Research Publication Series

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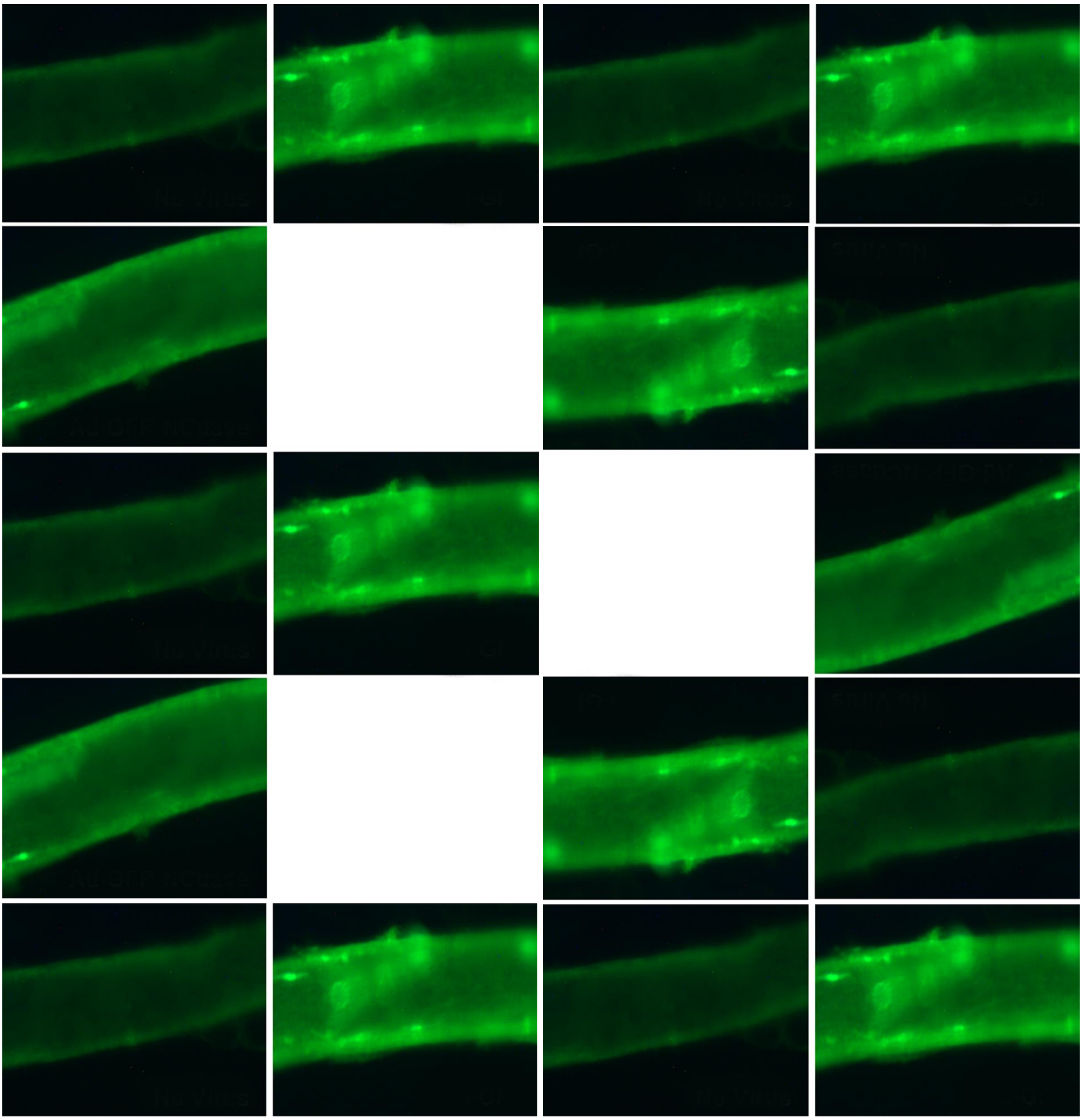
March 2020



About the Research Publication Series:

The Medical College of Wisconsin is a major national research center and the second-largest research institution in Wisconsin. Basic science, clinical, and translational researchers thrive in the unique setting of an academic medical center. The innovative work of our scientists leads to groundbreaking discovery that impacts healthcare and saves lives. The Research Publication Series is a sampling of recent publications by faculty, staff, and student investigators.

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Matthew S. Karafin, MD, MS
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Rebecca Bernstein, MD, MS
"Implementation of a Primary Care Physician-led Cavity Clinic Using Silver Diamine Fluoride"

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Cover Image from "Manipulation of the Sphingolipid Rheostat Influences the Mediator of Flow-Induced Dilation in the Human Microvasculature"

Matthew S. Karafin, MD, MS
Medical Director, Medical Sciences Institute
BloodCenter of Wisconsin/Versiti
Associate Investigator, Blood Research Institute
Associate Professor
Department of Pathology and CTSI
Medical College of Wisconsin

I am an Associate Professor of Pathology at MCW and a Medical Director for Versiti Wisconsin. I have been with MCW as an attending transfusion medicine physician since 2012. My research interests include the use of red cell transfusion for patients with sickle cell disease, etiology and prevention of red cell alloimmunization, benefits and risks of red cell storage for patients with sickle cell disease, benefits and risks of red cell transfusions in the elderly, and the etiology and prevention of transfusion reactions.

