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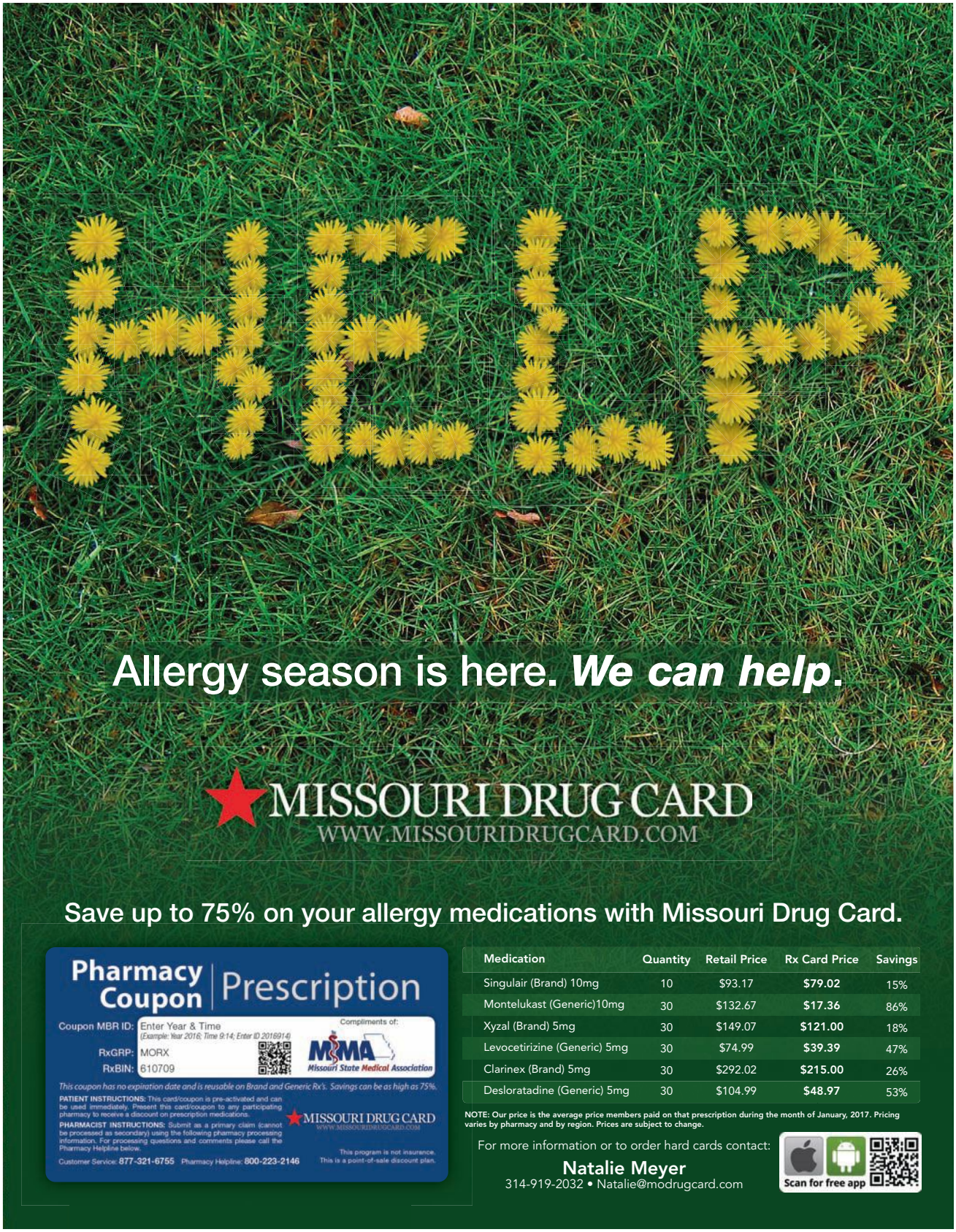
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EDITORIAL

USPSTF: Quit Clowning Around with Our Health!

by John C. Hagan, III, MD

It would be difficult to take USPSTF recommendations less seriously if task force members delivered them with red noses and clown suits.



The United States Preventive Services Task Force (USPSTF) is a federally-mandated group of primary care physicians making recommendations to Congress on many tests and diseases they do not have the expertise to diagnose or treat. That alone should give one pause.

Their analytical methodology and meta-analyses are often flawed. The recent walk-back (USPSTF Prostate Cancer Screening Final Recommendation 2018) of their tragic 2012 recommendations regarding prostate cancer screening is an example; the latest of their many erroneous pronouncements.

Between 2012, when this panel advised abandoning Prostate Specific Antigen (PSA) screening, and 2018 when USPSTF abruptly recommended PSA testing more in line with the American Urology Association, tens of thousands of men have unnecessarily died or been diagnosed at a much later stage of prostate cancer.

The USPSTF has not a single urologist. There is prostate cancer on both sides of my family. Most of my afflicted kin would be dead, instead of alive and doing well, had they and their physicians followed the USPSTF PSA guidelines. This is business as usual at USPSTF where mammography recommendations are set without breast surgeons or radiologists, skin cancer screening mandates without dermatologists and eye examinations for children without ophthalmologists. You get the idea, it hasn't registered yet with USPSTF or the geniuses in Congress.

Being a general practitioner for three years before specializing in ophthalmology, I have the greatest respect for primary care. But primary care physicians, statisticians, and 'preventive care experts' should not be presuming to set standards on tests and diagnostic procedures with which they have minimal experience or expertise. It is also an unwarranted intrusion into the doctor-patient relationship. Some, with good reason, regard USPSTF as a way to ration healthcare. Recommending against tests and procedures saves the government and insurance companies money. USPSTF has been frequently getting it wrong since 1984 when Congress created it.

For me and many other physicians, it would be difficult to take USPSTF recommendations less seriously if the task force members delivered them with red noses, clown suits, and goofy clown shoes. For valid advice look to physicians and their medical and surgical organizations that diagnose and treat these complex, serious diseases on a daily basis. Better to disband this committee or change the name to United States Preventive Services Task FARCE.



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Poisoning, Overdoses, Toxic Exposures

It's More Than POT: The Story of a Regional Poison Center Surveillance, Medical Toxicology, and the Detection of the National Synthetic Cannabinoid Outbreak

by Anthony J. Scalzo, MD & Andrea Rivera-Sepulveda, MD



Packets of synthetic cannabinoids and contents.

Background

The national poison center movement originated in the Midwest with actions of the American Academy of Pediatrics in Chicago, Illinois, in 1972. The Missouri Poison Center (MPC) was established in 1974. The MPC and other regional poison centers are essential to the public health locally and nationally. Trends in serious poisoning outbreaks such as the release of synthetic cannabinoids have been detected by real-time electronic surveillance by specialists in poison information and medical toxicologists.



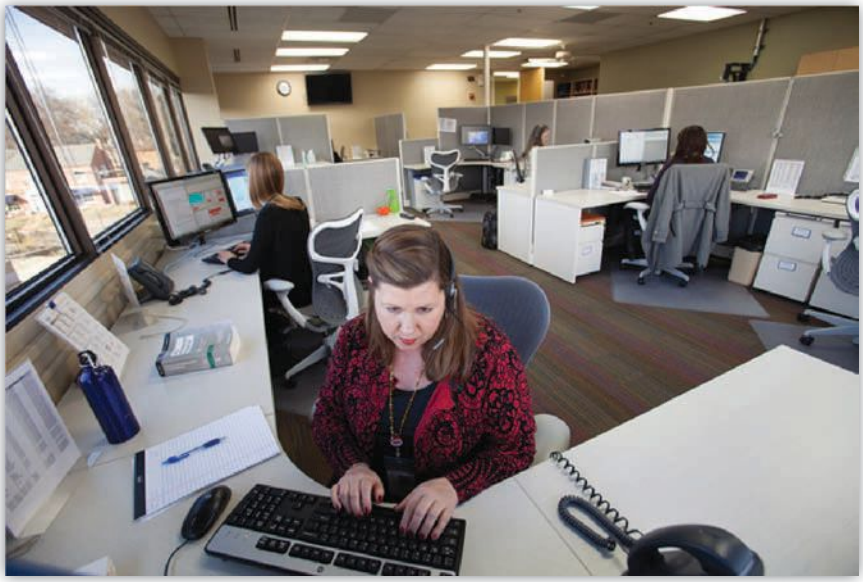
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Historically, the poison center movement began in the Midwest, with the American Academy of Pediatrics focusing on reducing deadly ingestions of aspirin in children and the first Poison Center opening in 1972 in Chicago. In the late 1970s the poison center at SSM Health Cardinal Glennon Children's Hospital was already fielding thousands of calls from citizens throughout Missouri. Fernando De Castro, MD, was the first medical director having served since 1974. Anthony J. Scalzo, MD, (currently Professor of Pediatrics and Internal Medicine at Saint Louis University School of Medicine and lead author of this article), was named the assistant medical director in the mid-1980s while the center was seeking accreditation by the American Association of Poison Control Centers. In 1984 the center received full accreditation status as a regional poison center and congruent with this status legislation was introduced in the State of Missouri (HB 435) to establish a Poison Prevention and Treatment Network. This legislation was enacted into law in 1986 and the Cardinal Glennon Regional Poison Center was designated to serve the entire state of Missouri. Over the years, the poison center sought to stabilize its funding from the state, hospitals, and the federal government and with that diversification in funding resources the center is now known as the Missouri Poison Center which serves over six million residents of Missouri and currently manages over 59,000 calls per year.[1]

