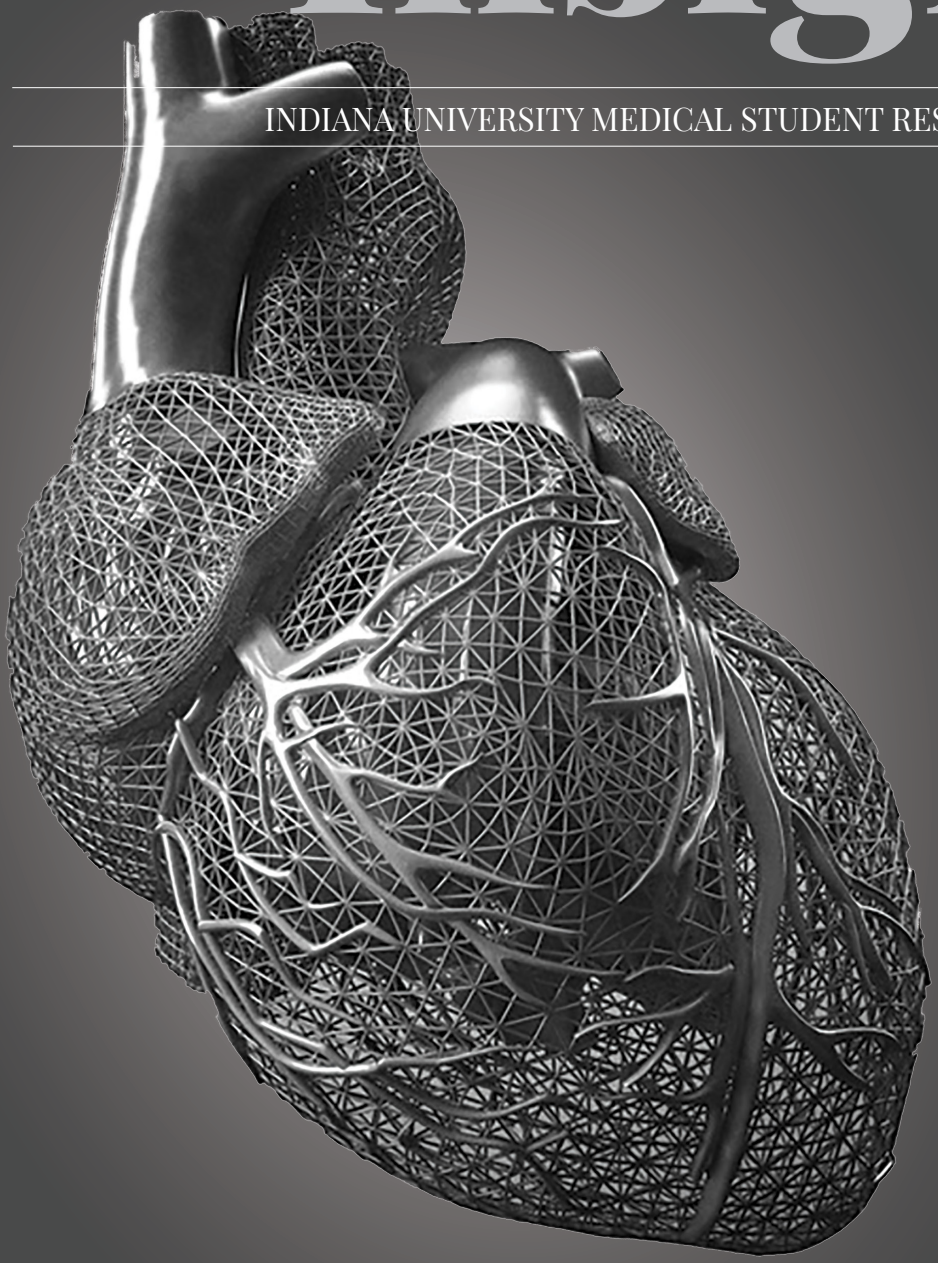
Insight

INDIANA UNIVERSITY MEDICAL STUDENT RESEARCH JOURNAL



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Letter From the Advisor

August 2, 2019

Dear readers,

One of the most remarkable features of the current phase through which medical education is passing is its heavy reliance on multiple choice testing. It may seem hard to believe, but not so many decades ago, there were no such tests, and test scores were not used to select and sort students. Now that such examinations rule the day, it is no surprise that medical schools dedicate much of their curricula and instructional methods to "test preparation." For years, medical schools have made their case that educational quality is increasing by pointing to rising test scores.

This increased reliance on multiple choice exams creates a significant burden for medical students. It promotes the imperative to study in ways most likely to increase test scores, an approach to learning that bears surprisingly little resemblance to the kinds of knowing essential to caring for patients. The sick do not present with multiple choice questions affixed to their chests, and a great deal of medical excellence is focused less on selecting the best response than knowing what questions to ask. Simply put, multiple choice test scores tell us little about who will excel as a physician.

I know a bit about this, having graduated at the top of my medical school class. Even at this early stage of medical education it was apparent that doing so deserved less respect than it garnered, an intuition born out through decades of practice. In truth, I can't even recall my MCAT or Step I scores. What has stuck with me and turned out to mean the most was not my ability to select the one best response but indelible impressions of the very best physicians on the faculty caring for patients as though it were one of the most important things in the world, which to them it was.

Multiple choice testing regimens distract students from knowledge that is poorly assessed by such questions. There are a host of vital medical excellences that such tests cannot assay: among them character, creativity, and compassion. There is no multiple choice test question that can reliably assess a medical student's dedication to truth, originality, kindheartedness toward the suffering, or eagerness to sacrifice in service to a greater good. Worse yet, the fact that such ways of knowing are not tested often fosters the presumption that they do not count.

There is a huge difference between the ease with which something can be counted and the degree to which it really counts, and in medicine what counts most often proves uncountable. I can think of many students with mediocre Step I scores we were eager to recruit into our residency program and others with sky-high numbers that we had no interest in ranking. Why? Such scores may predict how well a student will score on subsequent multiple choice tests, but they offer little insight into who she is, what makes her tick, and the importance she attaches to serving patients well.

Students who wish to thrive in medicine must strive for knowledge on which they will not be tested. This entails learning to listen, asking good questions, reading good books, making time for rich conversations, and amid studying for multiple choice exam after multiple choice exam, growing and developing as a human being worthy to serve the suffering. Our excellence as physicians depends on our worth as persons, and a robust program for developing the best of our humanity extends well beyond multiple choice test scores and curricula built to boost them.

Sincerely,
Richard Gunderman, MD, Ph.D.
Chancellor's Professor
John A Campbell Professor of Radiology
Bicentennial Professor

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

insight

2 August 2019 | Vol 2 | Issue No. 1

In This Issue

We extend our deepest gratitude to Anne Nguyen, Dr. Brittney-Shea Herbert, and the Indiana Medical Student Program for Research and Scholarship (IMPRS) for their support and guidance since the founding of this journal.

From the Editor's Desk

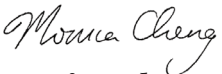
Dear readers,

Insight is a student-run medical student research journal dedicated to showcasing the research excellence and opportunities available at Indiana University School of Medicine. We are proud to highlight diverse student works that strive to improve public health and patient outcomes through research that pushes the folds of medicine. Whether it be looking at cardiovascular disease and methods to improve outcomes or how lead exposure affects our communities, we aim to continue offering a medium that allows our scientific community to not only discover forms of expression through original works of research but also become more invested in the progress of medicine.

This year we have worked to enhance Insight by expanding our editorial board to ensure accuracy of content, updating our website to improve accessibility, and including full-length research articles that have been accepted for publication in scientific journals nation-wide. Through these efforts, we hope to move forward in the way that scientific research moves forward, bettering ourselves as well as all those around us in the process.

As the journal continues to evolve, Insight will continue to be a voice for medical students and faculty—a way for everyone to have a seat at the table and show the amazing work that is being accomplished. Within these pages of our second volume, we invite you to continue on this journey with us, to strive for improvement, and to create a better future for everyone.

Sincerely,



Monica Cheng
Editor in chief
Class of 2021

Honglin Xiao
Editor in chief
Class of 2021

Pediatrics

"These are exciting times for those interested in Biomedical Research and Discovery. Access to emerging cutting edge technologies has permitted researchers to venture into areas of medicine they had only dreamt of. For instance, the advent of genomics combined with bioinformatics has allowed physicians to tailor medicine in a patient specific manner also known as "Precision Medicine" or "Personalized Medicine". This type of medicine is likely to revolutionize health care and will bring about significant changes in how medicine is taught in medical schools with much greater emphasize on research. To keep up with these changes, my advice to you is to arm yourself with the latest laboratory tools, learn to ask the most relevant questions, be imaginative, sharpen your communication skills, work relentlessly, don't get discouraged when failure hits you and find a way to keep the flame in your belly lit at all times. These are some of the key ingredients for a successful and impactful research carrier in medicine. Who said unraveling the mysteries of Life/Nature/God was going to be easy!"

Reuben Kapur, Ph.D.
Pediatrics
Frieda and Albrecht Kipp Professor of Pediatrics

Emergency Medicine

"I have always found it comforting to sit in the back of the room during my education at various stages in my life so that I would not be asked to speak nor ask questions. In hindsight that was counterintuitive, and research has now allowed me to ask questions not only for my own understanding of a subject matter, but also for the advancement of medical knowledge."

Benjamin Nti, MD

Gastroenterology

"The understanding of medicine and the delivery of care is bound to change at a fast pace because of several technological and scientific breakthroughs. One should choose a career path that continually builds on their knowledge base and skill set to allow for the delivery of best care. Equally important is to figure out an interest or passion in medicine that would create constant excitement. Whether it is teaching, research, or service through the creation of new programs...it should be a personal satisfier and not linked to any metrics."

Raj Vuppalanchi, MBBS
Associate Professor of Medicine

Epidemiology and Population Biology

"Public health and research expertise in medicine has never been more important than it is today. Health issues and the disparities that individuals face are persistent and often daunting. Engaging medical students in community-based and laboratory research will provide the real-world experiences that transcend traditional medical teachings which in turn would lead to a greater, more empathic understanding of the people in their care. We need passionate, thoughtful physicians to lead, advocate and problem solve to improve the quality of life of those in our community."

Heidi Beidinger, Ph.D.

Ophthalmology

"VISION is the greatest gift to mankind. While medical education prepares you as tomorrow's physicians, the research broadens your VISION, bringing current clinical challenges to the bench and innovating novel treatments. So keep your EYES wide open and never forget to ask WHY?"

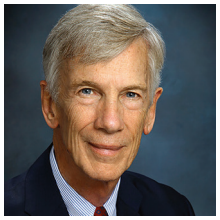
Ashay Bhatwadekar, Ph.D.
August M. Watanabe Translational Research Scholar
Assistant Professor

Otolaryngology & Head and Neck Surgery

"You should enter every patient encounter and research project with a prepared mind and always be asking 'why'. Caring for a single patient will give you instant satisfaction but taking time to advance the field through scientific discover by answering the 'why' has the potential to impact thousands of patients for years to come. So be curious with a prepared mind so YOU can discover the ***why***."

Rick Nelson, MD, Ph.D.
Assistant Professor
Auditory Neuroscience Research Lab

Neurology



"It has been my great good fortune to have careers in two deeply rewarding fields—academic neurosurgery and mathematical neuroscience. I am profoundly grateful to the many undergraduate and graduate students, medical students and residents whom I have taught and from whom I have learned so much. I always encourage them to follow their interests and dreams even if this requires educational preparations in seemingly dissimilar areas. One never knows where careers will lead!"

Robert Worth, Ph.D.
Professor Emeritus of Clinical Neurological Surgery

The Art of Authenticity

Dr. Sidhbh Gallagher is the Surgical Director of the University Gender Affirmation Surgery Program and Eskenazi Transgender Health and Wellness Program, and a practicing plastic surgeon.

BY SEUNGYUP SUN

Seungyup Sun sat down with Dr. Sidhbh Gallagher to learn more about her path to plastic surgery, her experiences with bringing gender-affirming surgeries to Indiana, and the important lessons she's learned along the way.

Seungyup Sun: Thank you for agreeing to sit down and talk with me today. To get started, could you tell us about your educational background and your path to plastic surgery?
Sidhbh Gallagher: I went to medical school in Dublin, Ireland where I was born and raised. When I was still a medical student, I came to Emory School of Medicine for three months. My first exposure to the OR was there. I did a month of general surgery and I thought, "This is pretty cool, but all these guys look stressed out and I'm not really into that." Then I did two months of plastics and I totally fell in love with it. At that point, I was probably the equivalent of an MS2.

I realized that as a foreign graduate, the integrated pathway in plastics was very competitive. So, the path I took was through doing general surgery first – five years of general surgery and then three years of plastics. General surgery was OK, but it was never my passion. I always liked plastics because of the creativity and because the surgeries were all so much more fun. In general surgery, it's "cookbook." You make the incision, you go after the gallbladder, it's step, by step, by step, each of which are memorized and don't really vary. Whereas in plastics, you usually have a problem where the steps aren't clearly defined, which is what I loved about it. It's highly variable, all ages, and all parts of the anatomy.

S: How did you then become interested in the gender affirmation field?
G: There were a few reasons I became interested in the gender affirmation field. Initially, I thought it was fascinating. I knew a couple of trans people and working with that population appealed to me, especially in Indiana because at this point, I knew I was going to try to stay at IU. When I was still in my fellowship in plastics, I did a few rotations out on the West Coast and I saw some of the surgeries. I found it fascinating because it was form and function. You get to make patients look good and they're still quite functional. One of my mentors calls the genital surgeries reverse embryology; it's taking the structures apart and using their embryological analogues to put them back together. That's how I fell in love with it.

I tried to seek out training in the United States but without much success, so I opted to take four months off to go travelling in search of this specialized education. I went to Serbia, Belgium, and Australia to learn the surgical techniques. I returned and began building the practice. Initially, I was unsure of how successful this was going to be but then insurance started paying and things took off from there. I'm the only one doing these surgeries in Indiana and in most of Illinois. There's nobody in Kentucky, and there are limited options in Ohio, so we have a really big catchment area. It's gratifying now that we have a more national presence. For example, I just had a patient fly in from LA for a surgery yesterday.

S: Could you speak on how mentorship played a role throughout your career development?
G: I didn't probably have any real mentors until maybe about three years ago. It was difficult in general surgery because I was in a field that I knew I wasn't going to stay in. I would say most people don't have lifelong mentors but there are people who are there at the right phase. A lot of it is modeling. You meet doctors and certain people who make an impression on you and you're like, "Wow, I want to do that!"

The ideal mentor to me is somebody who is ahead of me and has nailed all the things that I want to do. I don't have to reinvent the wheel; I can collaborate and bounce things off of them. The other thing that I strongly believe in is cross-pollination. You can learn a lot from different fields because they have different perspectives. So, finding a good mentor is a lot more about personality fit.

Right now, I would say my best mentors are an endodontist – a wickedly smart woman – and a famous plastic surgeon named Lee Dellon. Having exposure to these types of minds has inspired me. When I discuss a problem with them, they always put a lot of thought and effort into their advice. They've really helped me with ideas and innovations. At this point in my career, it's ideal to have a "board of advisors" rather than a single mentor.

One mistake I used to make in medical school was to think the most important thing was to fill my brain with medical knowledge, and I believed the way to do that was to isolate myself and to study. I believed social life was the enemy. I've learned the hard way that that's really not true. You get so much further with collaboration. I used to think for example that going for coffee with somebody was a waste of my time and that I should be using every minute to study. As I've gotten older, I've realized that going for coffee with somebody can be really enlightening because you gain another idea or more information. And besides, it's more fun. It took me a long time to fully appreciate that.

S: Thank you for those wonderful insights. I'd like to talk more about your role as director of transgender health programs at both Eskenazi Health and IU Health. Can you speak about the two programs and how they came to be?
G: The Eskenazi Transgender Health and Wellness Program was started by Dr. Janine Fogel just after I started offering gender affirmation surgery. It has been a wonderful, much needed go-to for the transgender community in the state, and I currently work with the program as the surgical director. However, a limiting factor has always been that many of the patients don't have

access to insurance that covers surgery.

I started my Gender Affirmation Surgery Program at IU Health about four years ago. We are the only such surgery program in the state of Indiana, and currently we see about 40% of our patients coming from out of state.

One thing about gender affirmation surgery is that it takes lots of different specialists. IU is a tertiary referral center and really, it's a matter of tapping into that multidisciplinary expertise. We're talking gynecologists, urogynecologists, urologists, family physicians, psychologists, licensed social workers, ENT surgeons, craniofacial surgeons, and endocrinologists. Transgender patients potentially need access to a long list of providers, many of whom are here already. Over the past few years, what we've tried to do is to make a more cohesive program with an easier flow. It's still an ongoing process and requires a lot of administrative support.

S: What challenges did you face in getting that program started?
G: The number one challenge was navigating insurance. Getting patients the care they need paid for is probably still our biggest barrier. The second part was patient education. Most of our patients are reliant on online resources and they're for the most part really poor quality. For that reason, we have embraced social media, which is so powerful. One of my educational YouTube videos has 30-some-thousand views. It's very hard to reach that many patients through traditional ways.

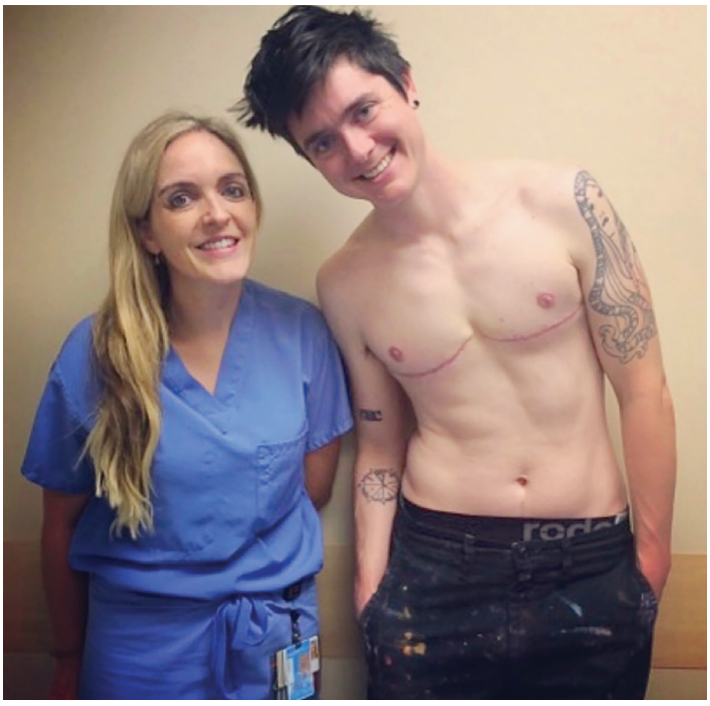
S: Your YouTube channel has an impressive following, and I can tell you're very passionate about patient education.
G: It's so funny because for the first half of my medical career, I was trying to convolute things. I was trying to learn logistic regression and all these statistical ways of making data really complex to put it in journals. That was my entire focus. Now, my focus is on simplifying concepts for the patient to understand, which I really love so much more. We understand now that this concept of "medical literacy" is so important now. When we are dealing with the general public, we are meeting people from very diverse educational backgrounds and one of the most common mistakes doctors make is that when in clinic, they use words that patients don't understand. So, that's my whole focus: trying to simplify and communicate these concepts.