"Chronic Pain Persists in Adults with Sickle Cell Disease Despite Regular Red Cell Transfusions"

Karafin MS, Mullins DE, Johnson ST, et al. *Transfusion and Apheresis Science*. 2019;58(4):434-438.

A convenience sample of chronically-transfused adults with SCD rated their pain on a scale of 0 to 10 each day over the course of 2-3 months. Ten subjects (63%) in this cohort completed the diary and were defined as having chronic pain, while the remaining four (27%) subjects had episodic pain. Despite chronic transfusion and a suppressed HbS% (22.5% (16.5-25.9)), we identified that 10 patients (63%) continued to report nearly daily pain, and on almost 70% of diary days, the pain was significant (≥5/10). When the relationship between HbS% and reported pain intensity was examined, no association was found. These results suggest that, even with regular transfusions and a low HbS%, daily pain persists in many adults with SCD.

Characteristic	Overall (n=14)	Chronic Pain (n=10)	No Chronic Pain (n=4)	p-value
Gender (n, % females)	8.0 (57.0)	6.0 (60.0)	2.0 (50.0)	>0.99
Age (median years, IQR)	30.5 (27.0-43.0)	30.5 (27.0-43.0)	28.0 (21.5-41.5)	0.6
Diagnosis (n, % HbSS)	13.0 (92.9)	9.0 (90.0)	4.0 (100.0)	>0.99
Time on Transfusion (median years, IQR)	4.1 (1.8-5.0)	4.1 (2.5-5.0)	3.1 (1.5-4.9)	0.7
Reason for Transfusion (n, %)				
Stroke	6.0 (42.9)	2.0 (20.0)	4.0 (100.0)	**0.02***
High utilization for acute pain	8.0 (57.1)	8.0 (80.0)	0 (0)	
Co-morbidity (n, %)				
Pulmonary Hypertension	1.0 (7.1)	1.0 (10.0)	0 (0)	>0.99
Renal Disease	0 (0)	0 (0)	0 (0)	NA
Avascular Necrosis	1.0 (7.1)	1.0 (10.0)	0 (0)	>0.99
Stroke	10.0 (71.4)	6.0 (60.0)	4.0 (100.0)	0.3
Transfusion Modality (n, %)				
Simple transfusion	8.0 (57.1)	6.0 (60.0)	2.0 (50.0)	>0.99
Exchange transfusion	6.0 (42.9)	4.0 (40.0)	2.0 (50.0)	
Morphine Equivalent Dose (median mg, IQR)	26.3 (0-60.0)	37.5 (22.5-180.0)	0 (0-0)	**0.02***
Hospitalizations (median days, IQR)				
ED visits in the last 12 months	1.0 (0-2.0)	1.5 (1.0-2.0)	0.5 (0-1.5)	0.3
Admissions in the last 12 months	0 (0-2.0)	0 (0-3)	0 (0-0)	0.2
Utilization (with or without crisis) (n, %)	2.0 (14.3)	2.0 (20.0)	0 (0)	>0.99
Laboratory Values (median, IQR)				
Pre-Hgb, g/dL[1]	9.1 (8.1-10.0)	8.7 (8.1-10.0)	9.5 (8.7-10.5)	0.4
Post-Hgb, g/dL[1,2]	10.0 (9.7-10.9)	10.0 (9.6-10.9)	10.4 (9.8-11.0)	0.8
Pre-HbS, %[1]	39.2 (34.2-43.2)	37.4 (34.1-41.5)	43.3 (38.1-48.3)	0.2
Post-HbS, %[1]	22.5 (16.5-25.9)	22.4 (13.7-25.9)	22.9 (19.0-30.1)	0.5
Key Pain Characteristics (median, IQR)				
Overall median pain score	5.5 (0-6.5)	6.0 (5.0-8.0)	0 (0-0)	**0.004***
% days with pain ≥ 5/10	67.9 (1.8-97.1)	86.0 (58.9-100.0)	0 (0-0.9)	**0.004***
Transfusion day pain score[1]	5.5 (3.0-8.0)	6.0 (5.5-8.0)	0.8 (0.3-2.0)	**0.004***

Figure 1. Bar plots of diary days by patient, excluding the two patients who did not report a pain score on more than 25% of diary days.

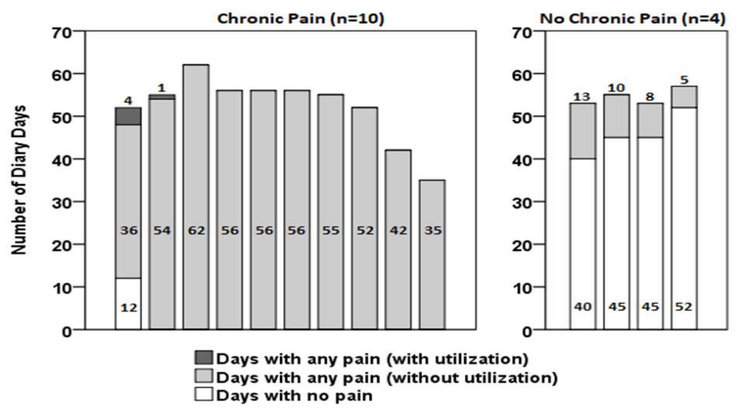


Table 1. Patient study demographics and pain characteristics. Patients with chronic pain (N=10) reported any pain on more than 3 days per week, and patients with no chronic pain (N=4) reported any pain on 3 or fewer days per week. Two patients were excluded from analysis because they had more than 5 missing diary days (or more than 25% missing diary days).