Economic and Public Health Value of the Poison Center

A special report published by the Hospital Industry Data Institute (HIDI) demonstrated how the Missouri Poison Center helped Missouri residents avoid $56 million in medical charges during 2011 alone.[2] The

poison center is an important element of our current health care system; not only does the MPC accept calls from the public, physicians, and other providers free of charge, but they also educate the public and health care professionals through trainings and awareness campaigns (Figure 1). A medical toxicologist is accessible to every hospital 24 hours per day without the costs of having multiple specialists on staff at each facility throughout the state. Additionally, a study performed at Saint Louis University School of Public Health showed that the center was second only to vaccines in cost-effectiveness. Poison Control Center (PCC) consultations prevented an estimated 3.26 emergency department (ED) visits per 10,000 population. Inferring from the sample to the Medicare population, PCC consultations prevented an estimated 13,741 unnecessary ED visits and costs of $6.6 million annually.[3]



MISSOURI POISON CENTER 1-800-222-1222

Figure 1. Missouri Poison Center workstations with Certified Specialists in Poison Information handling emergency calls from Missouri citizens and hospitals.

Poisoning surveillance functions in real-time at the Missouri Poison Center with redacted and confidential case data uploaded every 8 minutes to the American Association of Poison Control Centers (AAPCC) central office and log shipped every 15 minutes to the Missouri Department of Health. The web-based National Poison Data System software facilitates the detection, analysis, and reporting of surveillance anomalies. Over the years, poisoning prevention efforts have been evidence-based and driven by this data, focusing on all ages; not only prevention of poisoning in children with look-alike drugs and chemicals and child-resistant closures on medication bottles, but also adolescent drug abuse and overdoses, as well as medication interactions and miss-dosing of pharmaceuticals by senior citizens. Public education is a mission of the MPC. The service and value to the citizens of Missouri as well as health care providers have been immeasurable.

Value of the MPC in Educating Health Care Professionals

The value of the MPC to society and medical professionals goes beyond the cost-savings and guidance offered in patient care. As a rotation for Pediatric Emergency Medicine (PEM) subspecialty training, Toxicology allows for PEM Fellows to gain familiarity with the assessment and management of toxicologic problems while functioning as part of a toxicology team. This allows for health care professionals in-training to acquire the knowledge required to manage poisoned patients in the emergency department, outpatient clinic or hospital setting; as well as review the basic pharmacology and pathophysiology relevant to medical toxicology. As part of a comprehensive training in toxicology, PEM fellows rotate through the MPC, where they observe Certified Specialists in Poison Information (CSPI) help hospitals and individuals to care for poisoned patients by providing optimal care and serving as a safety net for risk management. The early involvement of CSPIs in poisoning cases has prevented unnecessary emergency department visits and fast-track treatment. This opportunity allows for the health care professional to learn basic clinical toxicology principles and experience the operations of the poison center, whilst also experiencing the dynamic and interactive guidance of a toxicologist and poison information specialist.

History of Poison Prevention in Missouri and the US

National Poison Prevention Week was started in Missouri by a pharmacist Homer A. George in the 1950s. George was concerned about nonexistent antidotes for some medicines and chemicals sold in his practice and realized that prevention was the best first aid.[4] A Morbidity and Mortality Weekly Report (MMWR) from the Centers for Disease Control (CDC) in March of 1986 reads as follows: "He perceived a need for greater public awareness of means to prevent childhood poisonings. In 1958, he convinced his town's mayor to proclaim a Poison Prevention Week, then persuaded Missouri's governor to proclaim a statewide Poison Prevention Week. Eventually, Homer George convinced his congressional representative to introduce national legislation. With assistance from the American College of Apothecaries, the American Pharmaceutical Association, and the Public Health Service (PHS), the enabling legislation was guided through the 86th Congress and signed into law by President John F. Kennedy on September 16, 1961."[5]

Results of Poison Center Surveillance Over the Last 5 to 10 Years

Fast forward a little of over 23 years from that MMWR report to November 2009 when on a routine day at the Missouri Poison Center a CSPI brought to Dr. Scalzo's attention a call to the center from a physician who is caring for a 14-year-old adolescent boy who had ingested a substance called "K2." There was nothing in the Poisindex® database or any on-line sources regarding "K2." The teen was about to jump out of a fifth story window when his friends stopped him. He was hallucinating, agitated, tachycardic, paranoid, and clearly intoxicated. So, what is K2? All we knew at the time is that it was something he smoked and it looked like marijuana (Figure 1). When looking up the term "K2," Dr. Scalzo discovered that it is second highest mountain in the world in the Karakorum Range of the Himalayas and is second to Mount Everest in elevation, but it is more treacherous to climb than Everest. That would prove to be prophetic. It was the "second" high to marijuana but would prove to be more treacherous and deadly.

After fielding several more calls over the next few weeks, the CSPI nurses and pharmacists at the center recorded a dozen cases of K2 exposures in Missouri. A supplemental redacted database of cases was setup for additional surveillance. Dr. Scalzo, as a public health official member of the CDC Epidemiological X (EpiX) user group, reported these 12 cases of K2 toxicity. There was a common case definition of "Agitation, Hallucinations, Tachycardia, Hypertension, and Paranoia." This information was shared nationally. He personally surveyed other major medical centers from New York, Boston, Chicago, San Diego and San Francisco, and no one had experienced more than one or two calls, or most commonly none for this substance. Soon the word spread as did the epicenter of what appears to be the release of K2 in the Midwest. Saint Louis University (SLU) Toxicology and the Missouri Poison Center team along with Christopher Long, PhD, Director of the SLU Forensic Toxicology Laboratory, partnered with the toxicology group at University of Massachusetts (UMass) where an assay for JWH018 and related synthetic cannabinoid compounds had been developed by Amanda Jenkins, PhD, and Chris Rosenbaum, MD, Toxicology Fellow. One of Rosenbaum's mentors, Ed Boyer, MD, Toxicology at UMass and Harvard was also involved and along with Gaylord Lopez, PharmD, Director of the Georgia Poison Center in Atlanta, and one of his physicians, Sean Ragone, MD. A total of 86 patient exposures and their symptoms were cataloged and studied with SLU Institutional Review Board (IRB) and UMass IRB approval.[6]

The word spread around the nation and with the help of the AAPCC various poison alerts were released to educate physicians, hospitals and other health care providers about the dangers of K2, now referred to as a Synthetic Cannabinoid Receptor Agonist (SCRA). The media was also instrumental in spreading the word about the dangers of synthetic cannabinoids. In an effort to help educate the public as well as other health care professionals, Dr. Scalzo was interviewed on CBS, CNN, NBC, and numerous local and Missouri affiliates. The original K2 samples in Missouri as well as patient's urine were tested at SLU Forensic Toxicology Laboratory, and also confirmed at UMass Toxicology Laboratory as positive by mass spectrometry for a compound called JWH018, a synthetic full-agonist for the cannabinoid receptor (CB1). The JWH series of compounds were named after the initials of their developer, John W. Huffman, PhD, Chemistry Chair at Clemson University. Dr. Scalzo personally met with Huffman in his office at Clemson in February of 2010 while attending a mid-year meeting of poison center managing and medical directors in Charleston, South Carolina. This helped

catapult the national investigation into the synthetic cannabinoid epidemic in the US.

Currently, hundreds of SCRAs have been detected including AB-CHMINACA, which was responsible for the death on July 16, 2014, of 19-year-old Connor Reid Eckhardt from Roseville, California. Parents of Eckhardt have single-handedly educated hundreds of thousands of youth and young adults in their travels all over the country and the world. They have almost a quarter of a million followers on Facebook and the number is growing. Borne out of his passion for stopping the use of K2 and related products, on his own accord and expense, Dr Scalzo joined the Eckhardts in May 2015 to support them in making a presentation to over 3,000 youth in Alpharetta, Georgia, an affluent suburb of Atlanta. The synthetic drug epidemic affects the rich, the poor, the privileged, and the underprivileged; it's an equal opportunity "destroyer."

