduce mortality. Life-threatening complications and poor indicators of prognosis for untreated PAN include ischemia, dissection, or pseudoaneurysm of multiple arteries, as well as hypertensive urgency and proteinuria. Early detection and treatment for PAN is essential to improve health outcomes, reduce complications, and improve mortality.

Khuder, Sabrina

An unusual presentation of Granulomatosis with Polyangiitis (GPA): Case report

Khuder, Sabrina; Gerber, Caleb; Davis, Samantha MD; Gilbert, Nathan MD; Fatima, Rawish MD; Nezam, Altorok MD

Introduction: Granulomatosis with polyangiitis (GPA) is a small vessel necrotizing vasculitis that involves the upper and lower respiratory tracts and the kidneys. Patients commonly present with symptoms such as sinusitis, otitis media, hemoptysis, and features of glomerulonephritis, such as microscopic hematuria and renal dysfunction. ANCA directed against proteinase-3 can be found in up to 80% of patients with this disease. Here we present an unusual case of GPA, with fever and jaw claudication.
Case Presentation: A 66-year-old Middle Eastern male was admitted to the hospital with a 2-week history of bilateral severe headache, jaw claudication, blurry vision, sinus congestion and feverish sensation. Medical history was significant for essential hypertension and type 2 diabetes. Sedimentation rate (ESR) was 83. The patient's symptoms were initially suspicious of giant cell arteritis (GCA); however, temporal artery biopsy was normal. CT scan of the sinuses showed complete opacification of the left frontal and left maxillary sinuses (image 1). The patient's urinalysis revealed microscopic hematuria with proteinuria and protein creatinine ratio was elevated at 1.5. Labs further revealed elevated ESR, positive C-ANCA, and proteinase-3 antibodies. A kidney biopsy showed evidence of focal segmental pauci-immune glomerulonephritis. Overall, kidney biopsy findings along with CT scan results align most consistently with GPA. The patient was started on Rituximab infusions and prednisone. On follow up visits, the patient has had complete resolution of his sinus congestion, jaw claudication, and blurry vision with decreasing ANCA and PR3 titers, and resolution of proteinuria.
Discussion: This case demonstrates an unusual presentation of GPA with the patient initially presenting with features of headache, blurry vision, and jaw claudication that mimics GCA. It is important to highlight unique cases such as this one to increase awareness to all primary care physicians, including rheumatologists, of how GPA may present to prevent delays in diagnosis and treatments.

Khuder, Sabrina S

Interstitial lung disease with autoimmune features successfully treated with mycophenolate mofetil: Case report

Khuder, Sabrina S; Davis, Samantha MD; Gilbert, Nathan MD; Altorok, Nezam MD

Introduction: Interstitial lung disease (ILD) is a broad term used to describe a group of lung disorders characterized by fibrosis of the lungs. ILD is classified into known factors including occupational and

environmental exposures, as well as idiopathic cases. ILDs can be associated with connective tissue disease including systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, or limited autoimmune features1. Patients will often present with dyspnea and non-productive cough. Mycophenolate mofetil (MMF) is an immunosuppressive drug that has shown to be well tolerated in ILD patients and restore pulmonary function2. Efficacy is not established yet in ILD with autoimmune features.
Case Presentation: Patient is a 58-year-old male who presented with shortness of breath at rest. Medical history was significant for hypertension and COPD. His pulmonary function testing shows DLCO of 30 (normal > 70%), FVC of 67% of age predicted, and FEV1 of 66%. Initial CT scan performed demonstrated mediastinal lymph nodes with upper lobe fibrotic changes. His lung biopsy showed inflammation and evidence of non-specific ILD (NSIP). Laboratory results were positive for ANA and elevated ESR while negative for other immunological markers. The patient did not have any known occupational exposure. On physical exam, he had evidence of clubbing. The patient met criteria for diagnosis of interstitial lung disease with autoimmunity. He was started on treatment with 1000 mg of MMF twice daily as well as oral prednisone 2.5 mg daily. The patient was found at follow up appointments to be responding well to treatment.
Discussion: The case highlights a unique presentation of ILD in a patient with features of an autoimmune process including a positive ANA titer. Although there is not much data in the literature to delineate treatment of ILD with autoimmune features, we believe this case may support use of MMF in larger clinical trials.