It's particularly important in gender affirmation. If you have appendicitis, you need your appendix out. It's pretty simple. You can safely say to the patient that this is what you need, and this is what we're going to do. In gender affirmation, it's such a personalized decision. A patient needs to be really well-educated in their surgical options or they may choose the wrong option for them. An example of that would be, and we see this all the time, a patient who is male and is transitioning to female. They want to look like a female, they want to function like a female, but they have no interest in having penetrative sex. The most dangerous part of that procedure is to create a vaginal canal that wasn't there before. New vaginas also have to be kept open by dilation for the rest of the patient's life. If the patient doesn't do that, they're going to close it off and it may even cause pain, drainage, and other problems. So, if that patient never wants to use that vagina, why are we exposing them to these risks? We can instead feminize their external genitalia and forego the creation of the vaginal canal in what we call a "zero-depth" procedure. Patients need to know all their options.

S: That is definitely critical. What would you say has been the most rewarding aspect of it all?
G: It's the most meaningful work I've ever done. There's no question.

The surgeries themselves are extremely gratifying. People talk about the concept of "flow," that feeling you get when painting a picture, riding on your skateboard, or whatever it is, and you get really engrossed in what you're doing and it feels blissful. That's why surgeons love operating, because we get into a flow state. We get into the OR, we listen to good music, and often times we have learners with us. Very few things go wrong. We have our protocols set out now, so the surgeries aren't very stressful at all.

We all get that Monday morning feeling – it's human nature – the 'here we go again' thoughts. However, with this work, I can remind myself that the person I will be operating on has been waiting for this day almost all of their life. That certainly gives



SIDHBH GALLAGHER | PHOTO

Dr. Sidhbh Gallagher (left) with her patient (right) post-masculoplasty.

meaning to my day. Or I look on Instagram and, coming into the warmer months, my patients will be there, posting their shirtless selfies of their top surgeries. It's not technically life or death surgery, but a lot of my patients would say these are life-saving procedures.

Another aspect is that I've always admired bravery in people because I have to work hard to push myself to speak up and to be authentic. And what's more authentic than a kid in rural Indiana who understands their identity and is willing to own that—despite all the adversity that they're going to face. Some of my patients pay a huge price to be authentic, and I admire their bravery immensely. It's fantastic getting to work with people like that. Also, traditionally the Midwest hasn't been a welcoming place for the transgender community and the medical profession does not have a good history with trans folks either. It's great to try to right those wrongs.

Perhaps the most gratifying aspect of providing these surgeries here in Indiana is helping to effect meaningful improvements. An example would be that we just recently did our first Medicaid gender affirmation surgery for one of our patients who won a 2-and-a-half-year court battle. As his doctor, I was able to help testify that his gender-affirming surgery was a medically necessary procedure.

S: Could you elaborate on that?
G: Traditionally, Indiana Medicaid didn't cover gender affirmation surgery. I saw Medicaid patients who we submitted but were denied. But now, these fantastic Indiana lawyers, who have dedicated themselves to civil rights, realized very quickly that there is a surgeon in the state who does this work. Before, there wasn't, so they could never fight this battle. Lawyers and patients fought this through the courts. It took two-and-a-half years, but a judge ruled that they should have their surgeries. This sets a precedent. Things are soon likely to improve for all patients in Indiana.

S: Wow. Not only are you fighting this battle on the healthcare side, but you've even gotten involved in the legal side as well. That's amazing.
To continue, can you speak on what role innovation and research play a role in your practice?
G: In the reconstructive world, you're faced with new problems all the time. You constantly have to apply principles and it's really like an art. I know this sounds a little bit grandiose, but you're often not even using the conscious part of the brain. I think most plastic surgeons agree that the plan often comes from the subconscious and from years of experience. We're always innovating. And being in a university or academic center, you also have really bright residents who come in with ideas, as well as all these other experts with their niches. This university is a really good breeding ground for innovation because there are lots of bright minds here and a lot of different disciplines.

However, it doesn't matter how many good ideas you come up with if you don't publish them. One of my mentors says that you can only touch so many patients in your life. But if you come up with something new like he has done over and over again, you're going to touch hundreds of thousands. And that's very true. I didn't like publishing before I started working with him. So, that's one of my goals.

One of the other projects I was working on last year was a drain-free technique of doing a top surgery. We came up with a specific name for it. We're calling it masculoplasty because the guys don't want to get mastectomies. And we just got a paper published of the first 306 of those. It's pretty cool because most people believe when you do a mastectomy, you should put a drain in. We showed in this paper you really don't have to.

Innovation is a huge part of my practice and with that comes gathering the data, watching the data, and publishing it to support what we do because we should always be practicing evidence-based medicine. And it's lovely for plastic surgeons since our results are there for everyone to see on Instagram. You can see the before and after pictures. There's no hiding.

"I've always admired bravery in people because I have to work hard to push myself to speak up and to be authentic. And what's more authentic than a kid in rural Indiana who understands their identity and is willing to own that—despite all the adversity that they're going to face. Some of my patients pay a huge price to be authentic, and I admire their bravery immensely."

S: To wrap this up, do you have any advice for medical students?
G: I'm going to give you my top 5 tips.

1. **Ask**. One thing I never knew, somebody had to tell me this – you can cold call, cold email, even cold DM pretty much any doctor. And we have an obligation, as doctors, to educate. The good ones accept this and understand this. It doesn't matter what level you're at, whether you are an MS1 or you are way into your career. People want to help and you're not bugging them (and if they think you're bugging them, they're the wrong person and you don't want to be with them). Ask to get on projects. Ask to come to clinic. Ask to come and watch surgeries. Your job as a medical student is to ask. Everybody above you knows that they should be teaching you.
2. **Apply for everything**. One fundamental thing I've learned is that if you never apply, the answer is automatically no. For example, coming from Ireland, I never applied for the integrated pathway in plastics because I just presumed I would never get it. But who knows? Since then, I've met other foreign graduates who have gotten in.

   The other thing is that I hear a lot of medical students say, "I'd love to do plastics, but I'm not good enough," or

whatever. No, don't accept that. I'm a foreign graduate, so I was starting at the bottom of the heap. There are definitely ways. It's the United States, it's huge, and it's the land of opportunity. It might take a little bit longer, you might have to take a little detour, but there are always ways. Don't presume you are not good enough for a specialty.

3. **Don't stress about where you're going**. The answers will come with time. You couldn't possibly know what your final destination is. When I was a medical student, I used to stress out a little bit because it was sort of foggy to me what I wanted to do. I was very stepwise; once I saw this, now I could see the next step, now I could see the next step. It's fascinating how people sort of find their way. I was maybe a PGY7 when I found the gender affirmation field, but now it's rapidly becoming the whole focus of my career.
4. **People go through phases**. If you look at your hobbies, you're passionate for a time about something. Oh, I don't know, surfing. And then something else catches your imagination and you're passionate about that instead. I've noticed that some of the most brilliant and successful people have careers that go in phases. Especially with modern careers. It used to be that you would be a 9-to-5 accountant for 40 years. You don't have to do that anymore so try not to worry too much. What your career looks like in the first few years may morph drastically. There's a lot of career adaptability.
5. **Be persistent**. There were numerous times in my nine formal years of training when I was telling the voice of doubt to shut up. I wasted a lot of time doubting. When you're a medical student and you're on your surgery rotation, you're going to be looking at the back of somebody's head for eight hours in a Whipple and saying, "This is nonsense." But sometimes you just have to hang in with it. I had to do five years of general surgery and at the time, I wasn't sure if it was worth it. I was burning out towards the end of my plastic surgery training and thinking, "What have I done? This was a bad idea." But it absolutely paid off. I'm so happy I did it. Hang in there; there will be so many doubts along the way but it's totally worth it. And if it's not, go back to tip four and you can go do something else.

S: Finally, for any students who are interested in serving this population of patients, how can they get involved?
G: From my point of view, students are always welcome either in the OR or at clinic. Best way to get me is either email or social media. And then, to add to that, there's always opportunities for research. The rule is, the earlier the better for research. You can come not knowing anything and you will be told exactly what to do. You just need to be literate. You don't have to come up with a big idea, a lot of these projects are rolling and you can be put in on something, which is super useful.

Also, we now estimate about three to six in a thousand people identify as transgender. That's as common as Type 1 Diabetes. It's no longer optional to be comfortable with this population as a doctor. It's no longer specialized care. It's just exposure, that's it. If you don't know anybody who is trans, it can be unnerving when you first interact with a transgender person. So, just being in clinic will help greatly improve your comfort levels, and no matter what specialty you go into, will ultimately make you a better, more well-rounded doctor.

Dr. Gallagher can be contacted by email at sigallag@iupui.edu. Follow her for updates on her work on social media.
Instagram and Facebook: @drsidhbhgallagher
YouTube: Dr. Sidhbh Gallagher
Twitter: @dr_sgallagher

Oral Presentations

INDIANA MEDICAL STUDENT PROGRAM FOR RESEARCH AND SCHOLARSHIP (IMPRS)

The following works represent the student finalists who were selected to give oral presentations to a panel of judges at the 2018 IMPRS summer internship program—a collaboration of Indiana University School of Medicine and Indiana CTSI.

A Bioinformatics Pipeline for Identifying Functional Explanations of SNP-Phenotype Associations on a Transcriptional Level

◆ **Stephan Hu**, Dr. Xi Rao, Dr. Yunlong Liu

Background: Genome-wide association studies (GWAS) have identified thousands of associations between single nucleotide polymorphisms (SNP) and traits of interest. These associations do not offer biological or functional explanations for differences in phenotype, and sorting through thousands to millions of SNPs makes finding explanations difficult. This study works on filling the gap between these associations and their functional effect on phenotype by identifying variants that are associated due, at least in part, to their effect on a transcriptional level.
Methods: GWAS analysis and RNA-sequencing was run on the post-mortem brain tissue of both heavy drinkers and non-drinkers. Genes that were associated with differential transcript production were overlaid with chromatin interaction data to identify potential enhancers. A number of properties of enhancers, such as their increased stability while bound, their location within topologically associated domains, and their location within transcription factor binding sites, were used to narrow down the list.
Results: Identified enhancers offer a potential functional explanation for the association between a SNP and trait.
Conclusion: A large gap currently exists between associations obtained from genome-wide association studies and a functional explanation of these associations. This study shows how a bioinformatics approach can fill this gap. This work can be extended from enhancers to include noncoding regulation such as miRNA binding and splice variation. The combination of these three will explain a large range of functional variation due to transcriptional differences. Future work should also consider methods of addressing functional differences on translation and post-translational levels. Although here it is used for an alcohol use disorder study, this protocol has the potential to be used in a wide range of statistical genomic settings to find functional explanations for associations between SNP and trait.

Stephan Hu is a third-year medical student currently undecided on his specialty of interest. He states that when it comes to research, having resilience and perseverance is just as important as being a critical thinker. Being able to work through numerous frustrations and setbacks, including many that have nothing to do with the actual science, was critical to the team's success.

Gabapentin Targeting and Bone Mineralization Defects: Proposed Mechanism for Increased Fracture Risk in Patients Taking GBP-Class Anti-Epileptic Drugs

◆ **Jonathan A. Wheeler**, Megan L. Noonan, William R. Thompson, Kenneth E. White

Background: Gabapentin (GBP) is an anti-epileptic drug and first-line therapy for neuropathic pain prescribed to 43 million patients in the US. Unfortunately, GBP use is associated with metabolic bone disease, leading to a 2 to 6-fold increased fracture incidence. Until now, the pathophysiology of this drug-induced bone loss was unknown. We hypothesize that the impaired bone mineralization and skeletal defects is a result of downstream effects of GBP targeting of the α2β1 subunit, the only known GBP receptor.

Methods:

In vitro: Murine mesenchymal progenitor cells (MPC-2) were treated with GBP doses varying from 0.5mM to 50mM while undergoing osteoblast differentiation for 1 or 2 weeks. Mineralization was assessed by Alizarin red stain. Gene expression was measured by RT-qPCR.

In vivo: The bone phenotype of mice lacking the α2β1 subunit was analyzed by longitudinal DXA analyses and examined histologically.

Results:

In vitro: MPC-2 cells treated with 50mM GBP while differentiating for 1 and 2 weeks had decreased osteoblast mineralization and a 7-fold reduction and 4 fold reduction, respectively, in DMP1.

In vivo: Male and female α2β1 knockout mice showed a significant decrease in whole body longitudinal (6 wk – 18 wk) bone mineral density (BMD) in males ($p<0.001$) and females ($p=0.014$), along with severe osteomalacia, displaying unmineralized osteoid in the trabecular compartment of the distal femoral metaphyses.

Conclusion: The impaired mineralization observed following α2β1 deletion, coupled with reduced differentiation of MPC-2 cells treated with GBP suggests that GBP regulates bone quality through a novel mechanism influencing phosphate wasting or 1,25 vitamin D deficiency leading to fracture. With this awareness physicians can monitor these patients for bone mass loss and prescribe drugs to prevent AED-mediated fracture.

Jonathan Wheeler is a third-year medical student.

How did you discover the specialty you are interested in pursuing?
"After two years of learning extensive medical knowledge down in Bloomington, and within the first day of starting my third-year rotations in Methodist Hospital with the Cardiology Consult Service, I knew this was my passion. Being able to take care of the hearts of your patients is such a central factor in their well-being and if I can do this every day of my career I believe I will be impacting every patient I see for the best."

What was your most important takeaway from your research experience?
The research I did with the IMPRS program over the summer between my first and second years was truly transformative for me; it illuminated how basic science research and clinical practice are inextricably linked. Whether it was performing bench work at my molecular genetics lab or shadowing the trauma surgery team at Methodist, that summer showed me how clinical medicine practices could not exist without the discoveries of basic science research and how research is vital to developing the knowledge to progress medical practice and meaningful health outcomes."

Pneumonia in Indiana Nursing Homes: A Retrospective Case Series

◆ **Andrew Shearn**, Kathleen Unroe, MD, MHA1, 2, 3, Jennifer Carnahan, MD, MPH, MA

Background: The Optimizing Patient Transfers, Impacting Medical Quality, & Improving Symptoms: Transforming Institutional Care (OPTIMISTIC) project is a Centers for Medicare and Medicaid (CMS) demonstration project, tasked with reducing potentially avoidable hospitalizations of nursing home residents. OPTIMISTIC-enrolled nursing homes are reimbursed by CMS for treating residents with pneumonia in place. The purpose of this study is to examine the diagnosis, treatment, and outcomes of episodes of pneumonia in OPTIMISTIC nursing homes.

Methods: This case series uses data from nursing home medical records of the seven facilities with the highest pneumonia caseload identified from the OPTIMISTIC database. Cases are from billing episodes spanning November 2017 through April 2018. Within each facility, cases of pneumonia were randomly selected for inclusion. Data were entered into an extraction tool designed by the study team.

Results: Data were extracted from 41 records of unique patients. Despite CMS reimbursing for a maximum of 7 days for treatment of pneumonia, 78.0% of patients were monitored beyond that time and with greater attention than usual care. Of all 41 patients treated with antibiotics, 53.7% were given a fluoroquinolone and 24.4% were given amoxicillin/clavulanate. CURB-65 scores showed 58.3% scored in a range recommending hospitalization. Most patients (87.8%) were stabilized in the nursing home; three (7.3%) were hospitalized, one (2.4%) transferred to hospice, and one (2.4%) died.

Conclusion: OPTIMISTIC-affiliated nursing facilities successfully provide enhanced care for most patients diagnosed with pneumonia in the facilities. Given the high incidence of fluoroquinolone use, one area for improvement is reduction of this medication contraindicated in the elderly.

Andrew Shearn is a third-year medical student with potential interests in anesthesia and psychiatry. "I think that I would enjoy the procedure-based aspect of anesthesiology," he said, "and I also have a continuing interest in mental health following my undergraduate major in psychology."

Minimally Invasive, Non-Terminal In Vivo Muscle Testing of a Porcine Tibia Fracture Model

◆ **Alexander W. Peters**, Benjamin T. Corona2, Anthony J. Milto1, Aamir Tucker1, Alex Brinker1, Michael Savaglio1, Gremah Adam1, Venkateswaran Ganesh1, Zachary Gunderson1, Paul Childress1, Roman M. Natoli1, Melissa M. Kacena1, Todd O. McKinley

Introduction: Tibia fracture can cause prolonged functional deficits and disability. The extent of the soft tissue injury surrounding tibia fractures is a key determinant of surgical care decisions and healing outcomes. To further elucidate the impact of muscle-bone interactions on musculoskeletal healing in a translational model, we have begun to establish a porcine tibia fracture model with or without a corresponding volumetric muscle loss (VML) injury in the adjacent peroneus tertius (PT) muscle (akin to the tibialis anterior muscle in humans). Herein, we present initial muscle function data testing the hypothesis that tibia fracture without VML induces an initial strength deficit that recovers within three months post-injury, while VML injuries present chronic strength deficits. The relationship of muscle functional capacity and fracture healing will be assessed.

Methods: A total of 15 castrated Yucatan minipigs pigs will be evaluated in the following groups: Tibia defect (TD)-only (unilateral, 2.5 cm mid-diaphyseal; fixed with medial and lateral titanium plates), TD+small VML (~20% excision of PT muscle midbelly), TD+large VML. To date, 12 have undergone injury, and 3 have completed the study (TD-only, n=2; TD+small VML, n=1).

In vivo muscle testing of the anterior compartment of the lower hindlimb was performed before and 1, 2, and 3 months post-injury using a custom-made muscle function testing apparatus (Aurora Scientific). Both limbs were assessed. Briefly, anesthetized pigs were placed supine on an operating table, the ankle and knee joints of the tested limb were arranged at 90˚, and the foot was securely fastened to a foot plate attached to a force transducer. Percutaneous needle electrodes were placed on either side of the common peroneal nerve and electrical stimulation was delivered to elicit maximal tetanic isometric torque (0.1 ms pulse width, 100 Hz, 800 ms train, 60 – 80 V) as a function of ankle joint angle from 0 to 40˚ of plantarflexion.

Results: Before injury the non-operative and operative limbs had similar peak muscle strength (11.8±1.0 vs. 10.8±0.6 Nm; p=0.42), and non-operative limb strength did not change during the study (ANOVA p=.89). Relative to pre-injury values, the tibia defect with VML injury presented 71, 77, and 79% strength loss, while the tibia defect-only limbs presented 46, 60, and 48% strength loss at 1, 2, and 3 months post-injury, respectively.

Discussion: The data are limited by low sample sizes reflective of the current progress of this ongoing project and corresponding fracture healing data are not currently available to determine their relationship with muscle strength deficits. The preliminary data do not appear to support the hypothesis, as limbs with TD-only presented persistent strength deficits, though potentially of lesser magnitude than VML injured limbs. The mechanism of strength loss following TD-only may be related to disuse.

Alex Peters is a third-year medical student who is drawn to Emergency Medicine for the excitement and unpredictability of the field as well as the prospect of saving lives. During his summer research experience, Peters valued the opportunity to work in a lab environment and the experience of working together toward a common goal.

Assessing Generalizability of a New-Onset Type 1 Diabetes Biobank

◆ **Colette Ciresi**, Kathleen Wendholt, Maureen Mullen, Carmella Evans-Molina, Linda DiMeglio

Background: Type 1 diabetes (T1D) is characterized by insulin deficiency due to autoimmune pancreatic beta cell destruction. The Wells Center Pediatric Diabetes Research Program is collecting blood and urine samples from children with new onset T1D admitted to Riley Hospital. These samples are being used to discover biomarkers predictive of disease heterogeneity and course. Since not every newly-diagnosed child enrolls in the Biobank, we examined if persons enrolled are similar or different from the at-large population of newly diagnosed children to know how generalizable samples collected are from our newly-diagnosed population.
Methods: Between September 2016 and May 2018, 71 newly diagnosed children (mean age 9.6±4.3 years) and their caregivers were approached by researchers and asked to provide blood/urine samples. Thirty-four consented/assented (as required); 21 had blood and urine collected; 13 urine only. We looked for differences in age, sex, race, BMI, socioeconomic status (based on zip code), and admission blood work parameters between participants and non-participants.
Results: Overall, participants were more likely to be white and have higher admission bicarbonate. Children who provided blood and urine had no other significant differences from non-participants. Children who provided urine only were more likely to be male and have higher admission bicarbonate than non-participants. Currently, we are obtaining data to make comparisons with the general population of all patients diagnosed at Riley.
Conclusion: Our Biobank will provide samples to explore novel biomarkers to facilitate highly targeted therapies and to screen future preventative treatments. As we continue to collect data, it will remain important to monitor and carefully consider its generalizability.