The US Regional Poison Center System and the MPC at Work Today

A more recent phenomenon of synthetic cannabinoids laced with a long-acting warfarin type compound namely brodifacoum is another example of a timely crisis monitored by regional poison centers in the US, including the Illinois Poison Center where most cases have been monitored but also the MPC. Brodifacoum has been commonly used in rat poison products. As of April 2018, there have been over 150 cases nationwide mostly from Illinois, but also from Missouri, Indiana, Wisconsin, and Maryland. Patients who smoked synthetic cannabinoids presented with unexplained bleeding and at least four individuals have died.[7] The common link appears to be smoking synthetic cannabinoid products and many patients have tested positive in their blood for brodifacoum. The index patient who was first identified in Missouri was found to have brodifacoum in his blood and he also tested positive in the Forensic Toxicology Laboratory at Saint Louis University for a metabolite of AB-FUBINACA (another common synthetic cannabinoid). The CDC and state Departments of Health are working in a coordinated effort with toxicologists and regional poison centers to track these cases on a local, state and nationwide basis. This surveillance is yet another reason that our state of Missouri and other states should support the efforts of their poison centers.

Conclusion

The Missouri Poison Center routinely monitors for the emergence of poisoning hazards in the state by reviewing reported exposures to discern unusual events or frequencies. The poison center can assist with acute or chronic drug exposures, including environmental or occupational cases. Clinicians are encouraged to report all adverse medication reactions, poisoning and overdose cases. Every case is important to help the MPC track and evaluate trends in poisoning and identify public health threats in our communities.

Coupled with bedside medical consultation by the Division of Toxicology at Saint Louis University and toxicologists at other academic medical centers, comprehensive poisoning care is provided to the citizens of Missouri. Thus, both patients and their physicians in medical offices, emergency departments, inpatient units, and those critically ill in Intensive Care Units are served. The MPC is available 24 hours a day by calling 1-800-222-1222 or visit the MPC website at www.missouripoisoncenter.org for educational opportunities.

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Hemp & Cannabidiol: What is a Medicine?

by R. L. Hilderbrand PhD



The current motivation of claims and advertising appears to be the financial reward to the marijuana industry rather than the health and well-being of the consumer.



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Colorado allowed medical marijuana for debilitating medical conditions effective in 2000 by an amendment to the Colorado Constitution.[1] The *Colorado Code of Regulations (CCR)Medical Marijuana Rules*, 1 CCR 212-1, establishes the regulatory framework for medical marijuana, primarily focusing on tetrahydrocannabinol (THC) as the active drug.[2] Approval of retail marijuana then passed in Colorado with Amendment 64 effective December 2012.[3] The references above are listed to identify three salient factors: 1) The constitutional amendments allow a variety of marijuana preparations including concentrates, mixtures, preparations and infused materials *with no restrictions on concentration;* 2) The 1 CCR 212-1 for some inexplicable reason states "Medical Marijuana-Infused Product" means a product infused with Medical Marijuana that is intended for use or consumption other than by smoking, including but not limited to edible products, ointments, and tinctures. Such products *shall not be considered a food or drug for purposes of the "Colorado Food and Drug Act."* Thus, a marijuana extract that is widely advertised and distributed as a "medicine" and is frequently included as an infusion in a food product is exempt from Colorado food and drug rules; and 3) Industrial hemp is exempted from the rules applicable to medical marijuana and the *final extracts are not controlled* by Colorado. These three factors create a regulatory abyss that Colorado has not successfully managed. In addition, the federal government has allowed the states with "legalized" retail marijuana to regulate and enforce the rules related to marijuana without federal interference, as long as the state has implemented strong and effective regulations.[4] The quality, contents, and concentrations are suspect both in extracts of marijuana[5] and hemp.[6]

In an attempt to differentiate between cannabidiol (CBD) from marijuana and CBD from hemp, some definition and limitations must be provided. Extracts from marijuana (Cannabis sativa with THC concentrations greater than 0.3%) produced as a "medical product" are regulated by the Marijuana Enforcement Division in Colorado and are subject to testing for contents and contaminants. Hemp (Cannabis sativa with a THC concentration less than 0.3%), having been excluded from medical marijuana rules, has been given to the Colorado Department of Agriculture (CDA) to manage and regulate. CDA's regulatory role with industrial hemp is limited to cultivation; CDA registers land areas for the intended use of growing and cultivation of industrial hemp. The CDA does not have jurisdiction over the processing, sale or distribution of industrial hemp and CDA does not license or verify contents or quality of any extracted product.

CBD as an Extract from Hemp

The focus of this article is CBD extracted from hemp which is generally defined as Cannabis sativa

with a total THC less than 0.3% dry weight in leaves and buds. I emphasize that the only distinction between marijuana and hemp is the concentration of THC. A quick calculation for illustrative purposes shows that when hemp containing 0.3% THC and 5.0% CBD is subject to extraction the final product will contain THC as about 6% of the CBD, since the THC and CBD are removed in an essentially similar manner. The extracted product may contain other cannabinoids, residual solvents, oils from the plant, herbicides or pesticides and other organic molecules. The significant point is that an extract of hemp that is not purified and monitored will certainly contain some concentration of THC. Effective January 13, 2017, the Drug Enforcement Agency (DEA) created a new controlled substances code number (7350) for marijuana extracts.[7] The DEA ruling is very clear that extracts of "any plant of the genus Cannabis, other than the separated resin" are included in Code 7350 in Schedule I of the CSA. This clearly includes extracts of hemp, which is a variety of the Cannabis plant; the US Court of Appeals for the 9th Circuit Court denied a request by petitioners to review the DEA final rule.[8] The DEA also notes there is no way to fully separate the THC from the CBD in extracts from the hemp. As a result, the CBD extracted from hemp remains a Schedule I substance.



The hemp industry, increasingly referred to as 'Big Weed,' is working to make CBD much more than a purported medication and is developing it in the US market as a food supplement that is widely used. Charlotte's Web™ is an extract of hemp that has been widely touted as an option for treating seizures as well as a range of other medical conditions.[9] The cultivar used by the Stanley Brothers is advertised to have a high-CBD content, which was specifically cultivated for a young epileptic patient named Charlotte.[10] This case is instructive as to the claims made by the Stanley Brothers Social Enterprises, LLC, on various websites that implied their products were treatment for depression, cancer, diabetes and other conditions. On October 31, 2017, the FDA, Division of Pharmaceutical Quality Operations IV, issued a warning letter to Joel Stanley, CEO, Stanley Brothers Social Enterprises to correct the claims that the products are drugs and intended to diagnose, cure, mitigate, treat or prevent disease.[11] In addition to being new drugs, the products were misbranded. The company has now modified their claims and provided disclaimer statements.[12] On the same date, the FDA issued similar letters concerning misbranding of CBD to That's Natural! Marketing & Consulting, Pueblo, CO[12] ; Natural Alchemist, El Dorado Hills, CA[13]; and Greenroads Health, Pembroke Pines, FL.[14] The City of Denver has established rules that apply to all CBD products sold or manufactured in the city.[15] This is a step forward to protect consumers from contaminated CBD or CBD from uncertain origin and improper preparation.

A significant challenge in current research and to any current consumer is to know and verify the composition of the material being studied or used. An anecdotal event of a study of a "pure" CBD that was sent for testing was found to be about 75% CBD. In Colorado the cannabinoids being sold at state approved dispensaries and used in oils and edibles may be augmented with CBD extracted from hemp – perhaps to reach a 1:1 ratio of CBD:THC. Testing of purity of these dispensary products should be completed; however, the CBD extracts from hemp may be sold to smoke shops or head shops with no regulation or testing. Purity and composition should be a very real concern to any investigation of CBD and certainly to any consumer.

CBD as a 'Medicine'

The view of CBD as a medicine that is demonstrated by the claims of the companies that are producing and selling CBD on a national scale is stunning. This

acceptance of, and advocacy for, the wildly inflated claims of benefits, seemingly by a large percentage of the general population of this country, leads to the need for an assessment of the actual benefits and adverse consequences. We have come to expect medications that are pure, of known and somewhat consistent efficacy, of a known mechanism, and from a manufacturer that is liable for the quality of the medication. At this time, most products marketed as CBD are suspect.

An exception is Epidiolex®. Epidiolex® is a pure CBD liquid formulation that is produced by GW Pharmaceuticals in the UK.[16] In June 2018 this CBD formulation was approved by the FDA for the treatment of two rare, severe forms of epilepsy (Lennox-Gastaut Syndrome and Dravet Syndrome.) GW Pharmaceuticals has received a number of patents that apply to the Epidiolex® which has a purity of at least 98% (w/w) CBD and THC is less than 0.15% (w/w) at a dose of 10 mg/kg/day.[17] As is appropriate for a medicine, the Epidiolex® is of known purity and concentration and the efficacy has been evaluated by studies approved by the FDA. These patients will be under the care of a physician that will monitor and determine efficacy of the treatment. Epidiolex® is also being evaluated as treatment for other conditions. This scientific approach to providing a medicine is in distinct contrast to the products being produced in many Colorado fields and barns by growers with no knowledge of quality control, extraction processes, contents, and quality of the final product, or the efficacy of the final product. The question is how aggressively GW Pharmaceuticals will address patent protection actions?