Anvitha Madhavaram

Polymyalgia Rheumatica treated with sarilumab: A case report

Anvitha Madhavaram; Bashar, Kahaleh MD

Background: Polymyalgia rheumatica (PMR) is characterized by bilateral subacute-to-chronic pain and stiffness of the shoulders and hip girdle with an elevated erythrocyte sedimentation rate (ESR), elevated C-reactive protein (CRP), and a normal creatinine kinase. Typically, rapid improvement is shown in PMR upon treatment with oral glucocorticoids. However, prolonged use can lead to significant side effects. Methotrexate is often used as a steroid-sparing agent, but some patients may not respond to or tolerate it. This case highlights the potential of sarilumab as a therapeutic option in PMR refractory to both methotrexate and glucocorticoids.
Case Presentation: A 74-year-old white male with chronic PMR presented to the office with continued consistent breakthrough 7/10 PMR pain (with 10 being the most severe) despite treatment with 20 mg prednisone and 20 mg methotrexate for the past six years. Upon presentation three months ago, his prednisone dosage was weaned from 20 mg to 5 mg and methotrexate was discontinued due to increasing breakthrough PMR pain, skin thinning, and decreased wound healing.
Vitals and physical exam findings were within normal limits outside of decreased range of motion of shoulders bilaterally. His latest labs showed an elevated ESR of 37 and CRP level of 15.3 consistent with ongoing PMR. Due to the refractory nature of his symptoms and prolonged steroid use, treatment with sarilumab was initiated.
Conclusion: Sarilumab is a human IgG1 monoclonal antibody that binds to IL-6 receptors, inhibiting IL-6 signaling. Several clinical trials have demonstrated the safety, efficacy, and tolerability of Sarilumab in RA patients. Furthermore, studies comparing Sarilumab with Tocilizumab in terms of safety and tolerability found no clinically meaningful differences. Sarilumab has a greater affinity to IL-6 than that of tocilizumab, which may even suggest a potential superiority.

Vanessa Pasadyn, BA

Unveiling the silent constrictor: A case report of Takayasu Arteritis manifesting as a vascular enigma

Vanessa Pasadyn, BA, Samantha Davis, MD, Rawish Fatima, MD, Nezam Altorok, MD

Introduction: Takayasu arteritis (TKA) is a rare large vessel vasculitis, most prevalent in Asia and affecting females ages 10-40 years. Through unclear etiology, it triggers chronic granulomatous inflammation leading to vessel wall thickening, stenosis, and occlusion. Manifestations vary from mild malaise to severe ischemic

complications. Diagnosis hinges on clinical criteria, including angiography, and exclusion of mimicking conditions like giant cell arteritis, fibromuscular dysplasia, or atherosclerosis. Treatment necessitates immunosuppression and anti-inflammatories to curb disease progression and limit complications.
Case Presentation: A 61-year-old Caucasian female presented with claudication of the upper extremities upon using the shower. She reported episodes of headache, myalgia, fever and chills of several months. She reported fatigue with overhead reaching and difficulty finding her pulse on her upper extremities. Labs were notable for elevated ESR and CRP. MRA chest showed smoky thickened appearance of the descending aorta wall, some missing wall thickening in origins of the left common carotid and left subclavian arteries. PET scan revealed diffuse hypermetabolic activity involving the bilateral common carotid arteries, peripheral aortic arch and descending thoracic aorta. With these ongoing symptoms and characteristic features on imaging, we established the diagnosis of TKA. She was started on 5mg oral prednisone daily and methotrexate 10mg weekly with daily folic acid.
Conclusion: This case highlights the diagnosis and treatment of a rare condition, Takayasu arteritis, the pulseless disease. TKA is a challenging condition to study and understand fully, but advancements in medical knowledge, imaging, and management are gradually improving our understanding and ability to diagnose and treat this condition. With increased awareness of this condition, earlier detection and monitoring will serve to benefit future patient populations.

Rabbia Siddiqi, MD

Are intravenous steroids better than oral steroids in treating COPD exacerbations in hospitalized patients? A systematic review and meta-analysis