***Statistically significant difference**

[1] There are multiple values per patient. Values used are averages of values across Transfusions 1 and 2 per patient. Transfusion 3 was not included in the averages because only 3 patients had 3 transfusions, whereas all 16 patients had 2 transfusions.

[2] For one patient, Transfusion 2 post-Hgb value was missing. For their average, Transfusion 1 post-Hgb value was used instead.

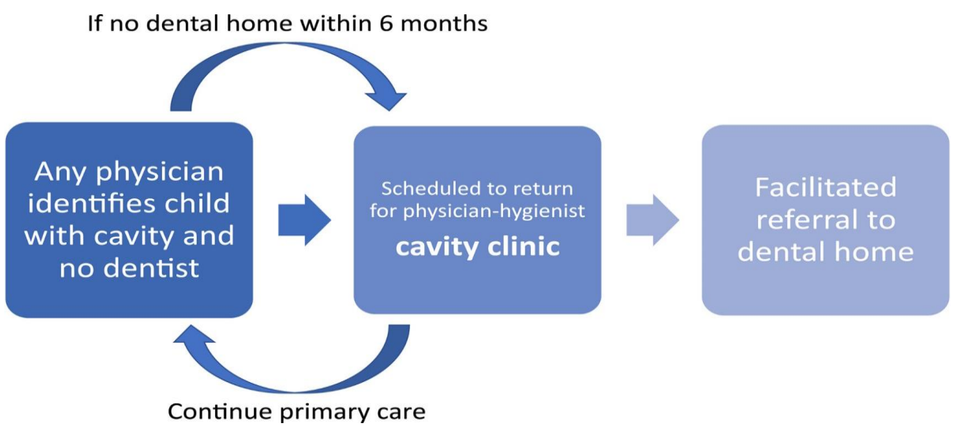
Rebecca Bernstein, MD, MS
Associate Professor
Co-Director of Medical Student Education
Family and Community Medicine
Medical College of Wisconsin &
All Saints Family Medicine Residency

I am an Associate Professor in the Department of Family and Community Medicine at MCW. I enjoy clinical practice, teaching residents and students, and doing primary care research. My special clinical interests are in vulnerable populations and primary care of complex patients, and I have experience working in a number of safety-net clinics. I teach community medicine in the M3 family medicine clerkship and co-direct the Urban and Community Health Pathway. My current research interests are in health disparities, oral health, immunization access, and chronic disease in vulnerable populations.

"Implementation of a Primary Care Physician-led Cavity Clinic Using Silver Diamine Fluoride"

Bernstein RS, Johnston B, Mackay K, Sanders J. *Journal of Public Health Dentistry*. 2019;79(3):193-197.

Figure 1: Cavity Clinic Patient Referrals

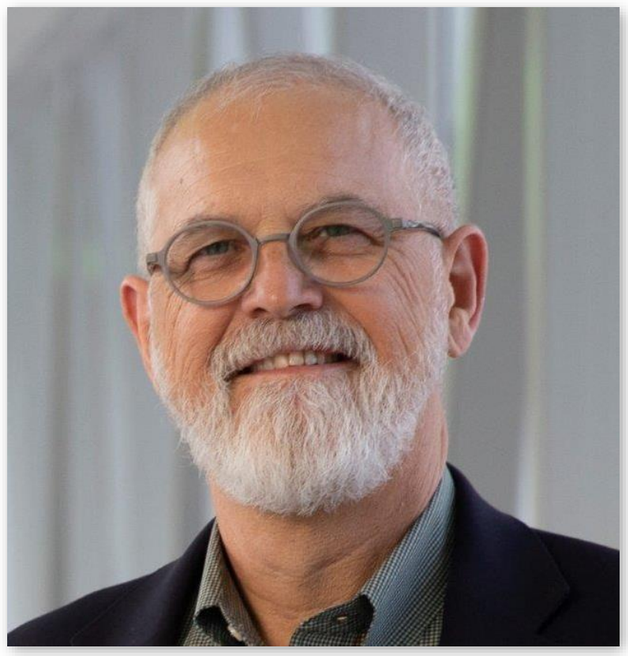


Appendix: Sample FAQs

Why schedule a return visit for a standalone cavity clinic instead of providing SDF as needed at the time of a scheduled medical appointment?
There are advantages and disadvantages clinics should weigh in making this decision. Advantages of the return visit include access to prophylaxis by a dental hygienist (not available full time in our clinic), adequate time to focus on oral health education, informed consent for SDF, and care coordination for dental referral, child is more cooperative with SDF without additional anxiety related to other medical procedures like immunization, and ability to have all patients seen by a physician with additional training and experience with oral exams and the SDF procedure. The major disadvantages of requiring an additional appointment are patient barriers to return for care, which are considerable, and delay in care.

What are the benefits of working with a dental hygienist? Could physicians use SDF without a hygienist?
Benefits of collaborating with a dental hygienist include cleaning of teeth prior to SDF application, additional patient and parent education, assistance with patient positioning and encouragement, and access to compressed air, which we have found most effective for drying prior to SDF application. Physicians can also apply SDF without a hygienist, as we have done on multiple occasions. Toothbrush cleaning should be done prior to SDF application. Cotton rolls and 2x2 gauze can be used for drying. Other medical staff can be trained to assist with set up and patient positioning.