A basic literature search of PUBMED displays numerous articles published in the last 25 years that propose a potential benefit of CBD as a medication for many purposes. That literature is too extensive to summarize here; however, a recent publication by S. Pisanti, et al. provides extensive information and references pertaining to CBD.[18] A significant concern is the proposal to use CBD as medication to treat the opioid epidemic.[19] Colorado statistics show a corresponding increase in the opioid epidemic and the use of cannabinoids, but no decline in opioid use with the legalization of marijuana.

A 2017 study looking at market share of products by a Cannabis investment group finds CBD is being used to replace traditional pharmaceuticals. The top conditions being treated included anxiety (67%), insomnia (60%), joint pain and inflammation (52%) and depression (43%). Respondents preferred CBD derived from cannabis to CBD derived from industrial hemp and only 9% of respondents indicated using hemp-derived CBD exclusively.[20] The preference for CBD from Cannabis is significant because, without purification, the CBD extracted from Cannabis will, most likely, contain a much higher percentage of THC than does CBD from hemp.

Summary

All physicians must be aware of the impact, not only of THC, but of CBD on treatment and prescribing of pharmaceuticals to CBD consumers. The advertisements of over-the-counter CBD product as pure, as miracle treatments for a plethora of diseases and as fully legal to sell are blatantly false. The recent approval of Epidiolex® for Lennox-Gastaut Syndrome, and Dravet Syndrome is the sole FDA approval of a CBD as a pharmaceutical. The efficacy of CBD for the many other proposed therapeutic uses has to be proven with legitimate scientific controlled studies. The companies that are advocating for CBD as a generally available health supplement are ignoring the Controlled Substances Act and the likely contamination with THC. CBD remains with a Schedule 1 classification and may place consumers, with no knowledge of the contents of the products, at risk. In a recent address at Institute of Cannabis Research, Dr. Di Marzo stated that the only effect of THC is to make a consumer high; thus, the CBD is the phytocannabinoid with the greatest current possibility to be useful as a medicine. Pharmaceutical preparations of CBD may ultimately be useful; however, current motivation appears to be the financial reward to the CBD industry rather than the health and well-being of the consumer.

Update

Following the Letters of Warning from the FDA, the Colorado Governor signed House Bill 18-1295 into law on May 30, 2018. This bill is significant and alarming in the attempt to prohibit the FDA from acting to control products containing industrial hemp. The bill is intended to establish, with no scientific analysis, that products are not (cannot be) adulterated or misbranded if they contain industrial hemp. HB 18-1295 defines "industrial hemp product" as a finished product containing industrial hemp that is a cosmetic, food, food additive, or herb and is for human use or consumption and contains … any part of the hemp plant (including extracts) but the finished product contains *THC at a concentration less than*

0.3 percent. A concentration limitation does not control the dose and the actual quantity of THC consumed clearly depends on the amount of food ingested. For example, if a baked muffin weighing 3 ounces (85 grams) contains a concentration of 0.3% THC the actual total dose of THC in the one muffin is 255 mg. Having been baked, the THC would be in active form and is many times the dose that may cause impairment and is a danger to an unsuspecting consumer. This law protecting edible hemp products is of particular significance in light of the prescribing information provided for Epidiolex (essentially pure CBD) which warns of potential liver damage and developmental toxicity and other adverse effects that should be monitored by a physician.

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Discloser

None reported. **MM**

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A.M. BEST

Unemployed Physicians

by Charles W. Van Way, III, MD

The National Intern and Resident Matching Program does a decent job, but they can't match into positions which don't exist.

Our political and economic communities are greatly encouraged by the current unemployment rate, hovering just below 4%. And rightly so. It hasn't been that low for ten years, and only occasionally before that. But … what about a physician unemployment rate of 4%? Would that be good? And what if that were the unemployment rate for fresh graduates? Suppose 4% couldn't get jobs? As the saying goes, a recession is when someone else can't get a job, but a depression is when YOU can't. Since pretty much all of us physicians have jobs, it's not a problem. Is it?

With that introduction, let's look at the results of March Madness. No, not the basketball games. The intern and resident match. NRMP. National Intern and Resident Matching Program. March 15, 2018. Actually, it's a full week. On Monday, everyone finds out if they matched. On Tuesday, Wednesday, and Thursday, those who were not matched scramble frantically to find a residency slot. The proper term is "participate in the Supplemental Offer and Assistance Program." SOAP. Great euphemism. It describes the process, without communicating the sense of devastation and the desperation of those who haven't successfully matched. Their whole lives are up for question. Someone whose dream was to be a neurosurgeon at Harvard has to settle for a family medicine residency in Omaha. You think failing to make the Beta fraternity was traumatic when you were in college? Hah.



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Ahem. As I was about to say before the rant, the whole match process works pretty well, for most people. Well, a lot of people, anyway. OK, for the majority. The training programs get filled really well. Even before the "scramble," 96% filled. After the "scramble," 99.4%. It's good for the training programs. Really good. Training programs love the NRMP. But just how good is it for the applicants? You know, our students? Our successors?

The NRMP puts out a report each year. Preliminary results are published within a week or two. Then, the "final" results are published a couple of months later. The final results are more accurate, of course. So, let's look at them.[1] Whatever else one can say about the NRMP, they are absolutely up front with their data. The final report runs to 116 pages, with 19 tables, 9 figures (Figure 1), and a listing of every residency program in the country, with results. It doesn't list results by medical school, which would be important for future applicants.

So. In the 2018 match, there were 44,000 "registrants" world-wide who initially applied to the system. And there were just over 33,000 jobs to fill, of which 30,000 were PGY-1 positions. (Figure 1) All of these numbers were a new high. Of those initial applicants, 19,000 were seniors at American allopathic medical schools. They did fairly well. Around 18,000 (94%) obtained positions, a few of which matched in the "scramble." Still … that's a 6% unemployment rate. It gets worse.

What about the other 25,000? First, many failed to complete their application and submit rank order lists. While there were 44,000 "registrants," there were only 37,000 "applicants" who put in a rank list. Why? Probably, because they didn't have any expressions of interest. The average US graduate fires out 40 to 60 applications and may get anything from 1 to 30 invitations to come interview. If an applicant, either in the US or abroad, fails to hear back from anyone, he or she may reasonably conclude that it's not worth putting in a rank order list.

That leaves 19,000. Just who were these other applicants? I mentioned "world-wide," didn't I? In fact, about 12,000 were international graduates, of whom 5,000 were US citizens and 7,000 non-US citizens. They did not all get jobs. In fact, assuming they put in a rank order

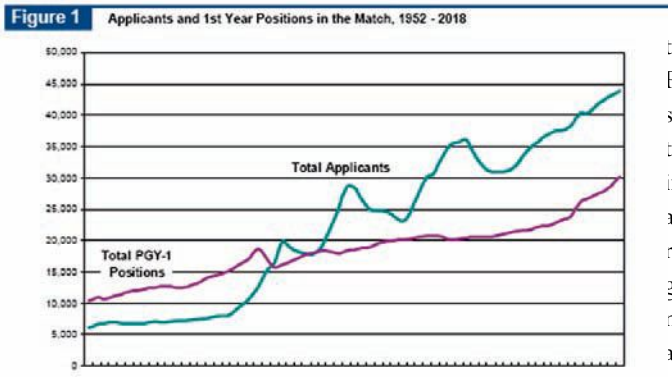


Figure 1. Intern and Resident Match over the past 68 years[1]

list, they had about a 56% chance of getting a job. Well, then, no harm done. The rest can just stay home and work there, right? No. The US citizens did slightly better than non-US citizens, but US citizens had only a 57% match rate. The biggest number of those were from Caribbean schools, but there are Americans in Europe, Mexico, and elsewhere. And when they go home, they're here, and they're unemployed. That's roughly 2,000 new and jobless MDs in our system. Each year.

What about osteopathic graduates? There were 4,600 in the match, a new high. They had an 82% match rate, the same as 2017, and the highest in history. There are still a number of osteopathic residencies around which match separately. Osteopathic graduates apply both to osteopathic programs and the NRMP. The true match rate is probably 85-90%, or even higher. Frankly, I've been unable to tell. With all osteopathic residency programs coming under the ACGME, all formerly osteopathic programs will soon be filled through the NRMP, and the match figures will become progressively more accurate.

So, let's say that there are 1,000 US allopathic graduates, 700 US osteopathic graduates, and 2,000 US international graduates out there after the match, looking for jobs. That's 3,700 doctors who are NOT going to help with our physician shortage. To be fair, a lot of them will find their way to training positions next year. Some will find other ways to be employed. Maybe not as physicians, but somehow. I'm told pharmaceutical sales is a fine career path.