Rabbia Siddiqi, MD, Nasir Shivani, MD, Nezam Altorok, MD

Introduction: Systemic steroids are routinely used in the inpatient management of chronic obstructive pulmonary disease (COPD) exacerbations and may be administered orally (PO) or intravenously (IV). IV steroids are often pursued as a more aggressive approach although there is no clear evidence of their superiority over PO route and may increase the risk of hyperglycemic events. Here we compare the effectiveness of IV versus PO steroids in COPD exacerbations.
Methods: PubMed/MEDLINE, EMBASE, and Cochrane databases were searched for randomized controlled trials (RCTs) comparing IV versus PO administration of steroids in patients admitted for COPD exacerbation. Primary outcome was mortality during the study follow-up period. Secondary outcomes included: mean change in forced expiratory volume in 1 second (FEV1) from baseline to end of steroid course; length of hospital stay; treatment failure; and readmission rate. Effect estimates were pooled using a random-effects model and reported as mean differences (MD) or relative risks (RR) with the corresponding 95% confidence interval (CI).
Results: A total of 3 RCTs were included, comprising 296 patients (IV group=150, PO group=146). Study treatment duration varied between 7-10 days, and median follow-up was 1-3 months. Our meta-analysis showed no statistically significant difference between the two groups in risk of death (RR 1.45 [0.34-6.29]) by the end of the study follow-up. Both groups (IV versus PO) had a similar mean change in FEV1 from baseline (MD -0.06 liters [-0.19-0.07]) and similar length of hospital stay (MD 1.88 days [-3.07-6.83]). There was no statistical difference in treatment failure rate (RR 0.96 [0.55-1.66]) or readmission rate (RR 0.93 [0.54-1.61]).
Conclusion: Our study showed that IV steroids have no benefit over PO steroids in patients admitted with COPD exacerbations. This suggests that IV steroids and their associated risks may be unnecessary and can be avoided in many patients.

Yongqing Wang

Epigenetic repression of eNOS in scleroderma (SSc) Microvascular Endothelial Cells (MVECs) is related to the downregulation of MicroRNA-152 by enhanced DNA methyltransferase 1 (Dnmt1) Expression

Yongqing Wang and Bashar Kahaleh

Objectives: Alteration in Scleroderma (SSc)-microvascular endothelial cells (MVEC) is related to epigenetic influences on gene expression level. Nitric oxide synthase gene (NOS3) repression is a prime example of epigenetic alteration of SSc-MVEC phenotype. The underlying mechanism of epigenetic imprinting in SSc-MVEC remains unknown. MicroRNAs (miRNAs), which are noncoding RNAs that regulate gene expression, are involved in diverse biological functions, including epigenetics regulation. It has been reported that downregulation of microRNA-152 induces aberrant DNA methylation by targeting the maintenance methyl transferase Dnmt1. In this study, we investigated miRNA-152 expression levels in SSc-MVEC and whether it is involved in the regulation of epigenetic imprinting in SSc.
Methods: MVEC cells were isolated from skin biopsies of SSc patients and matched control subjects. The NOS3, Dnmt1, and miR-152 expression levels in normal and SSc-MVEC were checked by real-time PCR. The epigenetic regulation of NOS3 was examined by the addition of DNA methyltransferase and histone deacetylase inhibitors to MVEC cultures and by analysis of CpG site methylation in the NOS3 promotor region. The effect of Dnmt1 on NOS3 mRNA expression was examined by transfecting SSc- MVEC with Dnmt1-specific siRNA and irrelevant control siRNA. The effect of miR-152 on Dnmt1 mRNA and NOS3 expression was examined by transfecting hsa-miR-152 into SSc-MVEC and transfecting miR-152 inhibitor into control- MVEC.
Results: A significant increase in Dnmt1 expression levels and a significant decrease in NOS3 expression levels were noted in SSc-MVEC. The addition of 2-deoxy-5-azacytidine and Trichostatin A to SSc-MVEC cultures normalized NOS3 expression levels. CpG sites in the NOS3 promoter were methylated in SSc-MVEC but not in control-MVEC. Transfection of SSc-MVEC with siRNA specific for Dnmt1 resulted in an 80% decrease in the expression levels and an increase in the NOS3 expression level. Since DNMT1 is one of the predicted direct targets of miR-152, we investigated the expression levels of miR-152 in SSc and control MVEC. Levels were significantly down-regulated in SSc-MVEC and were inversely correlated to DNMT1 expression levels. Forced expression of miR-152 in SSc-MVEC led to a reduction in DNMT1 expression at the mRNA level in comparison with the negative control, while inhibition of miR-152 expression in control-MVEC enhanced DNMT1 expression levels in association with reduced NOS3 expression level.
Conclusions: NOS3 expression level is down-regulated in SSc-MVEC and correlated with its promoter methylation. Dnmt1 expression is up-regulated in SSc-MVEC and inversely correlated to NOS3 expression levels. MiR-152 expression is downregulated in SSc-MVEC and inversely correlates with DNMT1 and relative correlates with NOS3 expression levels. MiR-152 may play a causal role in DNA methylation changes in SSc-MVEC through targeting Dnmt1.