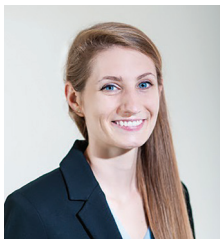
Colette Marie Ciresi is a third-year medical student considering the specialties cardiology or endocrinology. She graduated from IU Bloomington '17 with degrees in biology and animal behavior.

What is your most important takeaway from your research experience?
The blood and urine samples of individuals' various stages of type 1 diabetes (T1D) are extremely valuable to current research, particularly biomarker research. Biomarkers are detectable molecules such as autoantibodies, microRNA, and proteins. Discovering novel biomarkers of disease onset and progression will facilitate the creation of methods to screen populations at risk, personalized preventative treatments for those developing T1D, and targeted therapies for eventual cures of those with established disease.

Assessing Lead Exposure Sources at the Property Scale in Indianapolis

◆ **Emily Hentz**, BS; Gabriel Filippelli, PhD; Noah Springer, Emily Hopkins, MA, BS, BA; Isheka Orr, Rachel Smith, BA

Background: Lead (Pb) was phased out of paint and gasoline over 40 years ago due to neurotoxicity in humans, but has persisted in soils and poses a legacy threat to many. The Indianapolis 46218 zip code has had >10% children exhibiting Pb poisoning. This zip code has had historically high soil Pb levels, and is undergoing redevelopment. We hypothesize that redevelopment will act to re-expose new populations of people to the legacy Pb present in the area.
Methods: We sampled 5 parks and 7 playgrounds. Stratified random sampling based on permit type was used to select properties from 25 issued and 25 closed permits from 527 identified demolition permits. Nearby residential properties were selected, with permission of residents. Samples were taken near the dripline of the house, front yard, and street, or from each quadrant at sites without houses. Samples were dried, crushed, sieved to 150 microns, and assessed using X-Ray Fluorescence.
Results: Mean Pb levels from driplines (1026 ppm) were significantly higher than streets (p=0.001), parks (p=0.002), yards (p=0.001), and demolition sites (p=0.000). Pb concentrations for playgrounds had the lowest median lead levels (42 ppm), while dripline samples had the highest (289 ppm). The EPA standard for children's play areas is 400 ppm.
Conclusion: While all samples from playgrounds were below 400 ppm, children are also likely playing at their homes, where no legislation effectively protects them from potential Pb poisoning and values were found above 400 ppm. An immediate outcome from this project is the education. Residents who agreed to testing (n=42) received results of the test and guidelines to prevent Pb poisoning. More work remains to ensure preventive rather than reactive strategies are employed to protect children's health.



Emily Hentz is a third-year medical student currently interested in gastroenterology. She says, "Regardless of what field I go into, I hope to draw attention to important public health factors affecting my patients." Finding lead in Indianapolis soil brings to light just one of many environmental challenges that our community faces, and should prompt precautionary actions in order to foster a healthy living environment for all.

Cardiovascular Effects of Sodium Glucose Cotransporter-2 Inhibition in the Setting of Ischemia/Reperfusion Injury

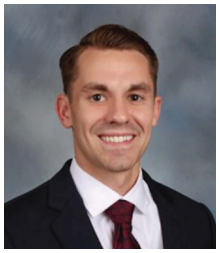
◆ **Sam Luebbe**, Hana Baker, Kieren Mather, Adam Goodwill, Blake Simon, Conner Earl, Johnathan Tune

Background: Recent evidence indicates that sodium glucose cotransporter-2 inhibitors (SGLT2i) significantly reduce the incidence of major adverse cardiovascular events in high risk patients. However, the specific effects of SGLT2i on the cardiovascular system remain poorly defined. This study was designed to test the hypothesis that SGLT2i improves cardiac function and mitigates myocardial infarct size following regional myocardial ischemia and reperfusion injury.

Methods: Lean domestic swine received placebo (n=6) or canagliflozin (n=6; 300 mg PO) 24 hours prior to and the morning of an experiment. Hemodynamics, left ventricular pressure and volume were measured in open chest, swine at baseline, during a 60 min coronary occlusion, and during a 2-hour reperfusion period. The degree of myocardial infarction was assessed by staining with 1% tetrazolium.

Results: At the onset of ischemia, SGLT2i produced a significant parallel increase in both left ventricular end diastolic (85 ± 9 mL to 129 ± 10 mL; $P < 0.05$) and end systolic volumes (29 ± 8 mL to 78 ± 9 mL; $P < 0.01$). This increase in ventricular filling was associated with significant increases in stroke volume ($P < 0.05$) and stroke work ($P < 0.05$) relative to untreated controls swine during ischemia. SGLT2i decreased infarct size from 9.4 ± 2.1% in control swine to 3.1% ± 0.98% in SGLT2i treated swine.

Conclusion: SGLT2 inhibitors significantly improve cardiac contractile function and mitigate myocardial infarct size following regional myocardial ischemia and reperfusion injury in domestic swine.



Sam Luebbe is a third-year medical student currently interested in internal medicine and pediatrics. Specifically, cardiology is the focus of his summer research through IMPRS, and Luebbe's more recent interest in pediatrics stems from his clerkship experience through the Pediatric Intensive Care Unit at Riley Hospital. "I found the resilience of the children to be inspiring," he said, "Their positivity is something I would like to be energized by for the rest of my career."

What is your most important takeaway from your research experience?

Prior to the IMPRS program, I had no research experience. Considering my time in the lab from that perspective, I am so grateful that my mentors were willing to take a chance on me. I now appreciate and will share with others my belief that learners at all levels, regardless of prior experience, can propel research forward.

Honorable Mention

Effect of Frataxin Knockout on Mouse Cardiomyocytes Using DsRed.T3 as a Quantifying Marker

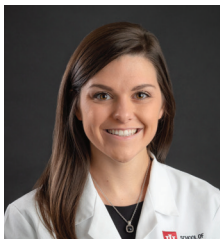
◆ **Eric Galante**, P Melanie Pride, Frances Chen MD, R Mark Payne MD

Background: Discosoma Red (DsRed) is a strong fluorescent marker that has many practical uses for scientific studies. We engineered a transgenic mouse expressing DsRed.T3 only in cardiomyocyte nuclei, and then crossed this with a conditional knockout mouse with loss of Frataxin (FXN) in heart. It is known that dysfunction of the Frataxin (FXN) gene can cause Friedrich's Ataxia (FRDA), a disease associated with ataxia, weakness and dilated cardiomyopathy in humans. The current study aimed to: 1) Determine if DsRed overexpression in cardiomyocyte nuclei would negatively affect cardiac tissue, and 2) Use the DsRed.T3 mouse to determine whether FXN knockout (KO) would cause a loss of cardiomyocytes.
Methods: The study was done by examining three different strains of mice: wild-type, DsRed.T.3 overexpressing Tg mice, and FXN KO mice with loss of FXN in cardiomyocytes. Mice were analyzed using genotyping, frozen immunofluorescent stains, α-actinin and Hoechst, TPLSM, confocal microscopy, western blotting, H&E, echocardiography, and heart:body weight ratios.
Results: DsRed.T3 is localized to the nucleus of cardiomyocytes. At 6.5 months of age, there were significant effects on cardiac function. It was also shown that there was a loss of cardiomyocyte nuclei in the FXN KO group.
Conclusion: This study shows how researchers can study the heart, and more specifically, Friedreich's Ataxia, while also shedding light on how FXN loss may ultimately affect the heart in FRDA patients.

Characterizing the Role of Orbitofrontal Cortex in Social Memory

◆ **Marissa L Bruce**, Katharine D Andrews, Elizabeth A Lungwitz, William A Truitt

Background: Social-enhanced safety learning is a psychosocial process used to reduce fear or anxiety by learning to discriminate fearful versus safe stimuli via a social safety cue. Learning to associate safety with a social cue requires intact social memory. Preliminary data in rats suggests inhibiting the orbitofrontal cortex (OFC) with pharmacologic agents impairs social memory. However, the specific mechanism by which OFC regulates social memory remains unknown. Because the OFC has broad functional implications including valuation, decision-making, social and emotional behaviors, olfaction, and non-social memory, we hypothesized that OFC inhibition was disrupting one of these specific processes, resulting in social memory impairment.
Methods: Cannulated adult male Sprague-Dawley rats were injected bilaterally in OFC with either saline vehicle, or 0.9 mM Muscimol, a GABAA agonist that transiently inhibits local neuronal activity. At 10 minutes post-injection, rats underwent behavior testing for either: social recognition, novel object recognition, social preference (innate gregariousness), or olfactory discrimination.
Results: Rats receiving Muscimol injection, but not rats receiving vehicle injection, demonstrated statistically significant impairment of social recognition, observed as a failure to discriminate between two conspecifics. Alternatively, rats receiving Muscimol injection, but not rats receiving vehicle injection, did not demonstrate statistically significant impairment of novel object (non-social) recognition, innate gregariousness, or olfaction, which were all intact in vehicle injected rats.
Conclusion: These data suggest OFC may be part of a unique neural circuit specific to social memory. Delineating the circuitry of social memory from non-social memory offers exciting possibilities in the advancement of precision therapies.



Marissa Bruce is a third-year medical student who is currently undecided on her specialty of interest.

What is your most important takeaway from your research experience?

With most research, we are looking for significant data—data that shows that what we are doing makes a difference. We are often disappointed if we get insignificant data. But sometimes insignificant findings can help rule ideas out and refocus your research. It can ultimately pave a more focused path to answering your question. This project in many ways embodied this concept. From this project, I was able to learn and appreciate that insignificant findings can be just as important and rewarding as significant data.

Research

Sildenafil As a Rescue Agent Following Intestinal Ischemia and Reperfusion Injury

Hannah M. Moore[1], Natalie A. Drucker MD[1,2], Brian D. Hosfield MD[1,2], W. Chris Shelley BA[1,2], and Troy A. Markel MD[1,2,3]
[1]The Indiana University School of Medicine [2]Department of Surgery, Section of Pediatric Surgery
[3]Riley Hospital for Children at Indiana University Health and Indianapolis, IN

Abstract

Background: Acute mesenteric ischemia carries a significant morbidity. Measures to improve blood flow parameters to the intestine may ameliorate the disease. Sildenafil, a PDE5 inhibitor, has been shown to increase cyclic GMP and has been shown to prevent the effects of ischemia when given before injury. However, its effects as a rescue agent have not been established. We therefore hypothesized that sildenafil, when given as a rescue agent for intestinal ischemia, would improve mesenteric perfusion, limit intestinal epithelial injury, and decrease intestinal leukocyte chemoattractants.
Methods: Eight to twelve-week-old male C57Bl6J mice underwent laparotomy and temporary occlusion of the superior mesenteric artery for 60 minutes. Following ischemia, reperfusion was permitted and prior to closing the abdomen, sildenafil was injected intraperitoneally in a variety of concentrations. After 24 hours, reperfusion was reassessed. Animals were euthanized and intestines evaluated for histologic injury and leukocyte chemoattractants.
Results: Post-ischemic administration of sildenafil did not improve mesenteric perfusion following intestinal ischemia and reperfusion injury. However, sildenafil did improve histologic injury scores in low dose treated groups. No difference was noted in histological injury with 100 mg/kg dose, and all members of the 1000 mg/kg group died and had significantly elevated intestinal injury scores compared to vehicle. Epithelial protection was not facilitated by the leukocyte chemoattractants RANTES, Mip1a, MCP, KC, or GCSF.
Conclusion: Administration of sildenafil following intestinal ischemia appears to protect the intestines via an epithelial mechanism rather than by promoting vascular dilation and improved blood flow to the mesenteric bed.

Hannah Moore is a third-year medical student interested in pediatrics or pediatric neurology. "I have always wanted to work with kids," she said, "and I have always been interested in neurology beginning with my neuroscience undergraduate degree at Indiana University." Her summer experience through IMPRS taught her the importance of following ideas and experimental hypotheses to the very end and keeping an open mind, because there may be findings or significant results that were not thought of or anticipated.

Introduction

Acute mesenteric ischemia (AMI) is a devastating disease that occurs when the blood supply to the intestine is cut off abruptly. The lack of blood flow to the small intestine leads to ischemia, cellular damage, intestinal necrosis and death if left untreated. Despite advances in medical care, mortality rates remain as high as 55-80% [1, 2]. In the pediatric population, intestinal ischemia can readily be observed with malrotation and midgut volvulus, incarcerated hernias, or with adhesive bowel obstructions [3]. Intestinal ischemia can also be seen in other disease pathologies such as congenital heart disease, fibromuscular dysplasia, abdominal compartment syndrome, or aortic thrombosis, to name a few [4]. Currently there are no medical therapies that allow for salvage of the ischemic and/or necrotic intestine. Patients that require small bowel resection can often require long term total parenteral nutrition or intestinal transplantation secondary to short gut syndrome. AMI causes significant morbidity and mortality; therefore, new treatment modalities are urgently needed. The discovery and development of new medical therapies to improve intestinal perfusion and decrease cellular compromise would drastically change the medical management of AMI.

In this regard, sildenafil has been observed to decrease the detrimental effects of intestinal ischemia and end organ injury when given prophylactically before an ischemic insult [5-7]. Sildenafil is a phosphodiesterase five (PDE5) inhibitor that works to decrease the conversion of cyclic guanosine monophosphate (cGMP) to GMP. This effect works to promote smooth muscle relaxation and improved blood flow to organs via cGMP-dependent protein kinase-dependent activation of K channels [8] (Figure 1).

It is often unclear which patients will develop intestinal ischemia until the insult happens. Although it is good to have preventative measures, there also needs to be appropriate rescue agents that can ameliorate injury or even rescue the intestine following injury. Therefore, it is likely that the use of sildenafil could improve and/or protect intestinal function and mesenteric artery integrity following injury. This protection would facilitate improved intestinal blood flow and decreased proinflammatory leukocyte influx into the injured tissue as measured by Regulated on Activation, Normal T Cell Expressed and Secreted (RANTES), Macrophage Inflammatory Protein 1 alpha (Mip1a), Monocyte Chemoattractant Protein (MCP), Neutrophil Activating Protein (KC), and Granulocyte Colony Stimulating Factor (GCSF).

We surmised that sildenafil, when given as a rescue agent after ischemia, would function much like it does when given prophylactically before injury. We hypothesized that sildenafil would stabilize the mesenteric vasculature and improve intestinal mesenteric perfusion, decrease intestinal epithelial injury, and limit leukocyte chemoattractants in the small intestinal tissues when given as a rescue agent following intestinal ischemia.

Method

Animals

The Indiana University Institutional Animal Care and Use Committee approved all experimental protocols and animal use. Male adult wild-type C57BL/6J mice weighing 25-30 grams underwent at least 48 hours of acclimation prior to any experimentation. Normal chow and water were provided and all mice were kept in 12-hour light/dark cycled housing. Animals were bred in house and treated in humane fashion according to the "Guide for the Care and Use of Laboratory Animals" [9].

Ischemia-Reperfusion Model

The murine intestinal ischemia and reperfusion (IR) protocol was performed as we previously described [10, 11]. Briefly, mice were anesthetized using 3% isoflurane followed by maintenance at 1.5% isoflurane in oxygen. Temperature homeostasis was achieved through use of a heating pad and the abdomen was prepped through hair removal and sterile preparation with 70% ethanol followed by betadine. One milliliter of 0.9% normal saline was injected subcutaneously in all mice pre-operatively to account for intra-operative fluid losses. Post-operative pain was managed with subcutaneous administration of analgesia (1 mg/kg buprenorphine and 5 mg/kg carprofen) given immediately following surgery.

Under sterile conditions, a midline laparotomy was performed and the intestines were eviscerated. The superior mesenteric artery was identified and clamped using an atraumatic microvascular clamp. The intestines were then placed back into the abdominal cavity and the abdomen was temporarily closed using silk suture to prevent evaporative losses. Following 60 minutes of intestinal ischemia, the abdomen was reopened and the atraumatic clamp was removed. The abdominal fascia and skin were then closed in a two-layer fashion with suture. Following surgery, animals were placed in warm cage and allowed to recover. Once fully awake and alert, animals were returned to animal housing.

Drug Administration

Sildenafil was obtained through a generous donation from Pfizer (New York, NY). It was reconstituted from its lyophilized powder in PBS daily for experimentation. Following removal of the vascular clamp from the superior mesenteric artery, sildenafil in PBS vehicle (250ul) was administered intraperitoneally. Experimental groups were: 1) PBS vehicle, 2) 0.01 mg/kg sildenafil, 3) 1.0 mg/kg sildenafil, 4) 10 mg/kg sildenafil, 5) 100 mg/kg sildenafil, and 6) 1000 mg/kg sildenafil.

Perfusion Analysis

Intestinal mesenteric perfusion was analyzed using a Laser Doppler perfusion Imager (LDI; Moor Instruments, Wilmington, DE) as we have previously described [11]. Perfusion images were acquired at baseline, at initial clamping of the superior mesenteric artery and at 24 hours following intestinal ischemia (N=8/group). Using images obtained, a region of interest was created around the entirety of exposed intestines. Using three images from each time point, a flux mean perfusion was acquired for the region of interest. Perfusion data was normally distributed and expressed as a percentage of baseline (mean±SEM). After the 24-hour recovery analysis, mice were

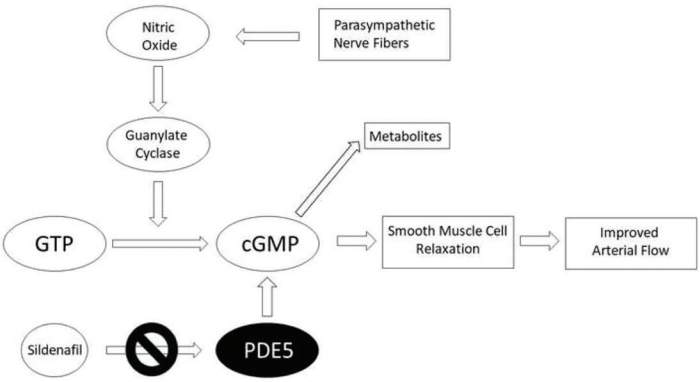


Figure 1: Mechanism of action of Sildenafil. Sildenafil inhibits PDE5, which then works to increase the concentration of cGMP. Elevated cGMP promotes vascular dilation by activation of potassium channels within the vascular bed.

euthanized with isoflurane overdose and cervical dislocation. Intestinal tissues were explanted for further analyses.

Histology Injury Score

Following euthanasia of experimental groups, terminal ileums were harvested and fixed in 4% paraformaldehyde with subsequent dehydration in 70% ethanol (N=8/group). Paraffin-embedded sections were prepared and stained with hematoxylin and eosin. Histological scoring of the depth of tissue injury was performed as previously described: 0, no damage; 1, subepithelial space at the villous tip; 2, loss of mucosal lining of the villous tip; 3, loss of less than half of the villous structure; 4, loss of more than half of the villous structure; and 5, transmural necrosis [12, 13]. Sections were evaluated blindly by three observers. Data were not normally distributed and are presented as median and interquartile range.