What's the final score? The overall PGY-1 match rate was 78.3%. That's the highest since 2003, and better than 2017. The number of applicants went up, and the number of non-US graduates went down. Among US seniors, 48% matched to their first-choice program, the second lowest on record; 73% matched to one of their top three choices. Of course, that means 27% did not.

Still think that the match does a good job? In grade terms, 78% is what we used to call a "gentleman's C". Perhaps we shouldn't call it March Madness, after all. We should call it the March Lottery. But it's not the fault of the NRMP. They do a decent job, but they can't match into positions which don't exist. The harsh truth is, we are educating more MDs and DOs than we can train as residents, and not by just a few. Counting the international graduates who are US citizens, we are educating about 15% more MDs and DOs than we can train. That's shameful, and it is most definitely our fault as a medical profession. We need to expand our training programs, and we need to do it now.

There are 5,500 acute care hospitals in the US. The ACGME says that only around 800 institutions educate residents. That overstates the situation, because some of those "institutions" cover several hospitals. But it's still a big mismatch. What about YOUR hospital?

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Streamlining the Insurance Prior Authorization Debacle

by J. Collins Corder, MD

There is a real opportunity to improve and significantly reduce the administrative burdens for both the physician and payers along with the patient experience by reforming utilization management and prior authorization programs.

Will streamlining ever be possible as long as we encounter more resistance in our daily care of patients?

Every day, I learn continuously from each patient I am blessed to care for and from the continued interaction with my fellow physicians. I hope this will continue throughout my career in internal medicine.

A common admonition we are hearing is the necessity to "streamline care" to become more efficient. At the same time, we are bombarded with government interference, EHR modernizations, the ups and downs of contracting with insurance companies, continued issues with billing and collection methodology, and last but not least, dealing with prior authorization. The maddening duties of prior authorization disconnect us from our daily clinical work flow and impede our delivery of care. This process involves obtaining prior authorization from insurance companies for pharmaceuticals, durable medical equipment and medical services. It is a burden that drains practices. It is time-consuming in its antiquated methods of using the fax or the telephone, which interrupts practice work flow and pulls the physician and staff away from their daily patient care.

Here is an example. My nurse was denied a prior authorization request, and a peer-to-peer contact was requested of me with the insurance company. My return call for the peer-to-peer that evening was unsuccessful as they had left after 4:30 p.m. I called the next day—and after being on hold for several minutes—I gave the same information that was delivered to the insurance company the day before. I was immediately given the authorization. The decision seemed to be predetermined without me giving any more information.

I asked the reviewing physician his specialty, and he said that he understood what I as a physician was going through as he had practiced medicine for 15 years. I explained to him that during a prior authorization, much of a physician's time is wasted. My day is much different than his day as are my concerns as an advocate for the patient—the one affected by the insurer's determination. I acknowledged that him being in the insurance position is likely the result of him being tired of doing what I have to do in order to practice in this age of medicine.

SLMMS Survey Shows Delays, Restrictions

In December 2016, SLMMS released results of a survey of physicians confirming that St. Louis-area patients are experiencing delays and restrictions in receiving needed care due to insurance company practices in prior authorization.

We undertook this survey to illustrate the problem to the community. Local insurance carriers were rated on a scale of 1-5. "The overall composite score of 3.19 translates to the letter grade of C,'" said Samer Cabbabe, MD, 2016 SLMMS president. "We are very concerned that these delays and restrictions impact our patients' ability to access needed care in a timely manner."[1]



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Findings in the survey revealed that 92% of physicians surveyed agreed or strongly agreed that their ability to practice medicine appropriately is influenced by this process of prior authorization. In addition, 93% somewhat agreed or strongly agreed that they had to alter a patient's treatment plan because of the restrictions from an insurance provider. "Physicians and their staff spend a significant amount of time trying to pre-certify exams and procedures for their patients," Dr. Cabbabe added. "They worry this can endanger patients who have illnesses requiring urgent diagnosis and treatment. Patients get frustrated waiting for approvals for these procedures and tests."[1]

Summarizing physician comments provided in the survey, Dr. Cabbabe said, "Physicians are telling us that the pre-certification process makes it more difficult to practice medicine. Patient conditions can worsen while waiting for insurance approvals, which can sometimes take as long as two weeks. … Through this survey, physicians told us they spend more time fighting insurance companies than they spend fighting disease, and that shouldn't be the case."

He also noted that physicians object to the level to which insurers insert themselves into a patient's care. "One respondent asked, why do we allow people from the insurance company who have never seen or examined the patient to determine the care they should receive?"[1]

AMA Survey Quantifies Impact on Physicians

A month later, the American Medical Association released the results of its survey on prior authorization. It echoed similar findings of physician frustration and how this process impairs our care to patients and creates potentially harmful delays in care. The enormous time wasted in prior authorization processing and cost to our practices and patients is illustrated in their findings. The bottom line is it affects patient care.

The AMA survey pointed out that during the course of the average workweek, a physician completes an average of 37 prior authorization requests. Physicians and their staff spend an average of 16.4 hours per week completing prior authorization requirements for patient medicines, procedures and medical services that they may need. Some 90% of the surveyed physicians in this AMA study reported that the prior authorization process delays patient access to necessary care. And some of these delays are often lengthy, with 26% of physicians stating that in the prior week, they waited three business days or more on average to receive prior authorization decisions from health plans. The study found that on an annual basis, 853 hours were consumed by tasks related to prior authorization.[2]

What this means is that one-third of physicians are required to employ staff members who work exclusively on prior authorization duties. These growing diversions from patient care serve as one of physicians' biggest source of professional dissatisfaction.[2]

The AMA believes that prior authorization is overused and that existing processes are too difficult. Due to its widespread usage and the significant administrative and clinical concerns it can present, the AMA believes that prior authorization is a challenge that needs to be addressed through a multifaceted approach to reduce burdens on physicians and patients.

In conjunction with the survey, the AMA and a coalition of 16 other organizations representing physicians, medical groups, hospitals, pharmacists and patients issued a comprehensive set of 21 principles designed to dramatically reshape the prior-authorization process. Among other things, the coalition calls for an end to repeated prior authorization requirements for patients already stabilized on a medication for a chronic condition. The coalition also seeks industry-wide standardization of the prior authorization process through electronic transactions that are incorporated into electronic health record systems. The 21 principles encompass clinical validity, continuity of care, transparency and fairness, timely access and administrative efficiency, and alternatives and exemptions.[3]

In addition to the AMA, the coalition includes the: American Academy of Child and Adolescent Psychiatry, American Academy of Dermatology, American Academy of Family Physicians, American College of Cardiology, American College of Rheumatology, American Hospital Association, American Pharmacists Association, American Society of Clinical Oncology, Arthritis Foundation, Colorado Medical Society, Medical Group Management

Association, Medical Society of the State of New York, Minnesota Medical Association, North Carolina Medical Society, Ohio State Medical Association and Washington State Medical Association.[3]

In 2016, the AMA House of Delegates adopted an in-depth policy on standardization and simplification of prior authorization. Several states have already passed legislation to protect patients from overly burdensome utilization-management requirements, with Delaware and Ohio among the most recent.[4]

Solutions to This Problem

A lot has been said about our problem and how it costs us time, money and good patient care. Now let us examine how the current state of prior authorization fails and a suggested way in which existing obstacles can be overcome. Our current system lacks the foundation of a widely adopted electronic data exchange, resulting in repeated manual methods and no centralized method of processing and responsibility for obtaining the preauthorization.

There are those that feel health care providers can gain tremendously from automated prior authorization screening and verification. This technology can focus on becoming more centralized, and by defining individual roles and working in consistent approaches to prior authorization. Correcting these disjointed processes, and establishing a better process to include real-time scheduling and EHR integration, will enable instant prior authorization decision making.

The present manual processing is no match for the level of complexity, limited commonality and frequency of changes and updates found among both payers and the different plans. It has been shown that among 23 major health plans, only 8% had a commonality in an analysis of 1,300 procedure-specific authorization policies. Many have their own independent prior authorization policies in their many sub-plans within health plans.[5]

Additionally, authorization details generated by a technology-enabled system would give providers a clear understanding of whether an upcoming treatment will be covered by the patient's insurance, thereby aligning physician and hospital pre-authorization objectives.[5]

Prior authorization is costly—in the range of $35 to $100 per occurrence, according to industry estimates. The cost of processing a claim has dropped to just $0.66 when providers have implemented electronic processing. Imagine what could happen with prior authorization costs when electronic processing ramps up from its current level of only 7% provider adoption?[5] This would occur by eliminating duplicative reviews, administrative savings, and fewer denials resulting in significant savings.

Automated prior authorization screening is already connecting providers to hundreds of payers, with hundreds more electronically linked payers expected to activate in coming months. Every day, repetitive and costly manual tasks are being replaced by codified and callable payer-specific policies, giving providers more control and making the pre-authorization process consistent and replicable.[5]

The effective use of screening and verification rules can slash the time required for research, while arming providers with definitive answers about whether a given service needs a prior authorization. From all indications, it's time to get on board with this vital market trend as providers and payers converge on an admission-centric approach with a keen focus on ROI and improved patient outcomes.