Early childhood caries (ECC) disproportionately affects lower socioeconomic status households and children insured by Medicaid have greater access to medical than dental care. In this article, we described a novel intervention utilizing physician-applied silver diamine fluoride (SDF) in a primary care "Cavity Clinic." Process outcomes were evaluated through chart review and structured field notes. From December 2017-December 2018, 30 patients were treated. Their average age was 5.5 yrs (2-9), 82% were African American, and all were insured by Medicaid. Most had severe ECC. Thirty-eight percent successfully established dental homes through participation. We concluded that it is feasible and acceptable for physicians to treat ECC with SDF in a primary care setting. This strategy holds potential for addressing the epidemic of ECC.



Alan Nyitray, MS, PhD
Associate Professor
Clinical Cancer Center
Center for AIDS Intervention Research
Department of Psychiatry
Medical College of Wisconsin

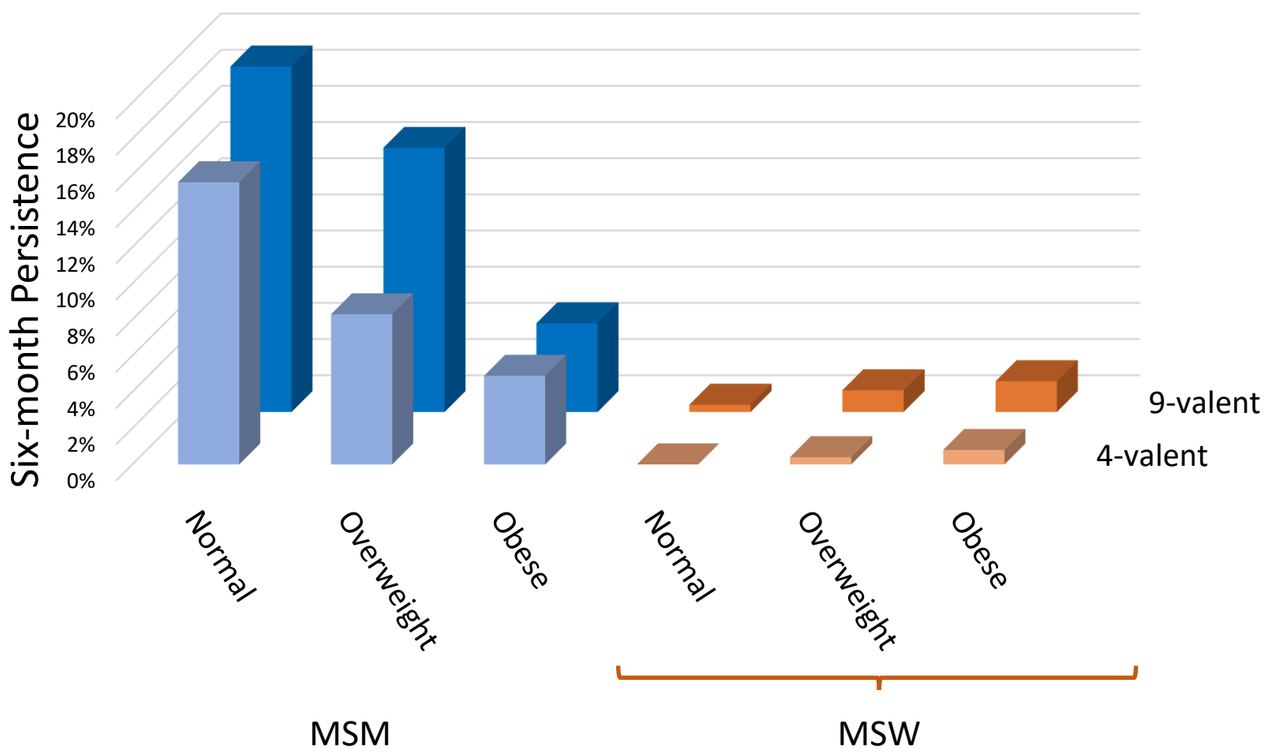
I am an Associate Professor of Epidemiology. I focus on the natural history of anal HPV infection and, more recently, anal cancer screening among gay, bisexual, and other men who have sex with men. An Early Stage Investigator until 2018, I am currently Principal Investigator for two US National Cancer Institute R01 grants which assess protocols for anal precancer and cancer screening including determining compliance with screening, assessment of HPV DNA and host/viral HPV methylation biomarkers, and determining the sensitivity and specificity of self-palpation for anal abnormalities. I have published more the 60 peer-reviewed papers on these topics. Prior to HPV research, I delivered HIV prevention in a service capacity for fifteen years.

"The Association Between Body Mass Index and Anal Canal Human Papillomavirus Prevalence and Persistence: The HIM Study"

Nyitray AG, Peng F, Day RS, et al. *Human Vaccines & Immunotherapeutics*. 2019;15(7-8): 1911-1919.

People with anal HPV infection and squamous cell carcinoma of the anus (SCCA) commonly report no lifetime receptive anal sex suggesting other factors may also increase risk for infection and persistence of HPV in the anal canal. Since obesity may increase the risk for perianal or anal canal lesions, we hypothesized that body mass index (BMI) was associated with HPV infection. HPV genotyping was conducted on anal canal specimens from 328 men having sex with men (MSM) and 1348 men having sex with women (MSW) who reported no lifetime receptive anal sex. Prevalence and adjusted prevalence ratios assessed the association between BMI and HPV infection. Among MSW, obese men had a higher prevalence of anal HPV-16 (3.1%), compared to normal weight men (1.3%). Among MSM, prevalence of HPV decreased with increasing BMI. A similar pattern was observed for persistence. Obese MSW had approximately 2.4 times higher odds of HPV-16 compared to normal weight men. BMI may be positively associated with anal HPV (especially HPV-16) among MSW and negatively associated with anal HPV among MSM which supports continued universal HPV vaccination programs.