Intestinal Chemokine Analysis

Mouse intestinal tissues designated for protein analysis were harvested, snap frozen in liquid nitrogen and stored at -80°C. Once ready to use, intestines were thawed and homogenized in RIPA buffer (Sigma, St. Louis, MO) with phosphatase and protease inhibitors (1:100 dilution, Sigma, St. Louis, MO) using a Bullet Blender tissue homogenizer (Next Advance, Averill Park, NY). Following homogenization, samples were centrifuged at 12,000 rpm to pellet extraneous tissue and supernatants were collected and placed into fresh Eppendorf tubes. Total protein concentration was quantified with the Bradford assay using a spectrophotometer (VersaMax microplate reader; Molecular Devices, Sunnyvale, CA).

Murine intestinal levels of Regulated on Activation, Normal T Cell Expressed and Secreted (RANTES), Macrophage Inflammatory Protein 1 alpha (Mip1a), Monocyte Chemoattractant Protein (MCP), Neutrophil Activating Protein (KC), and Granulocyte Colony Stimulating Factor (GCSF) were quantified using a Bio-Plex 200 multiplex beaded assay system (Bio-Rad, Hercules, Ca) with customizable multiplex plates for murine inflammatory cytokines (Millipore, Billerica, MA). Assays were performed at 1:25 dilution according to the manufacturer's instructions and are reported in nanograms of chemokine per gram of total intestinal protein. Data were not normally distributed, and so are expressed as median and interquartile range. Experiments were repeated to insure accuracy (N=12-13/group).

Statistical Analysis

Data were assessed for normalcy by the Shapiro-Wilk and KS normality tests. Normally distributed data were compared with Student's t test while nonparametric data were compared with Mann Whitney U test. All statistical analyses were performed using GraphPad Prism 7 (GraphPad Software, La Jolla, CA). Parametric data were expressed as mean ± SEM while nonparametric data were reported as median and interquartile range. p-values less than 0.05 were considered statistically significant.

Results

Perfusion

Mesenteric perfusion was noted to be depressed following clamping of the superior mesenteric artery. Once the clamp was removed, reperfusion was allowed (Figure 2). Sildenafil did not offer any significant improvements over vehicle when measuring mesenteric perfusion following intestinal IR. The highest dose of sildenafil tested was 1000 mg/kg. All animals died at this dose, and therefore, their perfusion was counted as 0 since they died before the 24 hour assessment. As a result, the 1000 mg/kg dose had significantly lower perfusion (0% +/- 0%) compared to vehicle (53.03% +/- 11.35) or any of the other doses of sildenafil tested (Figure 3, $p<0.05$).

Histologic Injury

Intestinal epithelial injury scores were significantly improved for the lower doses of sildenafil compared to vehicle (vehicle: 3 (IQR 1.75), 0.01mg/kg: 2 (IQR 2), 1.0mg/kg: 2 (IQR 1.75), 10.0mg/kg: 3 (IQR 3), $p<0.05$). There was no difference between vehicle and the 100 mg/kg dose (3 (IQR 2.75), $p=.309$). The 1000 mg/kg (5 (IQR 0)) dose was significantly worse than vehicle ($p<0.05$), and significantly

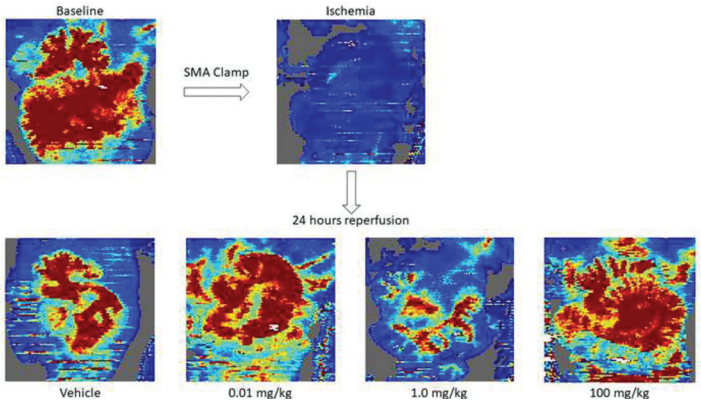
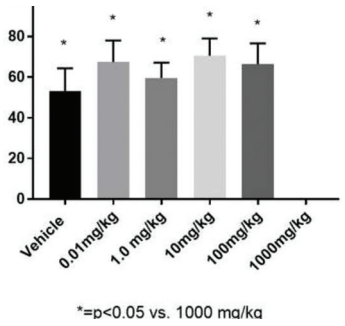


Figure 2: Mesenteric Perfusion. Representative Laser Doppler images assessing mesenteric perfusion with varying doses of sildenafil.

Figure 3: Sildenafil Did Not Improve Mesenteric Perfusion. Mesenteric perfusion was not altered with the majority of doses tested. However, the highest dose tested, 1000mg/kg resulted in significantly lower perfusion compared to any of the other tested groups (*=p<0.05 versus respective vehicle).



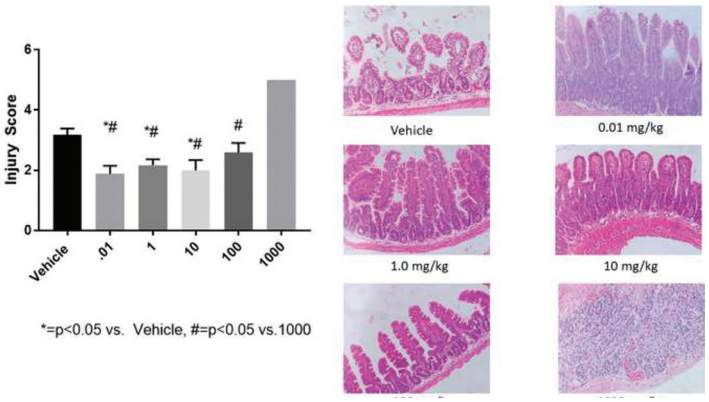


Figure 4: Intestinal Epithelial Injury. Intestinal epithelium had significantly less injury for the majority of sildenafil doses tested compared to vehicle. However, the highest dose tested, 1000mg/kg resulted in significantly worse mucosal damage compared to any of the other tested groups (*=p<0.05 versus vehicle, #=p<0.05 vs. 1000mg/kg).

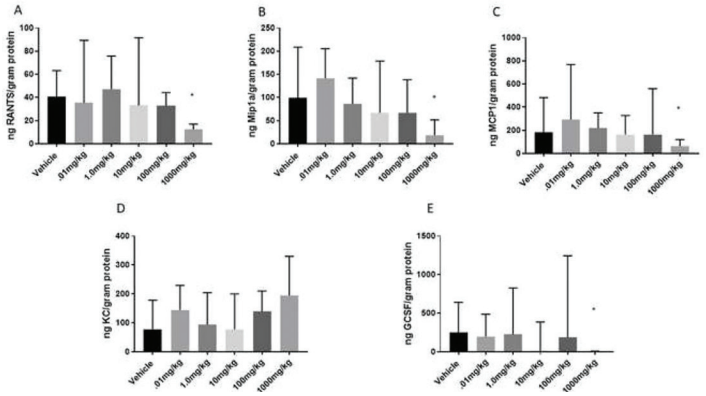


Figure 5: Leukocyte Chemokines. Intestinal levels of (A) RANTES, (B) Mip1a, (C) MCP, (D) KC, and (E) GCSF were not significantly different between vehicle and low/moderate sildenafil treated groups following intestinal IR injury. High dose sildenafil maintained lower levels of 4 of the 5 chemokines tested. (*=p<0.05 vs. Vehicle)

worse than all other tested doses of sildenafil (p<0.05, Figure 4).

Intestinal Chemokines

Intestinal lysates were normalized to total protein concentration. Sildenafil did not offer any significant improvements over vehicle with regard to the leukocyte chemoattractants RANTES, Mip1a, MCP, KC, or GCSF (Figure 5). The 1000 mg/kg dose was noted to have significantly lower RANTES, Mip1a, MCP, and GCSF compared to vehicle (p<0.05).

Discussion

Sildenafil has previously been shown to confer intestinal protection when given prior to ischemic injury [5-7]. Therefore, it seemed natural to expect that it would also provide protection when given following injury. Herein, we observed that sildenafil offered no improvements in mesenteric vascular perfusion, but did decrease the level of intestinal epithelial injury following ischemia. The highest dose of sildenafil was actually detrimental to animals as the 1000mg/kg dose yielded 100% mortality at 24 hours following injury. This translated into no mesenteric perfusion at 24 hours and the highest degree of mucosal injury.

Protective effects have been appreciated in intestinal injury with pretreatment of sildenafil. In a study by Soydan et al., sildenafil pretreatment prevented ischemia induced impairment of acetylcholine responses which could lead to dysmotility and impairments in vascular tone [7]. A 2005 study suggested that sildenafil releases endogenous mediators that work to increase nitric oxide production, which then activates guanylate cyclase to increase cyclic GMP levels. Elevations in these levels can then work to further vasodilate the end organ vascular bed [14]. It is difficult to understand why sildenafil offered no improvements in mesenteric perfusion when used as a rescue agent following intestinal IR. Perhaps a longer period between ischemia and measurement of reperfusion (greater than 24 hours) would have yielded notable differences. However, other studies that we have performed in the past have shown measurable differences in both perfusion and histologic injury after only 24 hours of reperfusion [10, 11].

Previous studies have also suggested that the generation of oxygen free radicals interferes with cellular function through the disruption of ionic homeostasis [15]. These radicals may exacerbate the injury seen following intestinal IR. Additionally, leukocytes have been observed to infiltrate the injured intestine following injury [16], and therefore it would be expected that leukocyte chemoattractants would be elevated as well [17]. However, herein, we did not see any alterations in common leukocyte chemoattractants following low to moderate dose sildenafil administration. This would suggest that the protective mechanism observed is more complex than simply limiting inflammation or leukocyte infiltration within the intestinal epithelium. The 1000 mg/kg dose did demonstrate significantly lower levels of four of the five chemokines measured. This is likely due to the severe ischemia that developed secondary to cardiovascular collapse, and the inability of the circulation to deliver chemokines and leukocytes to the intestinal tissue bed.

The discrepancy between sildenafil's ability to provide protection when given prior to injury versus its limited ability to facilitate rescue following injury is indeed perplexing. In our study we saw only epithelial (intestinal mucosa) protective qualities of sildenafil, but not endothelial (mesenteric vasculature) protection. Given that the superior mesenteric artery was clamped for 60 minutes it is likely that endothelial damage occurred in the mesenteric vessels. It is possible that this damage progressed beyond a state that would allow sildenafil to promote vasodilation and improved perfusion, although several other cellular and drug compounds have been shown to promote vasodilation in the post-ischemic period [10, 18]. Therefore, it is likely something specific to the compound's bioavailability or to the length of time that it takes from drug delivery to onset of action.

Previous studies have also suggested that sildenafil has specific epithelial protective properties as well. A study of cardiomyocytes suggested that the preconditioning of these cells prior to hypoxia was able to decrease necrosis and apoptosis. When eNOS was pharmacologically inhibited or genetically ablated these effects were attenuated [19]. Separate studies on acute lung injury have suggested that sildenafil can also decrease lung epithelial injury independent of vascular dilatation. In this model, sildenafil decreased epithelial leakiness, oxidative damage, and apoptosis [20]. These data would confirm our findings of epithelial protection and suggest a role for sildenafil beyond its vasodilatory properties.

Multiple dose ranges from 0.01 mg/kg all the way up to 1000mg/kg were tested. 0.01, 1.0, and 10.0 mg/kg did not alter mesenteric perfusion or intestinal leukocyte infiltration, but did appear to limit intestinal epithelial damage. The typical dose for humans with erectile dysfunction is between 50-100 mg, which is approximately 0.7-1.5 mg/kg for a typical 70 kg male [21]. This contrasts with the treatment of pulmonary hypertension in infants from the Sildenafil in Treatment-Naïve Children, Aged 1-17 Years, With Pulmonary Arterial Hypertension trials (STARTS-1 and STARTS-2) which used ranges from less than 1.5 mg/kg/day to greater than 7.5 mg/kg/day [22]. We therefore felt that we had an appropriate range of therapy based on previous well-established human trials.

Given the lack of effectiveness of the lower doses to improve mesenteric perfusion, we also elected to try 100 and 1000 mg/kg, which would be considered supra-therapeutic, at nearly 10 to 100 times the doses used in the trials previously noted. 100 mg/kg had no effect compared to vehicle. It offered no improvement in perfusion, mucosal injury, or chemoattractant concentrations within the intestine. However, 1000 mg/kg resulted in cardiovascular collapse and prompt demise within the first 12-24 hours. Clearly this dose had a profound effect on mesenteric perfusion and mucosal injury, albeit an adverse one. It is unclear why the lower doses had no effect on the animal's perfusion, but a measurable difference in mucosal injury, while the largest dose had a completely detrimental effect within the first 12-24 hours. It is likely that the distribution of specific isoforms of PDE5 are

most pronounced in the lungs and central cardiovascular system, and less available in other end organ vascular beds [23]. This would explain why sildenafil has an effect on lungs and erectile tissue, but minimal to no effect on the mesenteric vascular bed. However, this does not explain why sildenafil given prior to injury promotes improved intestinal blood flow while given following injury only appears to protect the epithelial tissue of the intestine.

This study has several limitations. The first is the animal model used to assess intestinal ischemia. In reality, most patients likely develop segmental areas of intestinal ischemia rather than pan-intestinal ischemia. Therefore, this model may be more severe than what is seen clinically. That being said, we feel that because it is more severe than what may be seen clinically, any benefit seen in the model should be translatable to the clinical setting.

Conclusion

Intestinal ischemia is a devastating clinical problem. Post-ischemic application of sildenafil does not appear to improve mesenteric endothelial protection through improvements in mesenteric blood flow but does appear to limit intestinal epithelial injury. This protection is not mediated by ameliorating leukocyte infiltration, as leukocyte chemoattractants were similar between vehicle and treated groups. Further studies are needed to explore the endothelial and epithelial disparities associated with the post-ischemic application of sildenafil as a rescue agent following intestinal IR.

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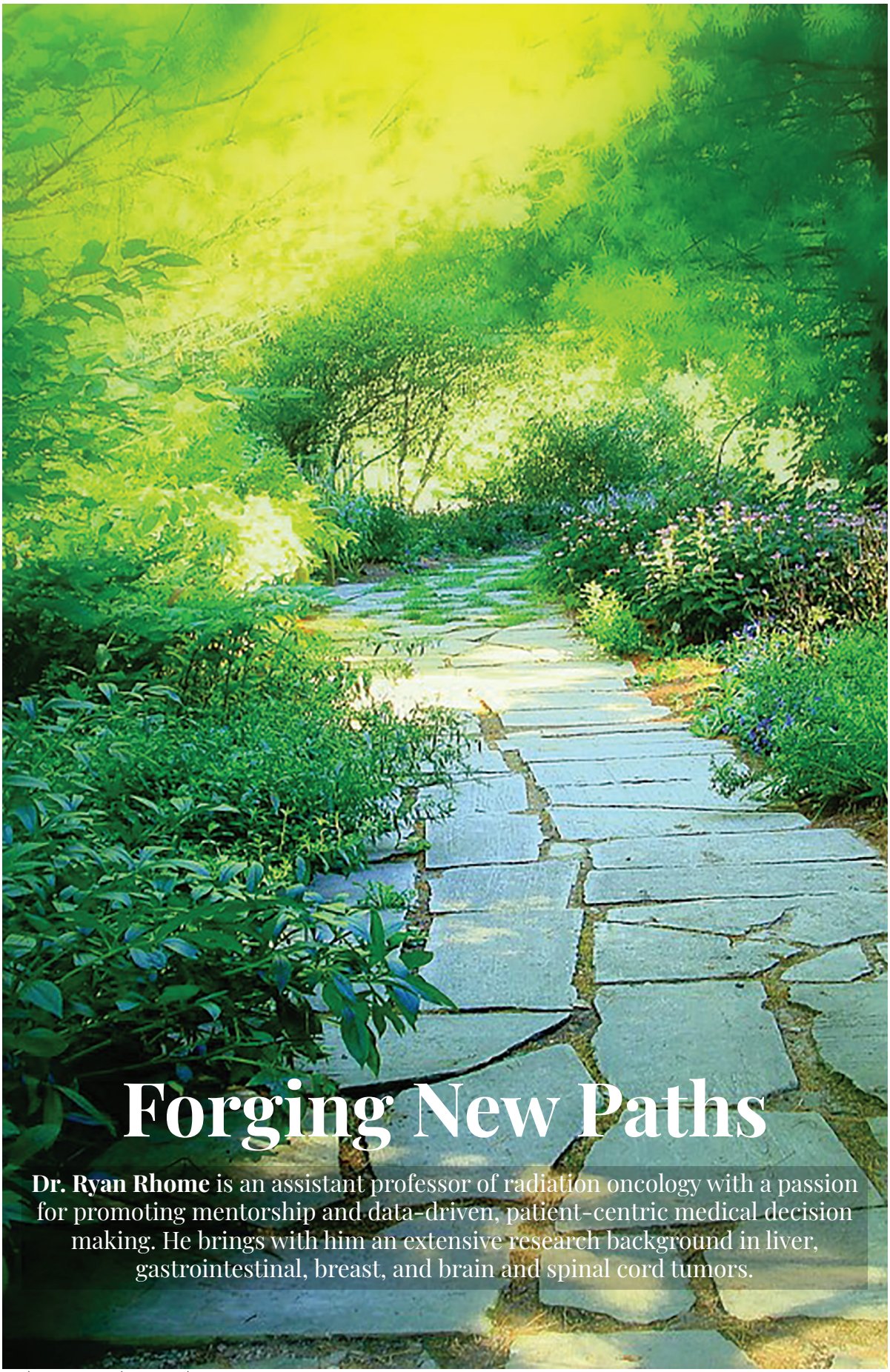
Oncology

Evaluating Inequalities in Breast Cancer Care for Uninsured Patients

◆ **Priya Parikh**, Sydney Keller, Kensey Pease, MD, Theresa Rohr-Kirchgraber, MD

Background: Around 1 in 8 women develop invasive breast cancer in their lifetime. Unfortunately, discrepancies exist in wait times between insured and uninsured women for initial visits, diagnoses, and treatment. Delay in treatment can lead to higher cost, increased tumor growth, and lower survival. We compare two women who noticed breast masses in 2018 and explore differences in timing of their diagnosis and treatment.
Case Studies: A 40-year old insured woman with no significant history felt a mass in her right breast in June 2018. Within two days, she visited her primary care physician and received a mammogram indicating a 1.2cm right breast mass. She underwent core needle biopsy two weeks later and was diagnosed with stage 1A invasive ductal carcinoma. She had a partial mastectomy in August of 2018 and was initiated on adjuvant hormonal therapy three weeks later.

Similarly, a 34-year old uninsured woman with no significant history felt a mass in her left breast in July 2018. She had no primary care provider and waited one month for the mass to resolve. She was then was seen at a local free clinic and received a mammogram three days later showing a 2.9 cm mass in her left breast and ultrasound indicating a thickened axillary lymph node. A month after her initial visit, she underwent core needle biopsy which exhibited stage IB invasive ductal carcinoma. She was started on neoadjuvant chemotherapy in September 2018.
Conclusion: The comparison of these two patients with similar initial symptoms and diagnoses illuminates the inconsistency in wait time for an initial visit and diagnosis. In addition to the increase in cost and worsened outcomes associated with late treatment, there is significant emotional burden associated with waiting for or avoiding care. Thus, increasing efforts are needed to reduce disparities in uninsured populations by supporting free breast cancer screening programs and connecting women with services to resolve abnormal screening.