There is a real opportunity to improve and significantly reduce the administrative burdens for both the physician and payers along with the patient experience by reforming utilization management and prior authorization programs. Physicians welcome the opportunity in working collaboratively with health plans to create a partnership which will build the foundation for a more efficient prior authorization process. Both the SLMMS and AMA surveys support the urgent necessity for these changes to be made to allow physicians to practice in both a time- and cost-efficient manner as we face these times of health care change and demands.

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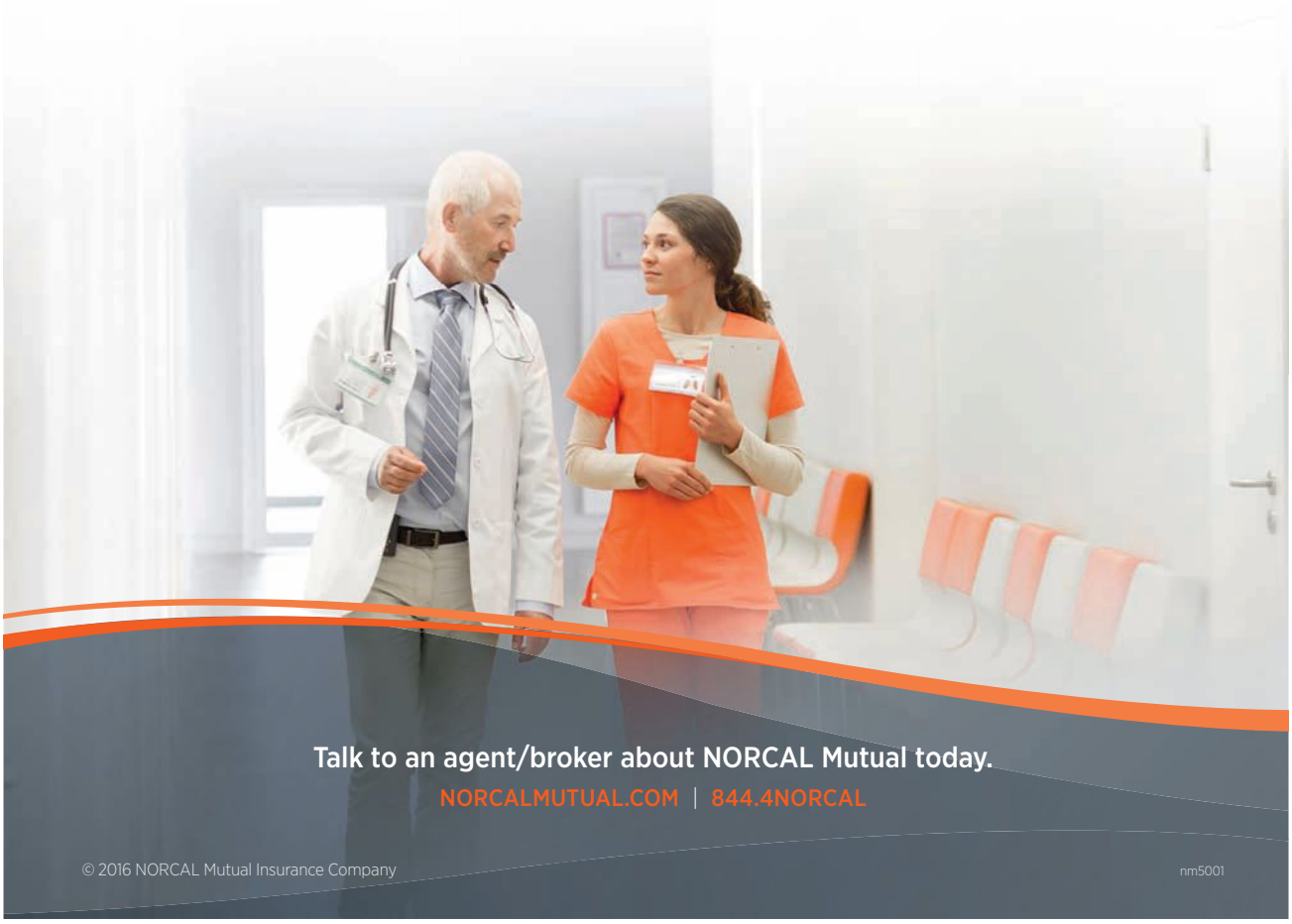
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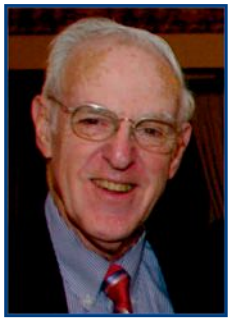
The Onerous Rules of the American Board of Internal Medicine and the National Quality Forum Reward Bureaucrats, Undermine Physician Morale, and Do Not Improve Patient Care

by Arthur Gale, MD

Rules issued by the American Board of Internal Medicine on maintenance of certification (MOC) and mandates on quality developed by the National Quality Forum (NQF) are onerous. The rules for MOC and the quality metrics required by so-called evidence-based medicine have been major factors in causing burnout and depression in physicians. Meanwhile executives in these organizations have been compensated with huge salaries and the industries that they have spawned have gained enormous profits.[1]

The American Board of Internal Medicine

Board certification by the American Board of Internal Medicine (ABIM) was initially for life. Doctors were required to keep up with expanding medical knowledge through continuing medical education (CME). In recent years the ABIM has required maintenance of certification exams known as Maintenance of Certification (MOC). MOC has been required by increasing numbers of hospitals and insurance companies. The ABIM even hired lobbyists who contacted Obama Care officials in order to make MOC a requirement for reimbursement.



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A recent pass rate for ABIM recertification was 78%.[2] If a physician failed the recertification process he or she was essentially deprived of practicing medicine and making a living. This scenario is not hypothetical. Some doctors have been forced out of practice.

One example was a single father with a handicapped child who could not afford the steep fees of thousands of dollars for study materials and the recertification exam. He had to discontinue practicing medicine when he failed his board examination. He had received excellent reviews from his patients. He was reduced to looking for a job as a high school chemistry teacher.[3] There is no proof that MOC improves a physician's performance in practicing medicine.[4]

In an expose´ of the corruption and conflicts of interest at the ABIM, *Newsweek* investigative reporter Kurt Eichenwald wrote:

"Millions have been paid out to senior officers of the ABIM with additional amounts for deferred compensation." The ABIM "has made millionaires of [its] top officers, financed a ritzy condominium, limousines, and first-class travel, all the while sucking huge sums of cash out of the health care system." Despite these high salaries the ABIM is in deep debt due to its lavish spending and financial mismanagement. While "the ABIM's net assets were negative $47.9 million on June 30, 2014, staff expenses for the fiscal year ended that same day climbed 13%, $3.5 million, to $30.7 million."[5]

According to Eichenwald a major reason for increasing the number of and costs of certification exams and educational materials was to pay for the inflated salaries of ABIM executives and staff as well as debts due to mismanagement.

Outraged at the actions of the ABIM a few courageous physicians decided that they'd had enough. They set up an alternative internal medicine certification board to compete with the ABIM.[6] Some excellent and well-known hospitals have accepted certification by this alternate board. And the costs of physician recertification by this board are miniscule compared to the ABIM.

Other physicians have sought to combat the excesses of MOC through legislation. Oklahoma was the first state to eliminate MOC requirements for state licensure.[7] Missouri, through the efforts of the Missouri State Medical Association (MSMA), passed a similar law. Current legislative efforts by the MSMA seek to broaden the current law to apply to hospitals and insurance companies.

As a result of physician backlash the ABIM has modified some of its more onerous and arbitrary rules on recertification but has not eliminated them entirely. Herein lies a lesson. Physicians facing unfair rules and regulations don't have to just give up and accept them as a *fait accompli*. The successes in the fight against the abuses of the ABIM show that physicians when aroused and proactive can win.

The National Quality Forum

Most physicians have probably never heard of the National Quality Forum (NQF) or understand what it does. The NQF has its roots in the Institute of Medicine (IOM) 1999 report "To Err is Human; Building a Safer Health System." (The Institute of Medicine is now called the National Academy of Medicine.) The report concluded that the nation had "an epidemic of medical errors." It estimated that from at least "44,000 to 98,000 persons die in hospitals each year as a result of medical errors that could have been prevented."[8] These numbers were picked up by the press and are still reported today as absolute fact.

The IOM report was based on two poorly researched studies that were never verified and hardly noticed when they were published. One was a study from Colorado and Utah that had not yet been published at the time of the IOM report and the other was the Harvard Medical Practice Study published in 1991 in the New England Journal of Medicine (NEJM).[9]

I remember reading the Harvard study shortly after it was published. I thought the research and the conclusions were unimpressive mainly because there was a lack of agreement on what constituted a medical error between the various teams of doctors and nurses who defined and measured errors. Also most of the patients were extremely ill, often near the end of their lives and it was uncertain whether errors or disease caused their deaths.