Figure 1. Prevalence of six-month persistence for 9-valent and 4-valent vaccine types among men who have sex with men (MSM) and men who have sex with women (MSW) stratified by body mass index (BMI).



Ivan M. Lang, DVM, PhD

Adjunct Professor of Medicine
Division of Gastroenterology and Hepatology
Medical College of Wisconsin

I graduated with BS in mathematics from University of Pittsburgh, MS and PhD in Physiology and Biophysics from Temple University, and DVM from University of Wisconsin. After the PhD, I obtained an NIH Postdoctoral Fellowship in the study of the Central Neural Control of the Cardiovascular System at Texas Tech University Medical School. I then came to MCW in 1982 as a Research Associate in the Department of Surgery to study the neurophysiology of the digestive tract, transferred to the Division of Gastroenterology and Hepatology in 1992, and became full Professor in the Department of Medicine in 2008. My research objective, i.e. study of the neurophysiology of the digestive tract, has not changed since coming to MCW, but currently my interest is centers on the esophagus.

"Characterization and Mechanism of the Esophago-esophageal Contractile Reflex of the Striated Muscle Esophagus"

Lang IM, Medda BK, Shaker R. *American Journal of Physiology. Gastrointestinal and Liver Physiology.* 2019;317(3):G304-G313.

Figure 1. EECR. This figure shows the esophageal effects of distending the esophagus by 2 cm at each level (2.5 to 17 cm from the CP) of the esophagus compared to a spontaneous swallow. Distension of the esophagus causes simultaneous contraction of the esophagus above the stimulus only and sometimes also activates secondary peristalsis. The distending balloon sometimes causes an artifactual rapid reduction in pressure in nearby recording sites. Distension at 14.5 and 17 cm from the CP causes little effect on the esophagus from 2.5 to 10 cm from the CP. CP, cricopharyngeus; E#, EMG recording # cm from the CP; M#, manometry recording # cm from CP, Eso location, location of the balloon from the CP.

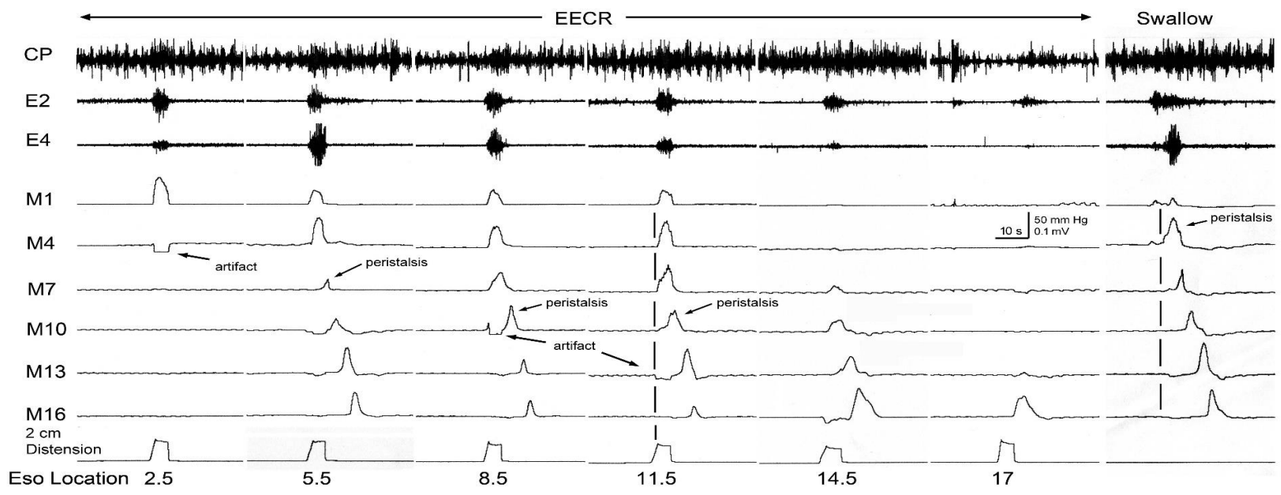
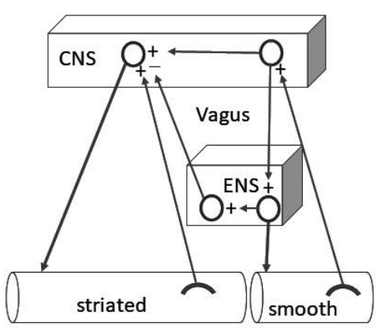
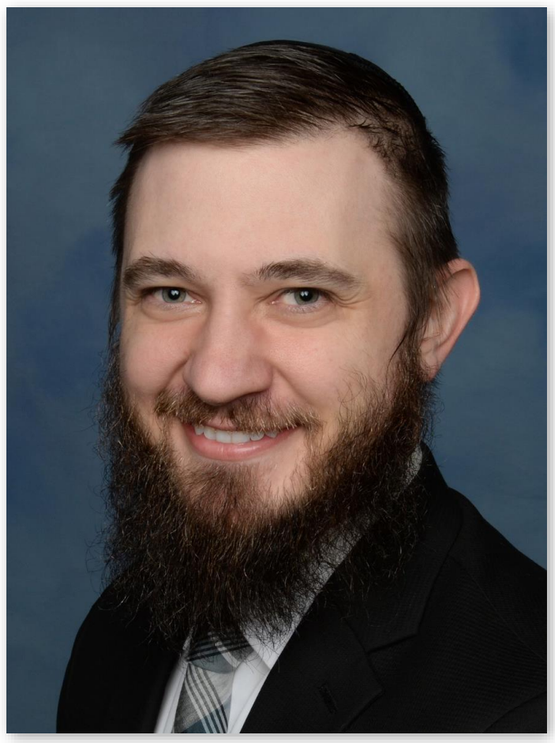