Yongqing Wang

Treprostinil inhibits functional activation of scleroderma (SSc) vascular smooth muscle cells (vSMCs) by inhibiting Yap and activating PPARG signaling

and Bashar Kahaleh, MD

Background: Progressive vascular wall thickness and fibrosis are the hallmarks of SSc vasculopathy. Overexpression of TGFB1 in SSc and activation of vSMCs are important steps in the pathogenesis of SSc vascular disease.
Objectives: In this study, we examined the expression levels of COL1, PCNA, PFKP, IP, EP2, IP, and PTGIS in SSc skin, the effects of Treprostinil (prostacyclin analog) on cell proliferation, TGFB1-induced collagen expression in SSc-vSMCs, PPARG expression and Yap nuclear translocation.

Methods: SSc and control skin biopsies were fixed and 10uM serial sections were cut for histological examination. vSMCs were isolated from involved skin and matched healthy subjects. The expression and distribution of collagen, PCNA, PFKP, IP, EP2, PTGIS, PPARG, and Yap were measured by immunohistochemical staining or immunofluorescent staining. Cell proliferation was measured by MTT assay. The mRNA expression levels were detected by qPCR.
Results: The protein expression levels of collagen, PCNA, PFKP, and EP2 were increased, while the expression levels of PTGIS and IP were decreased in vSMCs of SSc-skin, compared to the control. These results suggested that defective PGI2-IP signaling in SSc-vSMCs may contribute to vessel wall thickness and vascular fibrosis in SSc. Treprostinil inhibited vSMCs proliferation, COL1A1, and PFKP mRNA expression in SSc-vSMCs in a dose-dependent fashion. Treprostinil also inhibited TGFB1-induced COL1A1 mRNA expression in SSc-vSMCs via engagement of EP2. The PPARG expression was significantly increased in treprostinil-treated SSc-vSMCs. Treprostinil decreased the nuclear location of YAP which is induced by 10%FBS and TGFB1.
Conclusion: Defective PGI2-IP signaling in SSc-vSMCs is associated with enhanced expression of collagen, PCNA, and PFKP in SSc vessel walls. The antiproliferative and antifibrotic activity of treprostinil is mediated through the inhibition of YAP nuclear translocation and enhanced PPARG expression. YAP and PPARG might be promising therapeutic targets for the treatment of SSc-related vasculopathy.

Amy Waters, MBA, MS

Mesenteric lymphadenopathy: A rare case of Rosai-Dorfman Disease

Amy Waters, MBA, MS; Joan Gekonde, MD; Nathaniel Gilbert, MD; Nezam Altorok, MD

Introduction: Rosai-Dorfman Disease (RDD) is rare with approximately 100 new cases annually in the United States and a mean age of 20.6 years. RDD is characterized by massive lymphadenopathy and sinus histiocytosis. Bilateral cervical lymphadenopathy is the typical presentation, however extra nodal sites have been noted. This case discusses manifestations of a rare disease state.
Case Presentation: A 19-year-old male with a history of eczema and juvenile rheumatoid arthritis presented to the emergency room with four days of diffuse abdominal pain localized to the left upper quadrant, radiation to the right lateral ribs with nausea and diarrhea. He reported an unintentional weight loss of 30 pounds in the last three months. Physical exam revealed generalized abdominal tenderness and rebound. Computed tomography of the abdomen and pelvis (CTAP) along with routine labs were ordered. CTAP showed retroperitoneal lymphadenopathy up to two centimeters in the short axis (figure 1) and mesenteric adenopathy with a 15-millimeter lymph node in the right lower quadrant. Histopathology reported necrotizing granulomatous lymphadenitis with benign sinus histiocytes. Referral to rheumatology was made and treatment was initiated with prednisone 20 milligrams daily with plans for repeat abdominal imaging to evaluate for reduction of adenopathy.
Discussion: RDD coexists with immunologic disease in 10% of cases.3 It has been associated with systemic lupus erythematous, idiopathic juvenile arthritis, autoimmune hemolytic anemia,24 and one case of RAS-associated autoimmune leukoproliferative disease. The prognosis for RDD is indolent, 50% of patients experiencing resolution, one third with residual asymptomatic adenopathy and 17% with persistent symptomatology. Our case highlights our patient's associated history of juvenile rheumatoid arthritis now presenting with histological findings of RDD. A methodical approach to assessing patients with diffuse abdominal pain and ensured collaboration amongst different medical specialists will ensure favorable treatment outcomes.

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