The main author of the Harvard study, Troy Brennan, MD, was highly critical of the IOM report and wrote that the conclusions of the study did not support the report of the IOM.[10] Another prominent author wrote a stinging rebuttal to the IOM report in the NEJM.[11]

Nevertheless the damage had been done. The quality zealots and quality police immediately set to work. Despite the fact that the figures in the IOM report were based on faulty evidence the National Quality Forum (NQF) was formed and eventually procured millions of dollars to develop programs to improve "quality."

The IOM "sky is falling" report on errors in medicine created a fake medical crisis. The public accepted the crisis as real. The main goal of the report, however, was to control doctors and create a new "quality" industry. This new bureaucratic industry would then reap huge profits for its academic and business leaders. The NQF receives tens of millions of dollars annually to provide the Centers for Medicare and Medicaid Services (CMS) measurements of quality.

The creation of a fake medical crisis to enrich certain industries in the medical industrial complex is not new. A fake crisis over health care costs in the 1970s was the impetus for the creation of managed care. Health care costs only rose after the advent of managed care not before.[12]

Despite all the money being spent to improve quality none of the quality initiatives have been shown to result in meaningful improvements in clinical outcomes or a meaningful decrease in adverse events. A prominent researcher who initially strongly advocated for Value-Based Purchasing and Pay for Performance (P4P) recently wrote an article in JAMA stating that after years of study P4P has had little or no effect on improving patients' outcomes.[13]

The same can be said of electronic health records (EHRs) and meaningful use. In 2009 the government spent $30 billion for implementation of electronic health records (EHRs) and meaningful use to improve quality. Despite this massive expenditure, a major comprehensive 2014 study concluded that EHRs and meaningful use have not been shown to improve quality.[14]

To summarize, independent studies do not show that evidence based medicine, pay for performance (P4P), meaningful use, and EHRs improve quality. But ones thing is certain; these programs have enhanced the profits of the NQF and the medical "quality" and EHR industries and their well paid executives. And as noted above, these ineffective programs are responsible for significant physician frustration, burnout, and depression. They are also a major cause of physician shortages in certain medical specialties such as primary care.

After successfully combating some of the worst abuses of MOC by the ABIM physicians might consider directing their efforts to combating some of the abuses of P4P, meaningful use and EHRs. If successful, physicians would be able to stop their useless box checking and devote more time to listening to and caring for their patients and even once again enjoy practicing medicine.

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PART 2

The 1918 Influenza in Missouri: Centennial Remembrance of the Crisis

by David S. McKinsey, MD, Joel P. McKinsey, MD & Maithe Enriquez, PhD

Introduction

2018 marks the centennial of the 1918 influenza epidemic, the worst medical crisis in Missouri's history. Although influenza decimated each of the state's eight regions,[1] Missouri's military personnel and its cross-state sibling cities St. Louis and Kansas City absorbed the epidemic's worst blows. This article, second in a two-part series, will chronicle the experiences at Missouri's Army base, Jefferson Barracks, and its World War I field hospital staffed by St. Louisans, Base Hospital 21; review the brutal impact of influenza on the populations of St. Louis and Kansas City; and discuss the effectiveness of public health responses in these cities.

Flu Hits Military Barracks

In the St. Louis area, the first cases of influenza were reported at Jefferson Barracks, the nation's oldest military installment west of the Mississippi River, 17 miles south of downtown. Two hundred thousand enlisted men passed through the base during World War I. On October 1 the first influenza cases were identified; within a week 800 soldiers were hospitalized.[2] Assistance was requested from the Red Cross in St. Louis, and women received hurried training at Barnes Hospital as nurses' aides. Fortunately, despite its initial rapid spread the epidemic was controlled quickly. In total there were more than 2,000 influenza cases at Jefferson Barracks, a much lower figure than at many other military bases in the country. Dr. C. E. Freeman, the Barracks' chief military officer, attributed this better-than-expected outcome to emergency aid from the Red Cross nursing staff.

Missourians also valiantly battled influenza "over there." At the onset of World War I the Army and the American Red Cross created 50 base hospitals, designated as official military units, utilizing personnel from university medical centers. Physicians and nurses from Washington University immediately agreed to staff Base Hospital 21, one of the first six base facilities mobilized in the war. The unit was stationed at a 1,350 bed hospital in Rouen, France.[3] Base Hospital 21's medical services were directed by Lieut. Col. Walter Fischel, brother of Dr. Ellis Fischel who later established a cancer center in Columbia. Patient volume was brisk: there were 500-600 admissions daily. The 61,000 admissions during the war were evenly divided between surgical and medical cases.[4] The most common diagnoses were gangrene or nerve gas poisoning but Base Hospital 21 also served as a treatment center for influenza patients.[5] (Figure 1) In October, 1918, the hospital's daily census crested at an astonishing 1,950 patients, coinciding with the peak of the influenza epidemic in Europe.

In 1918 St. Louis, population 687,000, had a distinctly different heritage and culture than its cross-state rival 340 miles upriver, Kansas City, home to 248,000 citizens. Established in 1764 as a European outpost, St. Louis was the nation's fourth largest city in the early twentieth century. On the western side of the state, Kansas City was not chartered until 1850. Fortunately its founders rejected two of the initially proposed names for the new town, Possum Trot and Rabbitville. By 1918 St. Louis had hosted an Olympics and a World's Fair and had become one of the largest industrial centers in the country, but Kansas City was still considered a wide-open western boom town. If St. Louis was the older, famous, urbane Missouri sibling, Kansas City was its rambunctious younger brother with great potential but still-untamed behavioral issues, as will be discussed.



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Figure 1. Surgical Ward, Base Hospital 21 in Rouen, France 1918.

St. Louis

In late September St. Louis hoped to avoid the devastating experiences recently reported in eastern cities. The City Health Commissioner, Dr. Max Starkloff (Figure 2), son of a Civil War surgeon and great grandfather of the founder of the Starkloff Disability Institute, was a clear-headed, effective, and forceful leader during the emergency.[6,7,8] Mayor Henry Kiel granted unprecedented authority to Dr. Starkloff to implement closures of public places. On September 21, facing the inevitable arrival of the epidemic, Starkloff advised the public to avoid crowds, to get as much rest as possible, and to abstain from alcohol.



Figure 2. Dr. Max Starkloff, St. Louis City Health Commissioner during the 1918 influenza pandemic.

Once cases were confirmed in the city, he was authorized to "issue public health edicts and impose heavy fines on physicians who fail to report influenza cases."

On October 7 Starkloff sprang into action and, as described by Appel, began "shutting down the city"[6] by closing schools, theaters, moving picture houses (in the parlance of the day) and places of amusement (Figure 3). Public gatherings of more than 20 persons were prohibited. The next day closure orders expanded to include playgrounds, library reading rooms, fraternal lodges, pool halls, and Municipal Court. Even churches were closed, for the first time in the city's history. The use of streetcars was limited. Hours for busy downtown department stores, including Famous-Barr, were restricted. A staggered work schedule was implemented at factories to reduce streetcar crowding.[7]

The church closure order was protested by Archbishop (later Cardinal) John J. Glennon to no avail, leading him to suspend temporarily the obligation of Catholics to attend Mass weekly. Eventually churches were allowed to reopen, with strict attendance limits. Father Frederick Holweck, pastor at St. Francis de Sales Church, was turned in to the St. Louis police after 200 parishioners were seen in his church, a violation of the city's anti-crowding ordinance. Father Holweck explained that many worshippers had snuck in through the church's side windows out of his view. Charges were not pressed. Ironically, despite the severe restrictions placed on houses of worship, saloons were allowed to remain open throughout the epidemic (in both St. Louis and Kansas City), three months before the Volstead Act established prohibition.

The epidemic continued for weeks longer than had been expected. In the face of intense pressure from business interests, restrictions were relaxed. On Armistice Day, November 11, when the streets were filled with exuberant citizens celebrating the war's end and "church bells ran nonstop," Starkloff allowed merchants to sell American flags, but only on the sidewalks outside their stores.[8]

Throughout the darkest days of the epidemic, public health authorities received critically important assistance from the American Red Cross (ARC). Surgical dressings, influenza masks, clothing, and hospital supplies were produced by ARC volunteers. The ARC women's motor corps transported health care personnel and patients, including ill cross-country travelers who were picked up at Union Station and taken to nearby hospitals (Figure 4).