Figure 2. Diagram of Neural Control of EECR. This diagram depicts the neural control of the EECR defined by studies in this manuscript and the literature. The diagram shows that the EECR is activated by stimulation of esophageal mechanoreceptors (12) of the striated or smooth muscle esophagus, transmission to the CNS by vagus nerves (12), integration in the CNS, and activation of esophageal striated muscle vagal motor nerves, as defined by vagotomy and PEN transection. Smooth muscle activation due to smooth muscle distension includes the afferent CNS pathway, but also includes an efferent motor pathway that includes the ENS (16) as defined by the effects of vagotomy (12, 16) and ganglionic blockade (16). In addition, as defined by the effects of ENS blockade, distension of the distal smooth muscle activates CNS inhibition of the striated muscle CNS efferent neurons of the proximal striated smooth which inhibits the EECR. CNS, central nervous system; ENS, enteric nervous system.



We found in decerebrate cats that distension of the striated muscle portion of the esophagus activated esophageal contraction (EECR) rostral to the stimulus only, and distension of the smooth muscle esophagus primarily activated the smooth muscle esophagus. Esophageal perfusion with HCl repetitively activated the EECR of the striated muscle esophagus only. Vagotomy blocked the EECR in all regions of the esophagus. Hexamethonium blocked EECR of the smooth muscle esophagus and sensitized its activation in the striated muscle esophagus. We conclude that an EECR of the striated muscle esophagus exists which is directed in the orad direction only. The EECR is vagally mediated, and may be inhibited by mechanoreceptor input from the smooth muscle esophagus. The EECR may be an important striated muscle esophageal reflex which helps prevent of supra-esophageal reflux.



Bill Gross, MD, PhD
Assistant Professor
Departments of Anesthesiology and Neurology
Medical College of Wisconsin

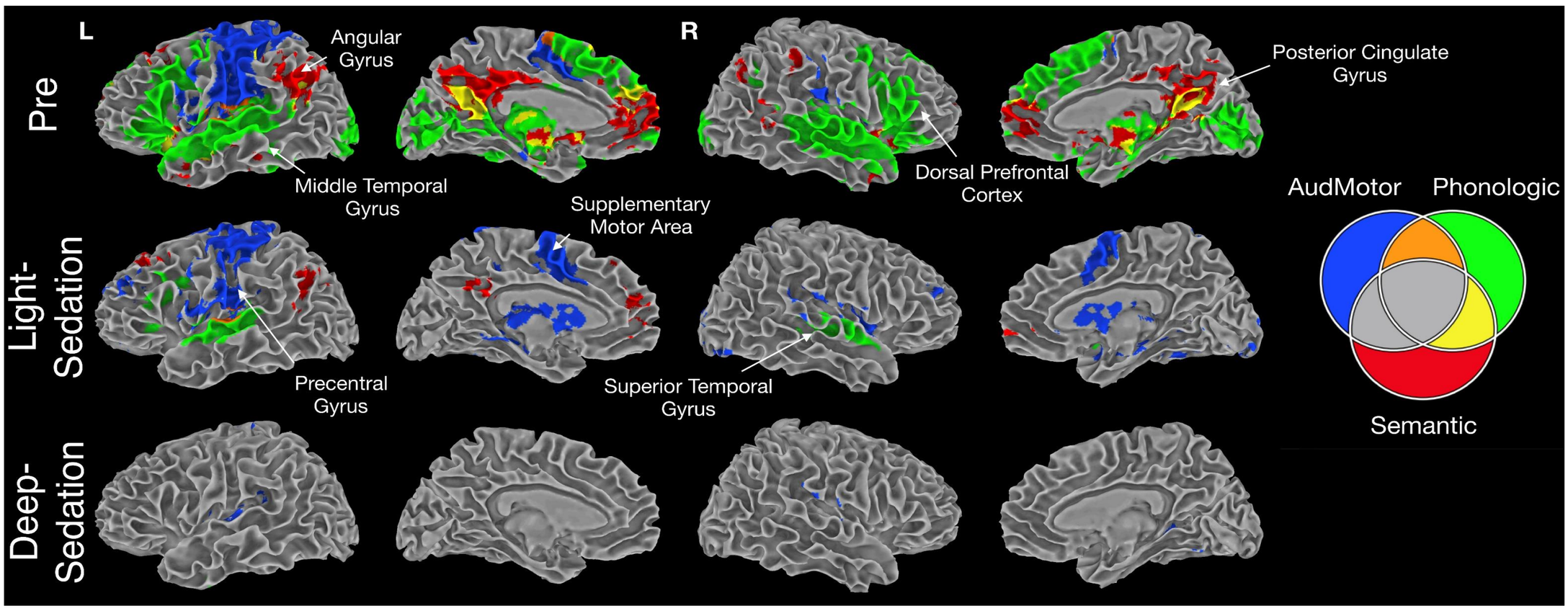
I am both a clinical Anesthesiologist, specialized in Neuroanesthesia, as well as a Neuroscience researcher. My research background is focused on language and consciousness, using both fMRI and EEG. My research goals are to develop our understanding of the brain using basic science techniques, and then developing applications that are relevant to Anesthesia and Neurosurgery.