Forging New Paths

Dr. Ryan Rhome is an assistant professor of radiation oncology with a passion for promoting mentorship and data-driven, patient-centric medical decision making. He brings with him an extensive research background in liver, gastrointestinal, breast, and brain and spinal cord tumors.

SIDHBH GALLAGHER | PHOTO

BY CHRISTINA HUANG

Christina Huang: Thank you for taking the time to sit down with us for this Insight Spotlight Interview. To get us started, please tell us a little about your educational background and your career thus far.
Ryan Rhome: Well, I went to college at the University of Georgia, in the south, and then I entered the MD-PhD program at the Medical University of South Carolina, where I did my PhD in biochemistry and graduated in 2012. Then I went to residency at Mount Sinai in New York City and graduated in 2017. I have been at Indiana University since then.

H: Can you tell me what guided you towards academic medicine?
R: When I was in college, I was fortunate enough to find a very proactive advisor who paired me with a senior geneticist. I worked in her lab starting late in my sophomore year. Her goal for students in her lab was to have a longitudinal experience throughout their college years. I was able to stay in the same lab with the same project. Prior to that, I was just considering clinical medicine alone, but with such an early and positive research experience, I became interested in the hybrid MD-PhD programs to marry the two. With any situation where you have research built into the curriculum or the training, you tend to gravitate towards more academic centers for employment, places that have not just the will but the substrate to do that research.

H: Do you have any advice for medical students on how to get started with research?
R: Yeah, that's a great question and can be quite a diverse and complicated answer. I would say that one way that seems very obvious is to talk to talk to upper classmen—always a good idea in general— for networking and understanding experiences. You can find out about different types of research experiences, ones that are more positive and ones that didn't work out the way they wanted. During your first couple years of medical school, often your lecturers researchers themselves and often will try relate some of their research to what you are learning in the classroom. If you find something interesting, usually they are very happy to have someone stay after class and talk about their research. Sometimes you can do a tour or a rotation in their lab just to see how it feels. Try to get as many types of research experiences as you can and even if it's just on a rotational basis, you can find what clicks with you and what your skillset is best suited for.

H: You make a good point about asking lecturers about their research. In the first two years of medical school, we hardly get any clinical exposure, so it's hard to know what we're interested in. What advice would you give to medical students about picking a specialty?
R: This is obviously a very hot topic in medicine. Everyone's trying to do this from day one. I would say that the first thing is to keep an open mind—seeing the subjects that you come across as potential careers for you. I think that dropping in on interest groups, even if you don't become a part of the group, is really helpful. In the end, your third year of medical school is where you see the reality, and there are definitely things that you can find yourself interested in on paper that may not translate to that reality. And also, it goes the other way. Things in practice can seem a lot more interesting than your experience in a lecture hall. Just try not to discount anything.

Also, make connections with people who are a few years ahead of you in class and pick their brains about their experiences. That was one advantage of being in the MD-PhD program, since my original classmates went on to their third and fourth years, then residency before I even got to that point. I was able to ask about their experiences in the hospital and on the residency trail. It's fine to take time to make these decisions. It's even fine to take extra time. If you need to take an extra year, as long as you make it useful and productive, it can be helpful. That year on the timeline of your career is going to be a blip. Don't be afraid to do that kind of thing.

H: How did you get started in mentorship and what would you say to medical students about how to find the right mentor?
R: I wanted to model my mentorship ethos after the people who mentored me. My college advisor was the first person that really guided me down a path. They were really careful to attune their recommendations and experiences to me. So just get to know the person. Get to know what they like, what they're strong in, what that person's really interested in doing, and where they really want to guide their own careers. The best productive relationship between a mentor and a mentee is something that's mutually beneficial. I could give a particular project to anybody and would get variable results on both sides because it just might not be a good fit. But if you really get to know that person, either in clinic or working with them in a lab setting, that's a really good way to have a personalized experience because one size does not fit all. Also, have the willingness to—I don't want to say be wrong—but to go down a path that won't be right for you. It's important to take introspective stock of what your experience was and what you want out of the next one. Each time, you learn a little bit more and finally you get to where you fit. That's how I did it as a mentee, so I try to keep that side in mind as a mentor. It's an evolving process.

H: You mentioned not being afraid of going down the wrong path. Can you give me an example of when you thought you were going to do something and then completed changed your mind?
R: Yeah, I do. My PhD is in biochemistry. The things I was most interested in my first two years of medical school, on paper, were oncology and infectious disease. I picked a lab that was a largely an infectious disease lab that was in an oncology focused department. During that time, I did some clinical shadowing and I found out that the infectious disease side was not that good of a fit for my personality but oncology was. The focus of my PhD thesis is more infectious disease. That's not the way I took my career, and it's not the way that I took my current research. That was a little bit of a divergent pathway, but the fundamentals of both the basic lab work and research were still there.

I think people are just so afraid of it being right and perfect from the start. I understand that, and obviously in an ideal situation you would not waste a second of your time doing anything else. Some of my favorite experiences in medical school were things I didn't think I would like but have still been extremely valuable. For example, I still use lessons I learned from my psychiatry rotation when I'm counseling patients. There are still things to learn from the fields you are not going to go into.

Dr. Rhome can be contacted by email at rrhome@iu.edu

Indiana University Student Research Symposium

The following works were accepted for presentation at the Indiana University Student Research Symposium, which serves to highlight student research from all levels of experience in order to ignite interest and support for scientific inquiry in the IUSM medical community.

A Rare Multiple Endocrine Neoplasia Misdiagnosed as Puetz Jegger's Syndrome

◆ **Hasnain F**
Contributing authors: Vaid S, Morgan R

Carney Complex (CNC) is an extremely rare multiple endocrine neoplasia caused by a germline inactivating mutation in protein kinase A type I-alpha regulatory subunit (PRKAR1A gene). The mode of inheritance is predominantly autosomal dominant; 25% of cases are due to de novo mutations. Only 750 world-wide cases have been reported. Most patients are diagnosed in the second or third decade of life. Clinical features include cutaneous myxomas, rare angiomyxoid nodules, lentiginous skin pigmentation, cardiac myxomas, and rare malignant endocrine tumors. These include but are not limited to prolactinomas, thyroid tumors, primary pigmented nodular adrenalcortical disease (PPNAD), psammomatous melanotic schwannomas, and large cell-calcifying Sertoli cell tumors (LCCSCT). Diagnosis is often challenging as disease manifestations occur sporadically over a large span of time.

A 28-year-old Caucasian male with PMH of HFrEF, HTN, Sertoli cell tumor status post orchiectomy, multiple vertebral fractures, and surgical removal of lip angiomyxoma presented to clinic for low testosterone levels. Upon physical examination, he was noted to have markedly distinct Cushingoid features with multiple facial lentigines above his eyes and on his lips. Based upon his incredibly eclectic medical history and unique exam findings, we conducted diagnostic workup to link all the findings. Computed tomography (CT) of his abdomen and pelvis was performed due to ACTH independent hypercortisolism, revealing a left adrenal nodule.

The combination of lentigines, skin myxomas, cushingoid features, rare lip angiomyxoma, LCCSCT and hypercortisolism lead to the diagnosis of Carney Complex. More than two major criteria for diagnosis were met. Treatment included bilateral adrenalectomy. Pathology report confirmed PPNAD. PPNAD and LCCSCT are extremely rare tumors almost exclusively linked to Carney Complex. Interestingly, family history did not reveal endocrine disorders, cancers, or severe illnesses. Genetic testing for a de novo PRKAR1A gene mutation is pending.

EMS Provider Bias

◆ **Heather B**
Contributing authors: Lardaro T

Purpose: To investigate the potential existence of EMS provider bias regarding the three level 1 trauma centers in Indianapolis: Eskanazi, IU Health Methodist, and St. Vincent's. Additionally, we aim to investigate the correlation this may have with the number of EMS transports to each of these facilities, comparing several reasons for transport (e.g. medical vs. trauma).
Methods: Paramedics and EMTs working for IEMS were emailed the opportunity to participate in the study using a survey via REDCap. That data was complied, analyzed, and correlated to quarterly reports on number of transports to each of these major hospitals from IEMS.
Conclusion: Based on the results of this study, we will be able to determine if the bias present among EMS providers impacts the number of transports that they bring to each of these Indianapolis level 1 trauma centers. Indianapolis is uniquely suited for this study because it is one of the few locations with multiple level 1 trauma centers in the same city. EMS provider bias may have an impact on transports in this particular situation. Level 1 trauma centers require a certain number of transports to their hospital to retain their certification. Therefore, the conclusions of this study will be important to these centers and give them some direction for quality improvement.

An Atypical Presentation of Mucormycosis in an Immunocompetent Host

◆ **Neupane A**
Contributing authors: Grabek L, Hui Y

Purpose: Many patients often present to the ED with one problem and if admitted, subsequently develop a novel medical issue which can often be more diagnostically challenging even for the advanced clinician when the presentation is atypical. Herein we present one such clinical case of mucormycosis in a patient who complained of headache and unilateral vision loss with a nonspecific soft tissue mass on CT imaging that had no significant risk factors.
Methods: Chart review of a patient with a prolonged hospital course.
Results: The patient was not a candidate for surgical debridement due to the deep location of the mass. She was started on liposomal amphotericin B in the hospital for 2 weeks and switched over to an oral azole afterwards upon transfer to a skilled nursing facility. She passed away a few weeks later.
Conclusion: Because of the significant morbidity and mortality associated with this condition, prompt diagnosis and treatment are paramount. In our case, high suspicion of a nefarious process drove the treatment team to invasive biopsy faster, which clinched the diagnosis. Even with appropriate treatment, patients with mucormycosis suffer a high rate of morbidity and mortality.

Gardnerella Vaginalis Causing Pulmonary Infection in Young Adult: A Novel Case

◆ **Bittar, J**
Contributing authors: Gazzetta, J

Gardnerella vaginalis is an anaerobic, gram-variable bacterium primarily found in vaginal microflora of women. Previous reports of G. vaginalis cultured in men are few and have primarily been limited to the gastrointestinal and genitourinary tract. Few reports of G. vaginalis causing severe infections have been reported in the literature, including septicemia and two cases of perinephric abscess. There has been one previously reported case of G. vaginalis causing pulmonary complications that occurred in a male alcohol abuser. In our case review, we aim to demonstrate an unusual source of a pulmonary infection and highlight the importance of proper microbial isolation to guide treatment. Our patient is a young male who presented following multiple gunshot wounds including one to his head causing an intracranial hemorrhage, hydrocephalus, and a dural sinus thrombosis. His hospital course was complicated by a decline in neurological status treated with a craniotomy and external drain placement and multiple pulmonary infections. During his fever work-ups, he found to have G. vaginalis on mini-bronchoalveolar lavage and was subsequently treated with metronidazole. After treating his G. vaginalis pneumonia and other infectious sources, namely Haemaphilus influenzae and coagulase-negative staphylococcus pneumonias, his fevers and leukocytosis resolved and he was successfully discharged to a rehabilitation facility for neurologic recovery. To our knowledge, this is the second reported case of G. vaginalis isolated from a pulmonary culture and the first in a previously healthy, immunocompetent young male outside of the urinary tract.

Body Dysmorphic Disorder: Prevention, Detection, Treatment

◆ **Roesler A**
Contributing authors: Jager S, Karim A

A 46 year old female presented with worsening migraines for three months along with a history of anorexia, nausea, vomiting, confusion, lethargy, menorrhagia, epistaxis, hematochezia, and constipation. Renal biopsy showed thrombotic microangiopathy with patchy acute tubular necrosis and mild hyaline arteriosclerosis. No specific glomerular immune deposits or light chain restriction are seen by immunofluorescence microscopy. This renal biopsy showed the etiology was drug-induced thrombotic microangiopathy from phentermine use. A thorough history revealed that although she had a normal body weight, she was extremely concerned about her appearance and had a history of taking phentermine because of her body dysmorphic disorder. This case report will help others diagnose body dysmorphic disorder quicker in the future to avoid the many consequences of not treating it. Physicians should become more informed on body dysmorphic disorder to understand how to detect, treat, and prevent it in order to better advocate for women's health.

Sleep-Related Issues in Pregnancy

◆ **Prieto J**
Contributing authors: Richardson R, Bennett RD, Haas DM

Background: Sleep position during pregnancy has been associated with several adverse pregnancy outcomes such as gestational diabetes, preeclampsia, and late preterm birth. Although these associations have been established, less is known about sleep habits in pregnant women. The objective of this study was to characterize sleep during pregnancy.
Methods: An anonymous 14-question survey about position, disturbances, and duration of sleep was distributed to pregnant women in two clinics in Indianapolis, IN to determine what is predominant during pregnancy. The questions were developed through literature review and expert consensus. The survey was approved by the IRB.
Results: The mean age and gestational age for the 85 women surveyed was 28 years old and 25 weeks gestation. The racial/ethnic distribution was 50.6% black, 28.2% white, 15.3% Hispanic, and 3.5% other. 60% of women reported falling asleep on their left side and 35.3% reported falling asleep on their right side, but 41.2% and 40% of women reported waking up on their left and right sides, respectively. Most pregnant women surveyed sleep 6-8 hours (38.8%) and 4-6 hours (29.4%) and use extra pillows (66.7%) between their legs (48.2%) for comfort. 61.7% of the women had heard about or been talked to about different sleep positions during pregnancy and were equally likely to hear about it from a nurse, doctor, other healthcare provider, friend, family, or website. 32.9% of the women had been told they snore and 95.1% wake up during the night.
Conclusion: Of the pregnant women surveyed, most fall asleep on their left side and sleep 6-8 hours during pregnancy. The majority wake up in the middle of the night and one-third had been told they snore. Given the associations of poor sleep with adverse outcomes, sleep hygiene discussions should be a routine part of prenatal care.

Acquired Acrodermatitis Enteropathica (AE) after Enteral Nutrition in an Elderly Female

◆ **Bittar JM**
Contributing authors: Etling A, Bittar N, Hess K, Rohr-Kirchgraber T

Elderly women are particularly at risk for zinc deficiency, and accordingly, for AE. AE is a disorder of zinc metabolism, resulting from either impaired absorption or deficient intake, and manifests as erythematous, desquamative dermatitis, cheilitis and diarrhea. Zinc deficiency and patients on long-term enteral nutrition have been linked, indicating the need to supplement zinc or add it to tube feeding solutions. Dysphagia is a significant problem in elderly women, with one study showing that 72% of elderly women with no history of dysphagia failed a screening swallow study.

A 72-year-old female presented to dermatology clinic with 2-month history of progressive rash on her scalp, lips, oral mucosa, trunk, and extremities. One day prior, she had a feeding tube removed that was in place for 3 months for dysphagia. She reported severe weight loss from poor eating, but was otherwise asymptomatic. She had no recent medication changes.

On exam, her scalp, arms, chest, back, legs, feet and periorificial area had large ill-defined and well demarcated red, scaly thin plaques. She also had erosions on vaginal lips, and erythema in the perianal area and oral mucosa. Erythematous macules with peripheral scale were noted on the feet. Laboratory evaluation showed zinc-deficiency with a serum zinc level of 551 mcg/L (Reference Range 700-1200 mcg/L), while ferritin, 25-OH-vitamin D, and Vitamin B12 were within normal limits.

A diagnosis of acquired Acrodermatitis Enteropathica (AE) was made and treatment was initiated with zinc gluconate. Zinc levels returned to normal limits and skin lesions promptly resolved.

Dermatomyositis-Like Reaction in a Patient Treated with Etoposide

◆ **Bell MC**
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Drug-induced dermatomyositis (DM)-like reactions have been reported in association with use of a variety of medications. Diagnosis can be challenging due to variability in skeletal muscle involvement and overlapping clinical presentation with drug induced cutaneous lupus. We report a case of a 36-year-old Caucasian male with a history of stage IV Burkitt's lymphoma, in remission, and hemophagocytic lymphohistiocytosis (HLH) who presented to the clinic with a 4-month history of an intensely pruritic photo-distributed papulosquamous eruption. Onset of eruption was two weeks after the patient had undergone treatment with etoposide, dexamethasone, and IVIG for his HLH. He denied muscle soreness or weakness. Physical exam revealed bright erythematous plaques with overlying scale on the bilateral upper arms, neck, and central face involving the nasolabial folds. On biopsy, there was perivascular and periadnexal lymphohistiocytic infiltrate with interface dermatitis. Lab evaluation revealed a mildly low C4, negative ENA, and normal ANA and C3 values. Given the clinical presentation, biopsy results, and coincident administration of medications, amyopathic etoposide-induced DM was suspected. No further etoposide was administered and treatment with hydroxychloroquine was initiated to hasten resolution. Prior to beginning hydroxychloroquine therapy, the patient noted improvement in his rash. DM is a paraneoplastic syndrome in patients with malignancy, however this typically presents within 3 years of malignancy diagnosis. The strong temporal connection between cessation of the etoposide and resolution of the DM, further supports a drug induced etiology. In cases where there is no underlying malignancy or autoimmunity, patients should be evaluated for these conditions.

Delayed Tracheal Rupture After Thyroid Lobectomy

◆ **Svenstrup T**
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Purpose: To report the rare presentation of delayed tracheal rupture with subcutaneous emphysema 12 days after a thyroid lobectomy.
Methods: We present the history, physical exam, radiographic findings, intraoperative images, and management of a patient with delayed tracheal rupture after thyroid lobectomy. We also performed a related literature review of the presentation, risk factors, and management of patients with this condition.
Results: A 41-year-old female presenting with globus sensation and pressure during swallowing for several months is found to have a large benign thyroid nodule on fine needle aspiration. The patient subsequently underwent an uncomplicated right thyroid lobectomy procedure and was discharged to home. On postoperative day 12 the patient presented to the emergency department with acutely worsening severe anterior neck pain, a productive cough, and cellulitic skin changes. CT imaging showed soft tissue edema and subcutaneous emphysema in the thyroid bed extending from the supraglottic larynx to the sternal notch as well as glottic narrowing. The patient was immediately brought to surgery for exploration that found three areas of tracheal rupture between each of the first, second, third, and fourth tracheal rings. A tracheostomy was then placed below the rupture, wound irrigated, and the defect closed with a strap muscle flap. The patient was discharged without issue four days later, and direct laryngoscopy 16 days after the repair showed excellent healing of the rupture. The patient later had her tracheostomy removed without issue.
Conclusion: Delayed tracheal rupture should be suspected in post-operative thyroid lobectomy patients presenting with respiratory distress, coughing, and subcutaneous emphysema. Treatment can be achieved by muscle flap placement, primary closure, or tracheal resection when indicated.

Rapid Progression of Optic Nerve Sheath Meningioma During Surrogate Pregnancy

◆ **Burgett KM**
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Case: A 37-year-old woman presents for re-evaluation of painless, unilateral, vision loss that rapidly progressed during a surrogate pregnancy. She presented almost two years previously with vague symptoms of unilateral blurred vision. Ophthalmic examination revealed unilateral optic disc edema with good visual function (visual acuity 20/20, normal visual field). Despite MRI scanning suggestive of an optic nerve mass, she was diagnosed with idiopathic intracranial hypertension (pseudotumor cerebri). After physician consent, she proceeded with a planned surrogate pregnancy. Still carrying the diagnosis of pseudotumor cerebri, she underwent serial lumbar punctures as subtle decline in vision occurred. More substantial visual loss occurred during the third trimester (visual acuity 20/200), and in an attempt to salvage her vision, the patient underwent optic nerve sheath fenestration surgery following delivery. Post-operatively, her optic disc edema improved; however, her visual function remained poor. Repeat MRI scanning demonstrated impressive growth of an optic nerve mass in the orbital apex suggestive of optic nerve sheath meningioma. Due to the rapid growth of the mass, biopsy was recommended. Incisional biopsy via lateral orbitotomy confirmed WHO grade I optic nerve sheath meningioma. By time of definitive diagnosis, vision had declined to hand motions level. Radiotherapy was deferred.
Conclusions: Female sex hormones likely play a role in the biological behavior of meningiomas. In addition to being more prevalent in women, meningiomas commonly express progesterone receptors and may progress rapidly during pregnancy. Surrogate pregnancy presents a unique, high progesterone state that may exacerbate meningioma growth.
Clinical Significance: This case demonstrates rapid growth of an optic nerve sheath meningioma during a surrogate pregnancy. It is the first reported case of optic nerve sheath meningioma exacerbation associated with surrogate pregnancy.