"Propofol Sedation Alters Perceptual and Cognitive Functions in Healthy Volunteers as Revealed by Functional Magnetic Resonance Imaging"

Gross WL, Lauer KK, Liu X, et al. *Anesthesiology*. 2019;131(2):254-265.

This paper used fMRI to study healthy volunteers as they were sedated with a common anesthetic, propofol. Using different task contrasts, we were able to segment the brain activation into primary motor and auditory processing (AudMotor), phonologic processing (Phonologic), and higher cognitive processing (Semantic). We found that brain activity in higher cognitive areas decreased with the level of sedation, whereas the activity in lower perceptual cortex remained, even under deep sedation. This is consistent with previous work showing that unconsciousness is not associated with cessation of brain activity, but rather a reduction in the communication across brain areas.

Figure 4. Combination of the three task contrasts, designated by color, to illustrate relative overlap.



Sheila Swartz, MD, MPH
Assistant Professor
Section of Hospital Medicine
Department of Pediatrics
Medical College of Wisconsin

I am an internal medicine-pediatric hospitalist in my third year of practice. My time is split 50/50 between Children's Wisconsin and Froedtert Hospital where I take care of hospitalized patients. Of my adult medicine time, about two-thirds is dedicated to the bedside procedure service where we teach residents to do procedures with the use of point-of-care ultrasound. Besides promoting the use of point-of-care ultrasound for procedures and rapid diagnostic evaluation, I am interested in clinical research looking at practice patterns of hospital medicine surrounding the management of neonatal infections. My current topics of interest include HSV evaluation in febrile neonates, duration of antibiotic therapy in neonates with urinary tract infection, and the use of procalcitonin in pediatric hospital medicine.

"Factors Associated With HSV PCR CSF Testing and Empiric Acyclovir Therapy in Young Febrile Infants"

Swartz S, Hadjiev J, Kolinski J, et al. *Clinical Pediatrics*. 2019;58(11-12): 1194-1200.

Neonatal herpes simplex virus (HSV) infection is a rare, devastating disease with an often subtle presentation. We examined patterns of cerebrospinal fluid (CSF) HSV PCR testing and empiric therapy in febrile neonates. Using chart review we identified hospitalized infants age ≤ 60 days with fever ≥38° Celsius who had undergone lumbar puncture. Of 564 infants, 5 had bacterial meningitis and 1 had HSV meningitis. CSF HSV PCR testing was sent in 26.2% and empiric acyclovir started in 17.8%. For high risk infants, 45-57% were not tested for HSV and 61-68% were not treated. In this cohort of febrile neonates, HSV testing and empiric therapy were appropriately associated with seizure, vesicles, and CSF abnormalities. High risk infants were untested and untreated at high rates even in the youngest age group.

Table 3: Associations of Risk Categories by Age with HSV Testing & Acyclovir Therapy

	Patient Risk Category					
	≤21 days		≤28 days		≤60 days	
	High Risk[a]	Low Risk	High Risk	Low Risk	High Risk	Low Risk
HSV Testing						
HSV Tested	46 (54%)	102 (21%)	67 (55%)	81 (18%)	99 (43%)	49 (15%)
Not HSV Tested	40 (47%)	376 (79%)	54 (45%)	362 (82%)	133 (57%)	283 (85%)
Empiric Therapy						
Acyclovir Started	33 (39%)	67 (14%)	47 (39%)	53 (12%)	73 (32%)	27 (8%)
Acyclovir Withheld	52 (61%)	410 (86%)	73 (61%)	389 (88%)	158 (68%)	304 (92%)

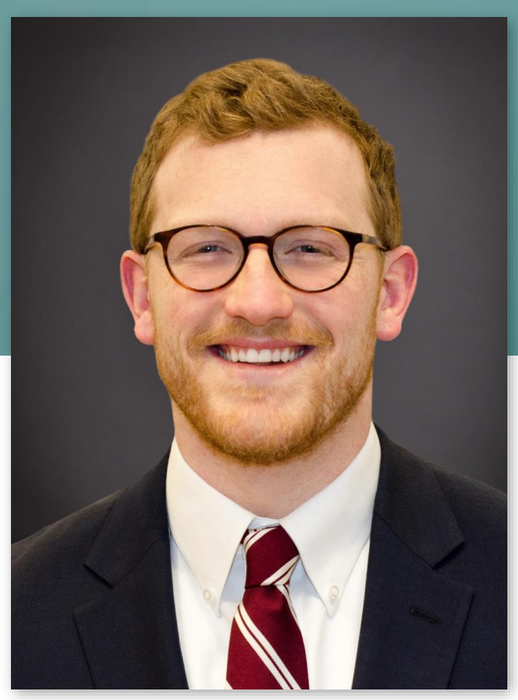
a. Vesicular skin lesions; history of seizure; transaminitis; CSF abnormalities including pleocytosis or elevated protein; ill-appearing (hypotension, irritability, lethargy, delayed capillary refill, poor tone, history of apnea); focal neurological abnormality; abnormal CNS imaging or EEG; maternal vaginal lesions

“Manipulation of the Sphingolipid Rheostat Influences the Mediator of Flow-Induced Dilation in the Human Microvasculature”

Schulz ME, Katunaric B, Hockenberry JC, Gutterman DD, Freed JK. *Journal of the American Heart Association.* 2019;8(17):e013153.