Case Report on a Challenging Diagnosis of Infective Endocarditis

◆ **Roesler A**
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Background: This case report presents a unique presentation and diagnosis of infective endocarditis secondary to Bartonella infection in a patient with a history of truncus arteriosus. We hope that this report of his presentation and evaluation will help expedite the diagnosis in future patients with the same condition and expand the differential diagnosis for any patient with a similar presentation.
Methods: A 16-year-old male patient with a history of truncus arteriosus with Contegra, bovine jugular vein, RV-PA conduit and conduit replacement presented to the hospital with hepatosplenomegaly, pancytopenia, fatigue, weight loss, and emesis. The hepatosplenomegaly with pancytopenia were concerning for malignancy which led him to be transferred to the hematology/oncology service.
Results: A pediatric patient presented with pancytopenia, weight loss, fatigue, and hepatosplenomegaly. The team was very concerned for malignancy but the bone marrow biopsy showed no evidence. After ruling out many other diagnoses, the patient was diagnosed with infective endocarditis secondary to a Bartonella infection, which he was at high risk for due to his history of truncus arteriosus status post repair. Thanks to a thorough history, it was also revealed that he had exposure to cats at home.
Conclusions: The case report of infective endocarditis secondary to a Bartonella infection was consistent with other recent case reports in the literature. After an extensive evaluation, he was diagnosed with culture negative endocarditis secondary to Bartonella and started on doxycycline and rifampin prior to discharge. The most important factors to confirm this diagnosis were his elevated Bartonella IgG titer (>1:1024), vegetations seen on conduit on cardiac MRI, and splenomegaly.

The Role of Autonomy with Conjoined Twins Diagnosed at 9 Weeks

◆ **Gensel A**
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Purpose: American women have autonomy over their pregnancy including the right to have a legal and safe abortion. As providers we provide extensive counseling, but regardless of medical indication ultimately the patient decides her own pregnancy course. An early diagnosis of conjoined twins would provide additional time for women to choose.
Results: A 21-year-old G2P010 female presented at 9+0 weeks with an ultrasound revealing a monochorionic monoamniotic twin conjoined from thorax down with one heartbeat. They each had one arm arising laterally and lower limb buds that did not appear to be formed normally. The patient was counseled about the rarity of conjoined twins and that conjoined twins sharing one thorax and heart usually do not survive due to inability to be separated. Options for the patient were discussed included termination which was declined.
Conclusion: Our patient and many women are presented with the difficult decision of termination or carrying a pregnancy to term with questionable viability. A multitude of factors must be considered including personal beliefs and possible outcomes. Unfortunately, conjoined twins are likely to be stillborn or die shortly after birth. If separation of the fetuses is needed, there is a likelihood of one or two fatalities. If the pregnancy is successful, mothers face a lifetime of financial burden, need for ongoing care, risk for depression and anxiety, etc. A complicating factor in this decision is time as abortions are often limited to the first trimester depending on state laws. Conjoined twins are not normally diagnosed before 10 weeks gestation often giving women no more than 2 weeks to make this life altering choice. In this pregnancy, conjoined twins were diagnosed at 9 weeks. Earlier prenatal diagnosis of conjoined twins gives greater opportunity for counseling and gives extra time for women to consider options and execute their decision.

Cutaneous Crohn's Disease without Internal Involvement

◆ **Bittar J**
Contributing authors: Hentz E, Behrend J, Burton K, Hyrnewycz K, Rahnama S

Case: A 42-year-old woman presented to dermatology clinic with 2-year history of verrucous plaques on her buttocks that had progressed to involve the perineum and umbilicus. The lesions were minimally tender, but the patient was otherwise asymptomatic, specifically without diarrhea, abdominal pain or hematochezia. She had previously been evaluated by colorectal surgery, plastic surgery, and OB-GYN. Colonoscopy and endoscopy were without significant findings. Lesions were refractory to topical mupirocin and ketoconazole. Outside biopsy had suggested the diagnosis of verrucous carcinoma. On exam, her intergluteal cleft had a large verrucous plaque extending towards the perineum, with less verrucous plaques on the mons pubis and labia majora. The umbilicus and right inguinal fold had similar lesions also with malodorous drainage. Repeat biopsy showed focal suppuration, sinus tract formation, and small noncaseating granulomas in the superficial and deep dermis, consistent with the diagnosis of Cutaneous Crohn's disease (CC). Treatment was initiated with Infliximab, yielding significant improvement with pain and drainage.
Conclusions: We present an unusual case of cutaneous Crohn's disease without gastrointestinal involvement that was missed on initial biopsy. It is important to consider Crohn's in patients, especially women, with skin disease of the genitals/buttocks even in the absence of intestinal symptoms.
Clinical Significance: Two thirds of patients with CC are women. The majority of cases involve the genitals, and while it can precede intestinal disease by 3 months to 8 years, some patients never develop internal symptoms.1 Accordingly, studies have shown that Crohn's can have significant impact on female mental health, libido, and pregnancy. For these patients, depressed mood is a strong risk factor for low sexual function.2 Although women with quiescent disease have normal fertility outcomes, women with active disease during conception or have higher rates adverse pregnancy outcomes.3 Early diagnosis and coordination of care between specialties should be encouraged to optimize patient outcomes.

Elevated Troponin in Pregnancy: Heart Disease or Not?

◆ **Russell AF**
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Background: Cardiovascular disease is the leading cause of death in women in the United States. Diagnosis of acute coronary syndromes (ACS) is often times difficult to recognize in women, especially young women, as presentation can vary. A raised cardiac troponin level in a patient is concerning and suggests significant cardiac damage, as seen in myocardial infarctions. However, it has been demonstrated that troponins can be falsely elevated during pregnancy. Proper work-up and management is necessary in order to determine the true etiology of elevated troponins in pregnancy.
Case: A 21 year old G1P0 Caucasian female at 8 weeks gestation with a past medical history of a bicornate uterus, cervical somatic dysfunction, and tobacco use presented to the emergency room with chest pain and associated nausea, vomiting, lower abdominal pain, and vaginal discharge of bright red blood. She reported that she has had intermittent left sided chest pain for the past month. She states that the pain is non-radiating, feels like burning/pressure, and is 9/10 on pain scale at its worse. Her vital signs were within normal limits, except for an elevated heart rate to 115 bpm. No significant findings were found on physical exam. Transvaginal ultrasound showed fetal cardiac activity. Troponin was found to be elevated to 1.3 with no acute changes found on EKG or chest X-ray. She was admitted and her chest pain resolved with rest with troponins down trended to 1.25. Follow-up with her OB/GYN and cardiology suggested troponin elevation was due to pregnancy and she was advised to start low dose ASA going forward.
Discussion: Heart disease is a major cause of morbidity and mortality in women. Studies have shown that women are less likely to receive preventive treatment or guidance, such as lipid-lowering therapy, aspirin (ASA), and therapeutic lifestyle changes, than are men at similar ASCVD risk. Even though this patient had a falsely elevated troponin attributed to pregnancy, proper diagnostic work-up and management is necessary and can lead to better outcomes in CVD in women.

Management of Pediatric Extranodal Rosai Dorfman Disease in the Head and Neck: A Systematic Review

◆ **Campiti V**
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Purpose: To comprehensively analyze all reported cases of extranodal Rosai Dorfman disease (ENRDD) in children and analyze the clinico-pathologic characteristics and management outcomes.
Methods: The search terms "Rosai Dorfman Disease" and "Sinus Histiocytosis" were searched in the Ovid/Medline, PubMed, and Scopus databases from their inception through September 30th, 2018. Studies were systematically reviewed in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) scheme. All case reports and case series reporting on ENRDD in children less than 18 years of age and involving at least one head and neck subsite were included. Studies reporting on the isolated involvement of the eye, brain, or both were excluded.
Results: A total of 32 ENRDD cases were identified (24 male, 8 female) with ages ranging between 1.2 to 17 years (mean=12.15 years). Ethnicity was reported for 17 patients, with African Americans being the most affected group (n = 6). The most common head and neck site involved was the nasal cavity (n= 13, 40%), followed by the paranasal sinuses (n=10, 31%). The nasopharynx was involved in 5 patients (15%) as was the laryngo-tracheal complex. Concurrent cervical lymphadenopathy was present in 20 patients (62.5%). Additional non-otolaryngologic sites were simultaneously involved in 10 patients (n= 31.25%). Histopathology showed the presence of histiocytes or emperiopolesis in all patients. Surgery was the most common treatment modality and was performed in 19 patients (59.38%). , The next most common was steroid administration in 11 patients (34.36%). Loco-regional recurrence and persistence rates were lowest in patients who received surgery. In 11 instances (34.36%), ENRDD was misdiagnosed for another pathologic process.
Conclusion: ENRDD is rare in the pediatric population with a high rate of delayed diagnosis and misdiagnosis. This review compiles the largest number of patients to date and suggests surgical management is the treatment of choice in these patients.

Early Engagement Has a Sustained Positive Impact on Medical Students' Perceptions of Surgical Careers

◆ **Virtanen PS**
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Purpose: Prior studies have demonstrated that brief, early medical student exposure to surgery is effective and creates positive perceptions of surgical careers. Opportunities for preclinical medical student exposure to surgery are not universally available nor are the long-term effects well-understood. Our aim was to determine the impact of early exposure to surgery on perceptions about surgery and the decision to consider pursuing a surgical career.
Methods: Our institution's Surgery Student Interest Group created a trauma surgery shadowing experience. Immediate (n=109) and 1-year (n=77) follow-up surveys were sent to participants from the study period (December 2016-July 2018). Data gathered included demographics, student perceptions about surgery, and the experience itself.
Results: 59 immediate surveys (54.1%) and 24 1-year follow-up surveys (31.2%) were returned. Of the 59 immediate responses, 55.9% (n=33) were female, 93.2% were first and second-year students (n=55), and 94.9% (n=56) would recommend the experience to a peer. Significantly more immediate responders were considering a career in surgery after the experience compared to before the experience (69.5% vs 61.0%, p=0.012). This was particularly evident in female responders (72.7% vs 57.6%, p=0.0112). The experience was felt to be relevant to the career choice process by 94.9% of students immediately after and 92.2% at 1-year follow up (p=0.90). At immediate follow up, 96.6% (n=57) of students recalled a specific trauma team member who made a positive impression on them and this was sustained (87.5%, n=21) at 1-year follow up (p=0.142).
Conclusion: Students reported a positive impact on their perceptions of, and were significantly more likely to consider, a career in surgery after the experience. Student recall of the personal connection made to the trauma team is sustained over a 1-year period. Early, informal shadowing experiences may increase interest in surgical careers, particularly for female students, and this engagement appears to be sustained over time.

Systematic Review of Metastatic Glomus Tumors: Immunohistochemical Characteristics and Outcomes

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Background: Consensus guidelines do not exist for the diagnosis and surgical management of metastatic glomus tumors. Our objective was to compile all data on the characteristics and outcomes of metastatic glomus tumors.
Methods: A systematic review of PubMed, Web of Science, Cochrane, Excerpta Medica database (EMBASE) was performed to identify all cases of metastatic glomus tumors.
Results: Of the 809 abstracts from the literature search, 26 manuscripts with 35 metastatic glomus tumors met inclusion criteria. Location of primary tumor was commonly soft tissue (45.7%, 16/35), lung 22.9% (8/35), and stomach 17.1% (6/35). 39.3% (11/28) reported metastasis at initial presentation. Immunohistochemistry results showed 100% positivity for smooth muscle actin (22/22), vimentin (13/13), and p53 (3/3), and 91.7% (11/12) for collagen IV. Negativity was 100% for S100 (16/16) and cerium ammonium molybdate 5.2 (5/5); 94.4% for cytokeratin (17/18), and 93.3% (14/15) for CD34. Resection of the primary tumor was performed in 88.2% (30/34) of cases. Lung was the most common site for metastasis (42.9%, 15/35), followed by brain (25.7%, 9/35), soft tissue (20.0%, 7/35), liver (17.1%, 6/35), intestine (17.1%, 6/35), lymph nodes (17.1%, 6/35), and bone (14.3%, 5/35). Other less common sites included the spleen, heart, adrenal glands, mesentery, kidney, peritoneum, thyroid and stomach. The average follow-up was 54.1 months. Rates of local recurrence (LRR) and mortality (MR) were 32.1% (9/28) and 63.3% (19/30), respectively.
Conclusions: Metastatic glomus tumors have high LRR and MR. Soft tissue was the most common primary site and lungs were most common site of metastasis. IHC findings showed high rates of positive staining for SMA, vimentin, p53, collagen IV and low rates for desmin, S100, CAM 5.2, cytokeratin, and CD34. The IHC profile may help diagnose glomus tumors with metastatic potential. More complete data are necessary to develop consensus guidelines for diagnosis and management of metastatic glomus tumors.

CRISPR/Cas9 Generated FGFR3 Knockouts in Keratinocyte Models of HPV Infection

◆ **May A**
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Purpose: Generate Fibroblast Growth Factor Receptor 3 (FGFR3) knockouts in keratinocyte models of HPV infection and observe how this may affect the viral lifecycle.
Methods: We utilized CRISPR/Cas9 to create FGFR3 knockouts in keratinocyte cell lines commonly used to model HPV infection. Western blot was used to determine whether knockout generation was successful. In lines where FGFR3 knockout was confirmed, quantitative PCR (qPCR) was used to measure viral copy load. To study FGFR3's potential effect on viral integration, qPCR was coupled with exonuclease digestion that degraded genomic DNA while leaving the viral episomal DNA unaltered. By comparing the quantity of DNA between digested and undigested samples, we can approximate differences in integration rates between experimental groups.
Results: FGFR3 knockout generation was successful in the CIN612 cells, a line of HPV-31 infected cervical keratinocytes. The remaining cell lines either did not tolerate the FGFR3 knockout or demonstrated continued FGFR3 expression on western blot analysis. Quantification of HPV DNA in the CIN612 cells did not show a change in viral copy number between knockout and wildtype groups. However, quantification of DNA with and without exonuclease digestion showed a possible trend towards increased viral integration in FGFR3 knockout CIN612 cells.
Conclusion: FGFR3 function appears to be necessary for the growth and survival of several keratinocyte models of HPV infection, making the generation of FGFR3 knockouts in these lines impractical. In cell lines where CRISPR/Cas9 knockout was unsuccessful, future studies may need to employ siRNA to simulate loss of the FGFR3 gene. Based on early observations of the successfully edited CIN612 cells, FGFR3 knockout does not appear to change the rate of HPV replication. However, FGFR3 may play a role in preventing viral integration, as knockout cells had a lower proportion of DNA remaining after exonuclease digestion of genomic linearized DNA than wildtype cells.

Improving Modifiable Health Outcomes in Uninsured Women Living in Rural Indiana

◆ **Prieto J**
Contributing authors: Borse V, Swanson K, Abernathy MP

Case: A 27-year-old G5P0221 woman with a history of poor pregnancy outcomes, episodes of diabetic ketoacidosis, cardiac arrest, and digit amputations due to poorly controlled diabetes presented with preeclampsia. Fetal ultrasound findings at 14 weeks were consistent with caudal regression syndrome. Glycosylated hemoglobin was 9.0% at the start of pregnancy. Social history is significant for unemployment, limited medical access in rural Indiana, and lack of insurance when not pregnant. She reported inability to afford insulin and often goes without it. The infant was delivered at 35 weeks and 3 days due to preeclampsia, required prolonged hospitalization, and will require multiple surgeries.
Conclusions: Perinatal risk factors such as lack of prenatal care, smoking, illicit substance abuse, and uncontrolled medical conditions account for 45-50% of infant deaths in Indiana annually. These risk factors can be modified with insurance and educational programs. Detecting and treating diabetes early by optimizing glycemic control before pregnancy can improve Indiana's infant mortality rate, ranked 7th highest in the US. Women who attend diabetes education programs have fewer adverse events, smoke less, and are less likely to take teratogenic drugs. However, many non-pregnant women living in poverty cannot afford insulin because they lack insurance, and the cost of insulin rose $2,864 from 2012 to 2016.
Clinical Significance: This case demonstrates the role that modifiable social determinants play on women's and infants' health. Decreasing adverse outcomes before, during, and after pregnancy by providing insurance coverage and creating educational programs would be more cost effective than long term care of a disabled infant or mother on Medicaid. To improve the lives of mothers and infants in Indiana, forward thinking policy planners must balance upstream costs of controlling medical conditions with downstream costs of consequences from pregnancy with uncontrolled medical conditions.

Treatment of Hirschsprung Disease in the Developing World: A Series of Six Cases

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Purpose: In the developed world, Hirschsprung Disease (HD) is generally diagnosed and treated in the first year of life. However, in the developing world, HD frequently goes without a diagnosis for years and without treatment for even longer. This case series discusses the presentation and treatment of a series of six cases of HD in the developing world.
Methods: Six individuals with HD, ages 20 months to 10 years, presented to a mission hospital in Togo, West Africa. These individuals presented late with HD having varying workups based on availability of resources. Each patient was diagnosed due to chronic constipation, lack of stooling, or obstruction, leading to either biopsies or enema studies to confirm HD. All patients had ostomies placed to prevent further disease complications from poor stooling. Quality of life was negatively impacted with ostomy placement as cleanliness was an issue. The necessary definitive surgical treatment was unobtainable due to financial constraints or lack of skilled providers.
Results: A modified Swenson procedure was performed on all individuals in order to definitively treat HD. In this procedure, the original ostomy was divided into a healthy, proximal segment and a distal, aganglionic segment. The distal segment was dissected down into the rectal vault. Next, a transanal dissection was started and the rectal wall was incised approximately 1-1.5cm above the dentate line. This circumferential incision was continued proximally until it reached the upper rectal dissection. The aganglionic segment was removed and the healthy proximal limb was anastomosed to the rectum creating a functioning large bowel. Diverting ostomies were placed to allow stress-free healing for two months at the anastomosis, then the ostomies were taken down.
Conclusion: The modified Swenson procedure is an excellent definitive treatment for HD in the developing world.

Looking Beyond BMI: Uncovering Eating Disorders and Nutritional Deficiencies in Obese Adolescent Females

◆ **Sawyer K**
Contributing authors: Maniar P, Khan M, Pease K

Case: A 13-year-old girl with no significant medical history presented with tooth pain and was diagnosed with an abscess and osteomyelitis of the jaw. During her admission, she was also found to have a hemoglobin of 4.8 g/dl and an MCV of 51 fL. Further studies were consistent with severe iron deficiency anemia. After obtaining additional history, the patient was noted to have minimal iron intake due to a self-restricted diet in the setting of body image issues. With normal body mass index (BMI) at the time of her admission and no readily available previous weights recorded, her recent 10% weight loss and risk factors for iron deficiency and malnutrition were not initially apparent to clinicians.
Conclusions: This patient's severe iron deficiency anemia was likely caused by poor dietary intake in an effort to lose weight. Dietary deficiencies and eating disorders are difficult to identify in patients who present with normal to elevated BMI, thus clinicians need to maintain a high level of suspicion in adolescents with risk factors.
Clinical Significance: Overweight and obese women are at increased risk for unhealthy dieting strategies and iron deficiency anemia compared with their peers. While all adolescent females require greater iron intake due to an increase in muscle mass, blood volume, and the onset of menses, obesity is an additional and lesser known risk factor. A higher incidence of unhealthy weight control behaviors such as skipping meals, taking diet pills, and inducing vomiting may partially explain the increased risk for iron deficiency in overweight adolescents. Additionally, there is evidence of iron dysregulation in obesity due to inflammation and impaired iron absorption. Patients with normal to high BMI should not be overlooked in screening for disordered eating and dietary deficiencies including iron deficiency anemia.