Flow induced dilation (FID) is a physiological mechanism to maintain tissue perfusion and vascular homeostasis. FID in healthy adults is dependent on nitric oxide (NO). However, in individuals with coronary artery disease (CAD), hydrogen peroxide (H2O2) replaces NO. We demonstrated that the sphingolipid ceramide promotes a transition to H2O2, mimicking the endothelial dysfunction found in CAD. Elevations in ceramide are associated with changed concentrations of other sphingolipid metabolites. Manipulating the sphingolipid balance towards ceramide versus S1P favors microvascular dysfunction vs. restoration of NO-mediated FID, respectively. Multiple targets exist within this pathway to treat microvascular dysfunction and potentially improve patient outcomes.

Mary Schulz, BA
Lab Coordinator
Department of Anesthesiology



Ryan J. Lau, BS
MD Candidate, Class of 2020
Department of Pediatrics

“Parent Preferences Regarding Home Oxygen Use for Infants with Bronchopulmonary Dysplasia”

Lau R, Crump RT, Brousseau DC, et al. *The Journal of Pediatrics*. 2019;213:30-37.

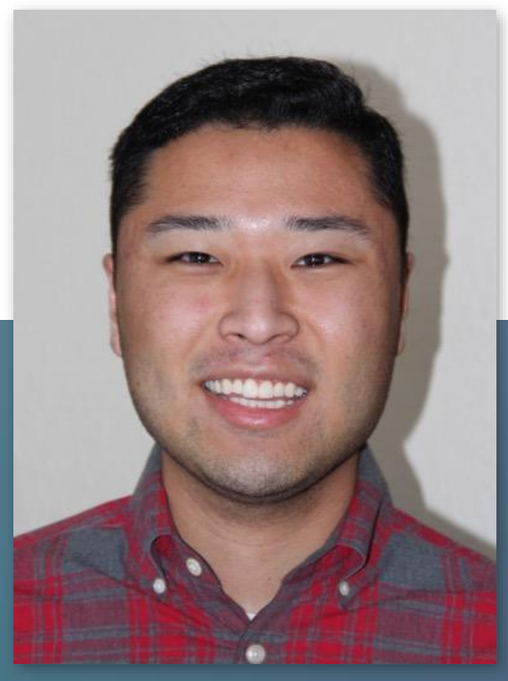
Objective of study was to determine parent preferences for discharge with home oxygen in infants with bronchopulmonary dysplasia (BPD). Parents were presented a hypothetical scenario of an infant who failed room air wean and 2 options: discharge with home oxygen or try longer to wean oxygen. Initial scenario reflected 1.5-week difference in NICU length of stay. Outcomes were increased or decreased until parent switched preference. Of 125 parents, 50% preferred home oxygen before discharge. Of the 110 parents who completed 3-month follow-up, 78% preferred home oxygen. Parents weigh differences in NICU length of stay and readmission risk similarly. After discharge, most prefer earlier discharge with home oxygen. Earlier education to increase comfort with home technology may facilitate NICU discharge planning.

“Safety-Relevant Environmental Sound Identification in Cochlear Implant Candidates and Users”

Hamel BL, Vasil K, Shafiro V, Moberly AC, Harris MS. *The Laryngoscope*. 2019. doi.org/10.1002/lary.28285.

Improved speech recognition and access to nonspeech environmental sounds are two commonly expressed goals among adults with sensorineural hearing loss considering cochlear implant (CI) surgery. We compared the identification of safety-relevant environmental sounds between cochlear implant (CI) users and CI candidates. We found no significant difference in safety-relevant environmental sound identification skills between CI users and CI candidates, with average scores of 68.1% and 67.9%, respectively. Although preliminary, these findings suggest that identification of safety-relevant sounds is a significant area of weakness for both CI-Es and CI-Cs, both of whom may benefit from rehabilitation.

Benjamin L. Hamel
MD Candidate, Class of 2021
Department of Otolaryngology



Wenwen Xu, MD, PhD
Postdoctoral Fellow
Division of Hematology/Oncology
Department of Medicine

“Immune Checkpoint Protein VISTA Regulates Antitumor Immunity by Controlling Myeloid Cell-Mediated Inflammation and Immunosuppression”

Xu W, Dong J, Zheng Y, et al. *Cancer Immunology Research*. 2019;7(9):1497-1510.

Immune checkpoint VISTA controls anti-tumor immunity and is a valuable target for cancer immunotherapy. This study has identified a novel role of VISTA in regulating Toll-like receptor signaling in myeloid cells and controlling myeloid cell-mediated inflammation and immunosuppression. Blocking VISTA augments their ability to produce proinflammatory mediators and diminishes their T cell-suppressive functions. These myeloid cell-dependent effects result in a stimulatory tumor microenvironment that promotes T cell infiltration and activation. We conclude that VISTA is a critical myeloid cell-intrinsic immune checkpoint and that the reprogramming of tolerogenic myeloid cells following VISTA blockade promotes the development of T cell-mediated anti-tumor immunity.

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