Clinical Presentation and Findings on Diagnostic Imaging in Creutzfeldt-Jakob Disease

◆ **Gidley P**
Contributing authors: Childress J, Ho CY

Creutzfeldt-Jacob Disease (CJD) is a rare transmissible spongiform encephalopathy that is uniformly fatal. This disease is characterized by the pathologic accumulation and deposition of an abnormally misfolded form of the host-encoded cellular prion protein. This accumulation leads to neuronal degeneration, astrogliosis, and characteristic spongiform change. This disease has an incidence of 1 per million and usually occurs spontaneously; however, a small number of patients will inherit the condition. Our patient is a 73-year-old female who presented with frequent bouts of coughing, gait difficulty, and memory complaints which had progressed over a 3-month time period. Her family stated that her symptoms seemed to correspond to a recent middle ear infection with associated vertigo. These symptoms were exacerbated by a recent fall which resulted in injury to her hip. Prior to this, she was independent and working full time. Initial MRI at an outside facility was non-specific and showed isolated T2/FLAIR hyperintensity of the basal ganglia with associated restricted diffusion, and a differential included possible carbon monoxide poisoning or infectious etiology. Lumbar puncture was performed for presumed encephalitis or inflammatory etiology; however, the results, including cultures, were grossly normal aside from elevated protein and glucose. Follow-up imaging three months later showed persistent restricted diffusion, most prominent within the caudate, putamen, thalamus, and parafalcine cortex bilaterally, which in conjunction with clinical history, was concordant with sporadic Creutzfeldt-Jakob Disease. Following these imaging findings, repeat lumbar puncture results showed positive RT-quaking-induced conversion (RT-QuIC), total tau protein >4000 pg/ml, and positive 14-3-3 protein. In combination, the findings were consistent with a diagnosis of probable CJD. In this report, we discuss her case as well as briefly review the typical clinical course, neuroimaging, and pathogenesis of CJD.

Stereotactic Body Radiation Therapy (SBRT) for T1 and T2 Medically Inoperable NSCLC in a Community Setting

◆ **Jenks C**
Contributing authors: Frondorf B, Vissing D, Wilson D, Zeller J, Frasier J, Taylor N

Purpose: Stereotactic Body Radiation Therapy (SBRT) is considered for definitive treatment of medically inoperable T1 or T2 non-small cell lung cancer (NSCLC). This study analyzes the local control (LC), progression-free survival (PFS), and overall survival (OS) of a large community series of patients, including factors that influence these survival distributions.
Methods: Between September 2012 and December 2017, 240 patients were treated for inoperable stage T1 or T2 NSCLC. 144 patients had T1 tumors, and 96 patients had T2 tumors. Patients received either a 5-fraction regimen of 50 Gy or less (86 patients) or 60 Gy (148 patients), while six received 3-fraction regimen of 54 Gy. Survival was measured via the Kaplan-Meier method to determine LC, PFS, and OS. Tumor, demographic, and patient characteristics were analyzed for impact on survival and toxicity.
Results: Median follow-up of all patients was 23 months (range 1-83 months). Grade 3 pneumonitis was observed in 2 patients, both in tumor sizes over 3 cm. No other grade 3 or higher adverse events were reported. Grade 2 or higher hemoptysis was not identified. Six patients experienced a local recurrence; 3-year LC was 97%. 31 patients experienced any location recurrence; 3-year PFS was 84%. Median OS was 48 months and was significantly higher for T1 versus T2 tumors (p=0.002). OS was significantly higher in patients treated with 60 Gy versus 50 Gy (p=0.006). No other factors were identified that significantly impacted OS, LC, or PFS.
Conclusions: SBRT is an effective treatment for medically inoperable T1 or T2 NSCLC patients treated in the community setting, with high levels of LC and PFS, and minimal toxicity. Dose escalation to 60 Gy when using a 5-fraction regimen resulted in higher OS, especially for T1 tumors, with no higher toxicity.

Skin Sympathetic Nerve Activity in Patients Undergoing Cardioversion

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Purpose: To investigate the effects of cardioversion and deep sedation on skin sympathetic nerve activity (SKNA) using neuECG methodology.
Methods: We recorded concurrent ECG and SKNA using one of two neuECG devices in 11 patients undergoing deep sedation with propofol administration and subsequent cardioversion for atrial fibrillation. The recorded signals were analyzed and bandpass filtered from 500-1000 Hz to show SKNA and eliminate muscle interference. The average voltage of SKNA (aSKNA) was then calculated.
Results: Of the recorded patients, 10 converted to sinus rhythm after cardioversion. Compared to aSKNA at baseline (1.1132 ± 0.2562μV), cardioversion significantly increased aSKNA (2.9102 ± 1.2938μV, $p<0.01$). 5 s aftershocks were delivered. Furthermore, each shock caused an initial burst of nerve activity followed by a second burst 2 s later. Deep sedation with propofol significantly suppressed aSKNA for at least 10 min after the last cardioversion shock (1.11 ± 0.25μV to 0.89 ± 0.36μV 5 min after injection, $p<0.01$).
Conclusion: In all patients who received a cardioversion shock, SKNA was transiently increased after the shock. Deep sedation with propofol decreased SKNA for at least 10 min after the last cardioversion shock. Deep sedation may have antiarrhythmic effects, which might help prevent immediate recurrences of atrial fibrillation after successful cardioversion.

Small-Group Activity to Reinforce Concepts in Acid-Base Physiology

◆ **Islam S**
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Purpose: To improve first-year medical students' understanding of acid-base physiology by introducing a small-group active learning exercise that stimulates discussion of underlying renal physiology as it pertains to acid-base handling, in the hopes of establishing a foundational understanding of the mechanisms involved.
Methods: Following an overview lecture on acid-base physiology, small groups of 4-5 students addressed questions based on 3 clinical cases. Students were asked to diagram nephron segments, illustrate and describe the function of regional transporters, channels, and paracellular movement, address the action of key enzymes and hormones, and make clinical correlations that included identification of patients' acid-base status. The exercise concluded with a series of rapid-fire review questions relating to acid-base imbalances (respiratory and metabolic). Learning strategies utilized in this activity included small group collaboration and elaboration through discussion.
Results: A pre- and post-concept quiz was administered to assess the impact of the exercise on student understanding of key concepts in acid-base evaluation. We found a significant difference in pretest and posttest scores; the average preconcept quiz score was 4.57 out of 6 while the average post-concept score was 5.30 out of 6 (n=56; p<.001). Based on frequency of Likert scale responses in a post-session survey, we learned that most students regarded the session as moderately helpful in clarifying lecture concepts and the rapid-fire questions as highly helpful in improving their ability to analyze acid/base status.
Conclusion: This acid-base exercise was an effective way to help students synthesize and apply the concepts introduced through lecture by allowing them to engage with the material and each other while reinforcing basic science principles. Qualitative data suggests that more content focusing on nephron segments and their anatomic components would be a welcome addition for students in the future.

Social Cognition in Women with Schizophrenia and the Potential of Oxytocin in Treatment

◆ **Tai M**
Contributing authors: Bradley E, Campellone T, Woolley J

Purpose: To investigate the effects of oxytocin on social cognition in women with and without schizophrenia.
Methods: We recruited twenty-seven women with schizophrenia and thirty-eight female healthy controls for a randomized, double-blind, placebo-controlled, cross-over study in which participants received 40 IU of intranasal oxytocin or saline placebo on two testing days several weeks apart. To measure social cognition, we used The Awareness of Social Inference Test (TASIT), which is divided into three parts that each test a progressively more complex aspect of social cognition: Emotion Evaluation Test (EET), Social Inference-Minimal (SI-M), and Social Inference-Enriched (SI-E). The task consists of a series of video clips depicting actors engaging in various types of social interactions, followed by questions that require social inferences.
Results: Women with schizophrenia performed worse than controls on all three social cognition tasks on placebo day: EET ($d = 0.71$, $p = 0.006$), SI-M ($d = 0.64$, $p = 0.035$), and SI-E ($d = 0.96$, $p < 0.001$). There were no significant Drug (oxytocin, placebo) x Group (schizophrenia, control) interactions for EET ($F(1, 61) = 0.28$, $p = 0.6$), SI-M ($F(1, 46) = 0.04$, $p = 0.85$) or SI-E ($F(1, 62) = 0.03$, $p = 0.85$). The dosage of anti-psychotic medications taken by women with schizophrenia, as measured by chlorpromazine equivalents, significantly moderated the effect of oxytocin on performance in the SI-E in that group. Patients taking higher equivalents of chlorpromazine showed less improvement with oxytocin in their scores in the SI-E than patients taking lower equivalents ($r(-0.447)$, $p = 0.025$).
Conclusion: Women with schizophrenia, compared to controls, have more impaired social cognition as measured by TASIT. Oxytocin does not impact performance in either group. Patients taking higher dosages of anti-psychotic medications show less improvement with oxytocin in more complex aspects of social cognition than patients taking lower dosages.

Retinal Oximetry and Ocular Perfusion Pressure Between Subjects of European Versus African Descent

◆ **Shah A**
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Purpose: To investigate the relationship between oxygen saturation in the retinal vessels and ocular perfusion pressure in healthy subjects of European (ED) and African Descent (AD).
Methods: 46 healthy subjects (35 ED, 11 AD) were assessed for retinal oximetry data (oxygen saturation in the retinal arteries and veins, mean arteriovenous (AV) difference in oxygen saturation) by non-invasive spectrophotometric retinal oximetry (MutliSpec Patho-Imager), for blood pressure (BP) by an automated ambulatory blood pressure monitor, and for intraocular pressure (IOP) by Goldmann applanation tonometry. OPP was calculated from BP and IOP. Pearson correlations were used to test for associations between measurements.
Results: The mean AV difference in oxygen saturation was $35.41 \pm 5.58\%$ in the healthy subjects of ED, and $37.95 \pm 6.37\%$ for the subjects of AD ($p=0.254$). The mean OPP was 48.71 ± 6.55 mmHg in the healthy subjects of ED, and 54.96 ± 8.99 mmHg for the subjects of AD ($p=0.052$). There was a negative and significant correlation between AV difference and OPP in ED subjects ($r=-0.39$, $p=0.020$), and a positive and significant correlation in subjects of AD ($r=0.721$, $p=0.012$), leading to a statistically significant difference between the two groups ($p=0.0101$).
Conclusions: Our data suggests that the relationship between retinal oximetry and OPP may differ between individuals of different racial groups. The positive correlation found in AD subjects suggests possible disruption in oxygen extraction and may explain racial disparities in ocular health.

Theoretical Predictions of Oxygenation in a Heterogenous Vascular Network of the Retina

◆ **Rowe L**
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Background: Glaucoma is the leading cause of blindness in the United States, affecting over 2 million people (1.86%). In primary open angle glaucoma (POAG), there is an increased resistance to aqueous outflow through the trabecular meshwork related to elevated intraocular pressure (IOP) causing retinal ganglion cell death, although the exact etiology has yet to be discovered. Recently, it has been shown that retinal blood flow may contribute; however, retinal blood flow is complex and contains a heterogeneous geometry of microvessels, which may lead to inaccurate predictions of oxygenation of the retinal tissue.
Methods: From confocal microscopy of mouse retina, a realistic mathematical model was studied representing interactions among vessels and tissue in a vascular network with non-uniform geometry. Oxygen diffusion in tissue is equated to oxygen consumption in tissue, and the resulting oxygen concentration at any tissue point is calculated by summing the oxygen fields produced by each of the surrounding blood vessels.
Results: Figure 1: Panel A shows the model-predicted contour map of the oxygenation of the arteriolar network and surrounding tissue under well-oxygenated conditions (incoming arterial saturation to all branches is 96%). In Panel B, the inflow saturation in one of the six arteriolar branches is reduced by 66%, decreasing the average tissue PO_2 in the entire network from 67.2 mmHg to 61.7 mmHg and the minimum tissue PO_2 from 18.7 mmHg to 8.1 mmHg, nearly a 57% reduction in tissue oxygenation.
Conclusions: This model allows, for the first time, more accurate predictions of retinal oxygenation in response to changes in oxygen demand, arterial saturation, viscosity, or hematocrit. Despite reasonable average PO_2 levels overall, many terminal arteriolar vessels will have abnormally low PO_2 levels, which can lead to areas at risk of hypoxia—an effect that would not be observed in a non-heterogeneous description of the network.

Reasons for Discontinuation of Apixaban or Rivaroxaban in Patients Diagnosed with Acute Venous Thromboembolism

◆ **Zappia JL**
Contributing authors: Kline JA

Purpose: Monotherapy oral anticoagulation in the home treatment of patients with low risk venous thromboembolism (VTE) is gaining acceptance. It remains necessary to document patient-centered reasons for treatment discontinuation. We report categorical reasons for discontinuation of rivaroxaban or apixaban prior to completion of treatment in patients discharged from the Emergency Department with low risk VTE.
Methods: We used a prospective, multicenter observational study, in which low risk subjects diagnosed with acute VTE (n=41 with PE) were treated with either apixaban or rivaroxaban for treatment. Subjects were low risk using Hestia criteria or clinician judgment and sPESI and were enrolled between July 2017 through December 2018. Outcomes were assessed by phone and medical record review of each subject following 30 days after discharge from the Emergency Department. Subjects who discontinued treatment prior to completion were asked for a categorical reason for discontinuation: 1. bleeding, 2. other side effect, 3. change in diagnosis, 4. Physician discretion, 5. worsening clot burden, 6. cost/insurance preference, 7. other.
Results: A total of N=203 subjects have been enrolled in the study including 37 treated with apixaban and 167 treated with rivaroxaban. Of the 203 subjects enrolled, 19 (9.4%) reported discontinuation of treatment prior to completion. The number of subjects reporting categorical reasons for discontinuation are as follows: bleeding, 4 (2.0%); other, 4 (2.0%); worsening clot burden, 3 (1.5%); cost/insurance preference, 3 (1.5%); other side effect, 3 (1.5%); change in diagnosis, 1 (0.5%); Physician discretion, 1 (0.5%). The most common forms of bleeding were hemoptysis (n=2) and menorrhagia (n=2). The main categorical reasons for discontinuation of treatment in subjects treated with apixaban and rivaroxaban were cost/insurance preference and bleeding, respectively.
Conclusion: Discontinuation of monotherapy anticoagulation is a significant problem in patients with low risk VTE treated as outpatients. The most common reason for discontinuation was bleeding.

The Ripple Effect – Analysis of the Cascade of Events Associated with Peripheral IV Loss and the Impact on Nurse Workflow and Resource Utilization

◆ **Frondorf B**
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Purpose: Peripheral intravenous catheters become dislodged and fail for a variety of reasons, consuming nursing time and hospital resources. Little research has been done to evaluate IV failure on a case-by-case basis to determine the clinical and financial impacts. The primary objective of this study is to characterize the costs for an IV dislodgement in a general medical hospital.
Methods: A prospective study of adult inpatient IV dislodgements and replacements (n = 51) were performed. Vascular access nursing staff filled out post-dislodgement surveys seeking demographics, causes of the dislodgement, disruption of care, time/resource utilization, and other factors. Time costs were based on Bureau of Labor Statistics average salary data. Resource costs were obtained from Deaconess Health System. Data was analyzed using Microsoft Excel.
Results: The average cost to reestablish a dislodged IV was $47.58 (Range $22.28 - $190.50). 74.6% of costs were due to supply utilization. The average time spent by an RN was 18 minutes, and the average number of sticks was 1.3. The average patient was 66.7 years old, with 54% of patients being male. Patients went, on average, 55 minutes without IV access (range 5-440 minutes). The plurality of dislodgements were due to patient "cognitive issues", followed by "patient transfers" and "other/nonclassifiable'. 50.4% of dislodgements occurred on medical critical care units, and 27.3% occurred in surgical units.
Conclusions: Dislodgements are more common in patients with cognition problems, on medical units and in the elderly. Due to Deaconess Health System utilizing a specialty vascular access team, the data presented may be an underestimation when compared to hospital systems using direct patient care nurses. This study represents a best-case scenario of IV reestablishment. Further study is warranted to investigate possible solutions to intravenous catheter dislodgement, with special attention to patients with cognitive issues or cognitive decline.

Facing the Risks of a Large Acoustic Neuroma Resection

◆ **Sandelski M**
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Case: A 17-year-old female was referred to our neurotology skull base center with progressive right-sided hearing loss, tinnitus, disequilibrium, and worsening headaches. She was found to have horizontal nystagmus, decreased corneal reflex, and right-sided profound deafness. Her family history was negative for neurofibromatosis type 2. A brain MRI revealed a giant 3.6cm x 4.3cm x 4.0cm right vestibular schwannoma (VS; also known as acoustic neuroma) with massive brainstem compression. VS are benign but can cause hearing loss, brainstem compression, and neurologic sequelae when large. Due to the tumor size and her young age, surgical resection was recommended. A large risk of acoustic neuroma surgery is facial nerve injury due to the severe stretching of the nerve from the tumor. During the 16 hour surgery via atranslabryinthine approach, the tumor was successfully freed from cranial nerves 5, 7, 9, and 10. Her immediate postoperative facial nerve function was normal. Two years after surgery, her MRI shows no brainstem compression and her facial nerve is normal. She is now in college studying nursing.
Conclusions: VS are Schwann cell-derived tumors that arise from the vestibular portion of cochleovestibular nerve. The overall incidence of VS is 1 per 20,000 people per year and a median age at diagnosis of 50. Young patients typically present with larger, growing tumors.
Clinical Significance: Given the tumor size, major stretch/compression of the facial nerve occurred, increasing the risk of facial paralysis after surgery. Facial paralysis is socially and functionally devastating, happening in >20% of large acoustic neuroma surgeries. Facial paralysis leads to difficulty eating, sequelae of the inability to close her eye, and altered facial appearance. However, watchful waiting here is not recommended given her young age and brainstem compression. Experienced team approach at high volume centers can lead to excellent outcomes.

Transjugular Intrahepatic Portosystemic Shunt (TIPS) Creation to Improve Surgical Candidacy Prior to Abdominal Operation

◆ **Schmitz A**
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Purpose: TIPS creation is typically reserved for patients with refractory ascites or variceal hemorrhage. While TIPS has also been created prior to planned abdominal operation to decrease morbidity related to portal hypertension, there is little in the literature supporting its efficacy in that indication. The goal of this study was to determine if preoperative TIPS creation allows successful abdominal operation and improves outcomes.
Methods: A retrospective review of records of 22 patients who underwent preoperative TIPS creation between 2011 and 2016 was performed. Clinical and serologic data were obtained for 21 patients because one patient was completely lost to follow up after TIPS creation. The primary endpoint was whether patients underwent planned abdominal operation following TIPS. Operative outcomes and reasons that patients failed to undergo planned operation were examined as secondary endpoints.
Results: The mean age was 56.4 ± 8.8 years, and the mean Child-Pugh and Model for End-Stage Liver Disease (MELD) scores were 7.2 ± 1.5 and 11.9 ± 4.3, respectively. Thirty-day mortality after TIPS creation was 9.5%. Eleven patients (52.4%) underwent planned abdominal operation and the thirty-day postoperative mortality rate was 0%. One of these 11 patients (9.1%) had recurrent ascites and developed a surgical site infection after operation that required drain placement. Reasons for failure to proceed to abdominal operation after TIPS included resolution of hernia symptoms, development of malignancy, TIPS revision, transportation issues, and death. In three cases the reason for cancellation of the surgical procedure was unknown.
Conclusion: In our population, TIPS allowed successful abdominal operation in the majority of patients, with thirty-day TIPS mortality of 9.5%, no perioperative mortality, and 9.1% major postoperative morbidity.

A Patient's Voice Guides Treatment of Pregnancy-Associated Breast Cancer

◆ **Huang CC**
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Purpose: Incidence of pregnancy-associated breast cancer (PABC) is increasing internationally, and treatment involves difficult decision-making with no clear guidelines. Open, honest communication is crucial for identifying patient values, and delivery of care should be tailored to each individual patient.
Case: A 35-year-old previously healthy female noticed a mass in her right breast. Imaging and core biopsy showed grade 2 triple negative invasive ductal carcinoma (cT2N0M0). A positive beta-hCG test confirmed the patient's suspicion that she may be 5-6 weeks pregnant. The patient faced the choice to end the pregnancy or wait until the 2nd trimester, when it would be safer for the fetus, to receive neoadjuvant chemotherapy. The patient's desire to stay alive for her 5-year-old son strongly guided her decision to not delay treatment. After consultation with Maternal Fetal Medicine and careful deliberation, the patient and her husband decided to terminate the pregnancy surgically in order to quickly proceed with standard of care chemotherapy. The patient went to Planned Parenthood for her abortion because, even with private insurance, it was significantly more expensive to terminate the pregnancy in the hospital. After chemotherapy, she had a bilateral mastectomy with sentinel node biopsy. Pathology showed complete pathologic response, and she remained recurrence-free after 18 months. Although treatment came with the risk of permanent menopause, her menses returned a year later. She was assured that her risk of breast cancer recurrence would not be increased with subsequent pregnancy.
Conclusions: The patient's complete remission was made possible through the excellent coordination of care between her multidisciplinary medical team and Planned Parenthood. Her priorities were clearly identified and understood by all parties—enabling coordinated and compassionate care aligned with her goals.

Beta Blocker Provoked Psoriasis: A Rare Exacerbation of Psoriasis in a Middle-Aged Woman

◆ **Haddad FC**

Background: Beta blocker provoked psoriasis (BBPP) is a rare condition characterized commonly by psoriasiform eruptions. Its presentation is subacute and seen in patients 1-18 months after the start of beta blocker therapy. Symptoms include exacerbation of current psoriatic lesions and/or the development of new lesions that can deteriorate into erythroderma. Management includes discontinuation of beta blocker, addition of topical and systemic agents, and prevention of transdermal fluid loss. However, beta blocker discontinuation rarely results in full resolution of symptoms.
Results: This case report is the presentation of BBPP in a 59-year-old African American female who started metoprolol two months prior for hypertension. She presented with a three-month history of a worsening, pruritic, nummular, and targetoid rash that covered 100% of her body surface area. Skin biopsy revealed psoriasiform dermatitis. The patient underwent triamcinolone wet wraps, fluid resuscitation, and discontinuation of metoprolol and was discharged on topical agents and hydroxyzine. Two month post discharge recovery showed mild xerosis, which was managed with cyclosporine.
Conclusions: Identifying and understanding BBPP is important due the prevalence of prescribed beta blockers. By being aware of the etiology and symptoms of BBPP, providers can be able to prevent and treat this phenomenon accordingly.

Association of Adverse Childhood Experiences, Attachment Styles, and Depression Symptoms in an At-Risk Perinatal Population

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Purpose: To examine the association of a woman's childhood trauma experience and attachment style with depression symptoms in the perinatal period for a population of inner-city women.
Methods: This is a cross-sectional pilot study of pregnant and postpartum women (up to 6 weeks postpartum) collected during a 3-month period. Specific questionnaires that assessed adverse childhood experiences (Adverse Childhood Experience survey – ACE), attachment (Experiences in Close Relationships-Relationship Structures – ECR-RS), and depression (Edinburgh Postnatal Depression Scale – EPDS) were completed during a woman's obstetric or postpartum visit.
Results: Of the 161 women in the final cohort, 36 (22.4%) were categorized as depressed with a score of ≥ 10 on the EPDS. ACE score was found to be an independent predictor of EPDS when EPDS was treated as continuous or categorical (OR 1.27, 95% confidence interval 1.08–1.49) while adjusting for covariates. Some ECR-RS subscales were also significantly associated with depression.
Conclusions: In this population of inner-city pregnant and early post-partum women, we found that women with a history of adverse childhood experiences were at an increased risk for depression during pregnancy and postpartum. This study also demonstrates a positive correlation between adverse childhood experiences, attachment style, and perinatal depression. These findings suggest that we may be able to identify key risk factors for depression which could be employed early in pregnancy or even preconception.

Congenital Insensitivity to Pain and Anhydrosis in Pregnancy: Defying the Odds

◆ **Hadley E**
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Case: Patient is a 26-year-old G2P1001 woman diagnosed at 2 months of age with chronic insensitivity to pain (CIPA). She presented to high-risk clinic at 26 weeks gestation. She has a history of undetected dental abscesses due to the absence of pain, resulting in extraction of all her teeth. She has a history of poor wound healing and osteomyelitis warranting bilateral above the knee amputations and a right arm amputation above the elbow. Prior obstetrical history includes a cesarean section at 38 weeks with delivery of a healthy male infant. A repeat cesarean section was planned for the current pregnancy. Anesthesia was consulted prior to delivery due to concern that the patient would not feel the sensations of labor and experience autonomic dysreflexia if proper anesthesia was not administered. At 37 weeks and 2 days, the patient presented for a cesarean section. She denied any contractions, vaginal bleeding, or leakage of fluid. She noted continued fetal movement and the non-stress test was reactive. Per ultrasound, the placenta was anterior, the amniotic fluid volumes were within normal limits, and fetal anatomy was normal. Patient underwent spinal anesthesia and cesarean section to deliver a female infant. Postpartum, her only complication was a chronic wound addressed by wound care.
Conclusions: CIPA is an autosomal recessive condition caused by mutations in the NTRK1 gene. When mutations arise, neuronal apoptosis of both sensory neurons and nerves in sweat glands occurs, causing the inability to feel pain or sweat. Given this, it is remarkable that the patient did not experience more complications with her pregnancies.
Clinical Significance: CIPA is an extremely rare disease with only 60 cases documented in the U.S. This may be the only reported case of a woman with CIPA of this phenotype having successful pregnancies.

Bibliometric, Authorship, and Collaboration Trends Over the Past 30 Years of Publication in the American Journal of Sports Medicine and Arthroscopy

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Purpose: To study bibliometric trends for the American Journal of Sports Medicine (AJSM) and Arthroscopy.
Methods: A bibliometric analysis over the past 30 years of AJSM and Arthroscopy was performed for published manuscripts using one representative year of each decade. Statistical analyses were performed with non-parametric methods for continuous variables and Fishers, Pearson's chi², and Cochran linear trend tests for categorical variables. P < 0.05 was considered statistically significant.
Results: There were 814 manuscripts from AJSM and 650 from Arthroscopy. For AJSM the number of manuscripts steadily increased from 86 in 1986 to 350 in 2016; for Arthroscopy the number of manuscripts increased from 73 in 1985/1986, to 267 in 2006, but then dropped to 229 in 2016. There were significant increases over time in all bibliometric variables for both journals, except for the number of citations, which had a slight decrease in 2016. Arthroscopy had a greater percentage of manuscripts from Asia compared to AJSM (19.3% vs 11.5%) while AJSM had a greater percentage from North America (70.3% vs 59.2%); both journals had similar percentages from Europe (18.2% for AJSM and 21.6% for Arthroscopy) (P = .00002). For AJSM the percentage of female first authors was 13.3% and increased 4.1 times from 4.7% 1986 to 19.3% in 2016 (P = .021); the percentage of female corresponding authors was 7.3%. For Arthroscopy, the percentage of female first authors was 8.1% and increased 5.6 times from 2.8% in 1985/1986 to 15.7% in 2016 (P = 0.00007); the percentage of female corresponding authors was 6.5%.
Conclusion: With the rising demands of publishing in academic medicine, understanding changes in publishing characteristics over time and by region is critical. AJSM and Arthroscopy showed an increase in most variables analyzed. Although Arthroscopy is climbing at a higher rate than AJSM for female authors, AJSM has an overall greater percentage of female authors.

Audiologic Improvement Following Middle Cranial Fossa Approach for Management of Spontaneous Cerebrospinal Fluid Leaks

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Purpose: To determine the audiologic improvement after middle cranial fossa (MCF) approach to repair spontaneous cerebrospinal fluid (sCSF) leaks.
Methods: Twenty-four consecutive patients (27 ears) with temporal bone sCSF leak over a 4- year period underwent MCF repair of temporal bone sCSF leak with audiometric testing including preoperative and postoperative pure tone average (PTA), air bone gap (ABG), and word recognition score (WRS) in the sCSF leak ear. Patient characteristics (age, gender, ethnicity, BMI), location of CSF leak, and presence of encephalocele(s) were recorded.
Results: Out of 27 ears, 55% had multiple tegmen defects and 82% had ≥1 encephaloceles. There were no recurrent CSF leaks at a mean [SD] follow up of 8.6 [10.3] months. The mean [SD] pre-operative PTA and ABG were 40.58 [15.67] dB and 16.44 [6.93] dB, respectively. There was significant improvement in mean PTA (9.38 [9.92] dB; p < 0.001; Cohen d=0.95) and ABG (8.22 [9.29] dB; P<0.001; Cohen d=0.88) after sCSF repair. Mean WRS improved (by 2.92 [6.33] %; p=0.024; Cohen d=0.46) from a mean pre-operative WRS of 93.16 [9.34] % to a mean post-operative WRS of 96.11 [7.00]%.
Conclusions: MCF approach for repair of sCSF leaks yields significant improvement in conductive hearing loss and is highly effective in management of the entire lateral skull base where multiple bony defects are often identified.

The Role of Social Determinants of Health in Prenatal Counseling

◆ **Abam C**
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Purpose: Most research to date focuses on the medical implications of prenatal testing. Regarding young pregnant moms, little research has been done on the social determinants of health that influence decision making after prenatal testing. Furthermore, limited literature exists on how education, socioeconomic status, and family support impacts the decision making ability of mothers.
Methods: We present a case of a 5-month old girl prenatally diagnosed with mosaic trisomy 9 complicated by congenital diaphragmatic hernia born to a 20 year-old G3 P2111 at 36+5 weeks via cesarean section. This was a high risk pregnancy due the prenatal diagnosis as well as a complex social history in mom which included a history of substance abuse, poor social support, and seeking care from multiple providers.
Results: Physician advocacy bridges clinical care with the identification of individual social determinants of health and or psychosocial stressors to ensure patients are provided with the best health and care.
Conclusions: This case highlights the challenges with predicting outcomes for patients with complicated diagnosis like trisomy 9 wherein the provision of effective prenatal counseling. Effective prenatal counseling including identification of the individual psychosocial stressors, and social determinants of health that impact patients is vital to ensuring that families make informed decisions. One that is fostered by adequate counseling about outcomes and implications postnatally, encouragement to seek multiple opinions and guidance through maintaining clear concise communication and continuity of care.

High Intensity Focused Ultrasound for Localized Prostate Cancer Treatment

◆ **Ceballos B**
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Purpose: To investigate the efficacy and side effect profile of High Intensity Focused Ultrasound (HIFU) on localized prostate cancer.
Methods: Between May 2016 and October 2018, 22 patients had HIFU as primary treatment for localized prostate cancer. The most common approach was hemi-ablation in 12 (54.5%) patients, hemi-ablation with "hockey stick" in 6 (27.3%), focal unilateral in 3 (13.6%), and focal bilateral in 1 (4.5%). Our follow-up includes Prostate Specific Antigen (PSA), complications, and quality of life assessments at 1, 3, 6, and 12 months. A confirmatory MRI-fusion biopsy was performed around 6 months post-HIFU in all patients.
Results: Pre-treatment biopsies of the 22 patients were graded using the Gleason Score (GS). These biopsies demonstrated that 9 (40.9%) patients were GS 3+4, 6 (27.3%) patients were GS 4+3, 2 (9.1%) patients were GS 4+4, and 1 (4.5%) patient was GS 3+3. In the 18 patients that received a 6-month confirmatory biopsy, tumor persistence was demonstrated on the treatment side in 4 (22.2%) patients (all Gleason 3+3). This also showed contralateral tumor presence in 3 (16.7%) patients of Gleason 3+4 and 3 (16.7%) patients with Gleason 3+3 that were newly diagnosed. Of the 18 patients, the median PSA was 5.68 at baseline and 2.2 by 6 months, showing a 61.3% fall. The most common side effects were hematuria, urinary obstructive symptoms and incontinence. Respectively, these occurred in 9 (56.3%), 3 (18.8%), and 1 (6.2%) patients at their 1-month follow up (16 total), and occurred in 0, 0, and 1(5.6%) of patients at 6 months (18 total). Only 1 (6.2%) of 16 patients experienced worsened erectile function at their 1-month follow up, while 1 (5.6%) of 18 patients noted this at their 6-months. There were no intraoperative complications.
Conclusions: In our cohort, HIFU showed few short-term side effects and no clinically significant infield recurrences.

Iatrogenic Peroneal Nerve Palsy Rates Secondary to Open Reduction Internal Fixation for Tibial Plateau Fracture

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Purpose: The purpose of this analysis is to report the rate of peroneal nerve palsy secondary to intraoperative skeletal traction during open reduction internal fixation (ORIF) for lateral unicondylar and bicondylar tibial plateau fracture (TPF) repair and associated epidemiology.
Methods: One hundred twenty-four patients that underwent ORIF for TPF were identified, of which 10 were excluded as medial unicondylar tibial plateau fractures. Of the remaining 114 patients, complete medical records were available for 64 patients due to loss of previous EMR data. An additional 4 patients were excluded due to development of compartment syndrome, leaving a total of 60 patients for this review. Of these 60 patients, 21 lateral unicondylar and 40 bicondylar TPFs underwent surgical repair via ORIF. All cases utilized a distractor to provide intraoperative traction, pneumatic tourniquet, and peripheral nerve blockade.
Results: There were a total of 21 lateral unicondylar and 40 bicondylar TPFs repaired via ORIF in 60 patients identified during the study period. The incidence of iatrogenic peroneal nerve palsy secondary to intraoperative skeletal traction was 16.4% (10 of 61). Only 60% (6 of 10) of peroneal nerve palsies recovered clinically with a mean recovery time of approximately 14 weeks. Comparison of demographics in patients with peroneal nerve palsy versus those without yielded no significant difference in patient sex ($p = 0.08$), age ($p = 0.27$), fracture type ($p = 0.29$), tobacco use ($p = 0.44$) or alcohol use ($p = 0.78$).
Conclusion: Peroneal nerve palsy is a common sequela of ORIF for TPFs involving the lateral compartment, constituting 16.4% of cases. Many patients (40%) who develop peroneal nerve palsies do not recover, leading to permanent loss of motor and/or sensory function for 6.6% of patients studied. None of the epidemiologic variables evaluated yielded predictive value for development of peroneal nerve palsy or subsequent resolution.

Role of Covalent Modification of Hyaluronan with Inter-Alpha Inhibitor Heavy Chains During Acute Lung Injury

◆ **Ni K**
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Purpose: The presence of heavy chain (HC)-modified hyaluronic acid (HA) in the extracellular matrix is a feature of several inflammatory lung diseases, but its role in the onset and resolution of inflammation is incompletely understood. Recent reports indicate that covalent modification of HA with the HCs of serum protein inter-alpha-inhibitor (IαI) is critical to neutrophil sequestration in liver sinusoids and to animal survival during experimental lipopolysaccharide (LPS)-induced sepsis. Using mice deficient for tumor necrosis factor α (TNFα)-stimulated-gene-6 (TSG-6), the exclusive mediator of HC-HA formation, we investigated its role in the initiation and resolution of lung inflammation in models of acute lung injury (ALI) induced by respiratory infection.
Methods: Mice received a single intratracheal instillation of LPS or Pseudomonas aeruginosa. Lungs and bronchoalveolar lavage fluid were studied for up to six days post-instillation. HC-HA formation was determined via hyaluronidase digestion and HA fragments were detected by gel electrophoresis. Lung inflammation was assessed by flow cytometry, as well as albumin and RAGE levels in the bronchoalveolar fluid. TSG-6 secretion by TNFα- or LPS-stimulated human alveolar macrophages, lung fibroblast Wi38, and bronchial epithelial BEAS-2B cells was assessed by ELISA.
Results: Extensive HC-modification of lung HA, with predominant peri-broncho-vascular localization was notable during early inflammation and markedly decreased during its resolution. Whereas human alveolar macrophages secreted functional TSG6 following both TNFα and LPS stimulation, fibroblasts and bronchial epithelial cells responded to only TNFα. Compared to wild type, TSG-6-null mice, which lacked HC-modified HA, exhibited moderately greater lung injury.
Conclusions: Respiratory infections induce rapid HC modification of HA followed by fragmentation and clearance, with kinetics that parallel the onset and resolution phase of ALI, respectively. Further studies are needed to understand how HCHA can critically promote survival during systemic LPS-induced vascular shock while only conferring modest protection against localized intratracheal LPS exposure.

Atypical Presentation of Herpes Simplex Virus Esophagitis in an Immunocompetent Patient

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Introduction: Herpes Simplex Virus esophagitis (HSVE) is a well-documented opportunistic infection affecting immunocompromised patients. It can rarely manifest in the immunocompetent patient, with the most recent review in 2010 demonstrating 56 documented cases. Such patients commonly present with acute odynophagia, fever, and retrosternal pain. Here, we report a case of HSVE affecting an immunocompetent patient with a more subacute presentation.
Methods: A 37-year-old Nigerian female presented with generalized weakness, weight loss, and new onset dysphagia of two months duration. The dysphagia had progressed from solids to liquids with intermittent odynophagia. She denied fevers, chills, hematemesis, and melena. On exam, she was afebrile and exhibited no oropharyngeal lesions. Her abdomen was nontender to palpation and she demonstrated no hepatosplenomegaly or palpable masses. Labs showed severe iron deficiency anemia requiring transfusion, a normal white cell count, and a negative HIV screening test. An upper endoscopy (EGD) showed multiple small non-bleeding erosions throughout the middle and distal esophagus. Esophageal biopsy demonstrated squamous epithelium with viral inclusions and multinucleated cells. Immunohistochemical stain was focally positive for HSV supporting the diagnosis of herpes esophagitis. She was subsequently started on 7-day treatment of oral acyclovir 400 mg three times a day and had resolving symptoms one week later at her primary care visit.
Discussion: This case illustrates the importance of considering a diagnosis of HSVE in immunocompetent individuals, who present with a subacute course of worsening dysphagia without systemic symptoms. Moreover, as HSVE endoscopic lesions can vary in appearance and location, gastroenterologists should have a low threshold for biopsying atypical lesions in the immunocompetent. In a recent study comparing endoscopic features of HSVE in immunocompromised and immunocompetent patients, endoscopists were more likely to mention the possibility of viral esophagitis on the endoscopy report in patients that were immunocompromised. Although HSVE in the immunocompetent is typically a self -limited disease, treatment with oral acyclovir can result in resolution of symptoms within 1-2 weeks. The etiology of HSVE in the immunocompetent may represent a primary infection of traumatized esophageal mucosa or reactivation after a previous infection.

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