More than a million four-page informational pamphlets, containing such pithy advice as "cover up each cough and sneeze, if you don't you'll spread disease," were distributed to the public. The St. Louis Red Cross chapter was so effective during the 1918 influenza epidemic that almost a century later it was described as a "model chapter."[9]

The medical community in St. Louis was inundated by influenza victims. At Barnes Hospital, 410 influenza cases were admitted including nine pregnant women, six of whom died. Among 71 patients at Barnes who had frank pneumonia there were 27 mortalities. Ten of the hospital's 23 residents (so-called because they resided at the hospital throughout their training periods) developed influenza, one of whom, a stalwart young man, succumbed. Nurses fared better: among the 57 who became ill only one developed pneumonia and none died, a finding attributed at the time to mandatory immediate bed rest.[10]

A few scientific observations were reported by academicians, although research opportunities were curtailed by heavy clinical responsibilities. Dr. John Zahorsky, Director of Pediatrics at Saint Louis University School of Medicine, reported that his young patients fared relatively well: almost all had mild, self-limiting illnesses.[11] At Jefferson Barracks, psychiatrist Dr. F. M. Barnes noted a "usual number of deliria… but only one case of a true psychosis."[12] The most notable academic contribution was made by Dr. Eugene Opie, Chair of Pathology at Washington University, who led an Army commission assigned to study pneumonia at military camps. Dr. Opie published a book describing his commission's seminal research into secondary bacterial pneumonia.[13]

Kansas City

The first influenza cases in Kansas City were reported at the Sweeney Automobile School, a private facility converted to military use, during the last week of September. Within a week 800 fell ill. In all, 2,300 of 3,000 Army recruits studying to become mechanics developed influenza and 15 died. The first civilian cases were reported across the street at Fred Harvey's restaurant in Union Station on September 27.[14] Initially all influenza patients in Kansas City were treated at General Hospital, the predecessor of Truman Medical Center. However, after General filled to capacity St. Mary's Hospital was asked to open its doors to influenza victims. All of the nursing sisters at St. Mary's, each of whom worked 24 hour shifts, developed influenza.



Figure 3. "Life's Darkest Moment" *Kansas City Times*, October 19, 1918.

Sisters Mary Cypriana Mertens and Mary Antonia Schlochtermeyer and the Reverend Father Edmund Joseph Unruh all died from influenza acquired in the line of duty.[15]

In Kansas City the implementation of epidemic control measures was impacted substantially, in a negative way, by local political dynamics. Although St. Louis Mayor Kiel was accused by some of being a machine politician, a historian concluded that "St. Louis fought the epidemic without political involvement."[16] This certainly was not the case in Kansas City, which was in a league of its own with regard to municipal corruption.

For several decades in the late 19th and early 20th centuries political bosses ruled the city. According to the *Kansas City Star* in 1918, "practically every member of the health and sanitary departments (held) their jobs by the grace of the bosses." Further complicating matters, in 1918 Tom Pendergast and Joe Shannon had reached a "50-50 agreement" to share power with the result that public board members were split in their allegiances. The palpable animosity among board members severely hampered an effective public health response. A detailed description of this dysfunctional situation is provided by Sykes-Berry.[15]



Figure 4. American Red Cross workers, St. Louis 1918.

The key figures in Kansas City's highly politicized public health squabble included the city's two top health officials, Dr. A. J. Gannon, Director of the Health Department's Contagious Diseases Department and Dr. E. H. Bullock, Kansas City Health Director and Superintendent at General Hospital; Mayor James Cargill; and W. T. Motley, a non-physician who was president of the Hospital and Health Department. Physicians at General Hospital served on an advisory board, but their advice often went unheeded. Mayor Cargill initially sought political cover from angry businessmen, who faced financial losses, by delegating controversial decisions to the advisory board. Subsequently he accused the Board of "incompetence" and overturned its decisions.[15,16]

Early in the epidemic Gannon sought to implement a number of measures but was overruled and publicly criticized by Motley who initially supported Bullock, who issued his own proclamations. Daily newspaper headlines trumpeted the arguments among these factions. Gannon became a scapegoat for the epidemic and, in a profane shouting match at a public meeting on November 26, was dismissed from his position. The public's frustration was evident: a *Kansas City Star* editorial described "the utter futility of the present hospital and health board coping with the influenza epidemic so long as it is a politically controlled body and forced to accept the dictates of political bosses."

Despite the public authorities' disagreements (one alderman called a ban of public meetings "Hun propaganda"), most of the same measures undertaken in St. Louis were implemented in Kansas City. Public schools were closed on three separate occasions (no other city in the country closed schools more than twice.) On October 10, classes at three dental schools and eight barber colleges were suspended. The latter were considered especially high-risk environments given that one towel typically was used on up to 50 clients. Spitting in public was declared a misdemeanor subject to arrest.[15, 16]

In addition to official closures and restrictions implemented by city government, general advice and recommendations from both the medical community and the lay public abounded. Dr. Gannon "believe(d) the epidemic had its start (here) by girls kissing soldiers in the Army schools and cantonments ...There is a lot of kissing ... and if a ban should be placed on it there would be less influenza."[16] Gannon also offered the following advice: "stay out of crowds, avoid dust, take laxatives, drink plenty of water, and spray (the) nose with dilute Listerine or salt water." He imputed a preventative role for garlic and onions, based on the lower incidence of disease in the city's Little Italy district. Gannon required saloons, soda fountains, and restaurants to close for 30 minutes twice a day to boil their dishes in soda and water. He suggested fumigation of schools and factories with formaldehyde candles, and recommended the use of disinfectant finger bowls for cashiers.[15,16]

His adversary Dr. Bullock recommended that citizens spend the nights on their sleeping porches. Bullock and Gannon both believed incorrectly that "freezing weather and rain would eliminate the influenza epidemic by clearing the air." Dr. J. D. Griffith suggested consuming a teaspoon of soda in boiled water three to four times a day. As was the case elsewhere in the country, authorities insisted on the use of cotton masks for everyone who came into contact with the public; these masks were ineffective. In 2010 Dr. Charles White (1905-2014), who began his medical practice in Kansas City about a decade after the 1918 epidemic, told the authors that in his early years he and his colleagues "used to come up with very elaborate treatment protocols; of course there was no scientific basis for any of it." The same statement is applicable to many of the influenza prevention strategies promoted in 1918.

The general public joined in advocating a variety of practices to prevent influenza: wearing skunk oil vials around the neck; smoking; drinking; eating rock candy; and placing sliced onions on window sills. One

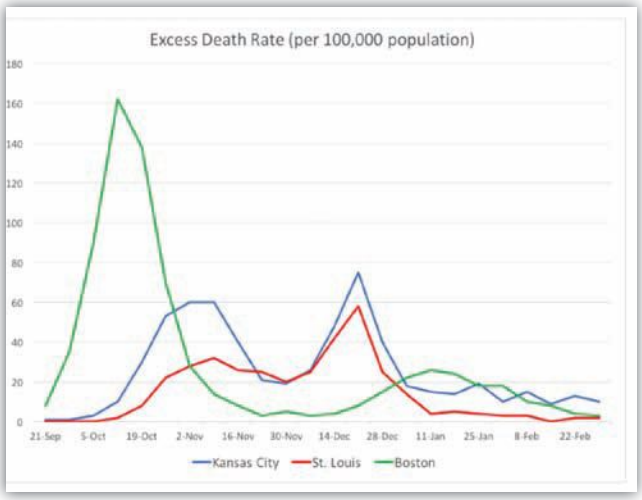


Figure 5. Weekly excess death rate per 100,000 population in Kansas City, St. Louis, and Boston during the 1918 influenza pandemic.

Table 1

Setting	Influenza/Pneumonia Deaths, last 4 months of year	Excess deaths over baseline	Mortality rate/100,000	Mortality ratio 1918:1915	Mortality above rural (%)[2]	Rank among 49 US Cities
Missouri						
-Total[3]	12,250	10,657	476	3.3		
-Excluding large cities	7,643	6,743	339[4]	N. A.	N. A.	
St. Louis	2,883	2,407	537	3.4	21	32
Kansas City	1,724	1,507	718	4.1	41	17

1. data are from 1918
2. rural defined as population <100,000
3. data include figures from St. Louis and Kansas City
4. estimate
N.A.: not available
Sources: Mortality Statistics 1919[20]; Hatchett[19]

lady ate a cake of yeast a day as a prophylactic. Although she was spared from influenza, she experienced severe abdominal pain, bloating and eructation; her friends told her she was "rising." In 1918 saloons lined the Missouri side of State Line Road; on the other side of the street in Kansas, the sale of alcohol would not be legalized until 1948. Many of these establishments advertised prophylactic quinine and whiskey to their patrons.[15,16]

As in St. Louis, community volunteer organizations in Kansas City played a crucial role in responding to the epidemic. The city's first meaningful action was taken by the Chairman of the Kansas City Chamber of Commerce, Bernard Parsons, who summoned the Mayor, the ARC, the Hospital and Health Board, and leading businessmen to action. The ARC volunteered the services of its personnel and the use of all its facilities and donated supplies valued at thousands of dollars to General Hospital. The Visiting Nurses Association (VNA) staff was mobilized into service immediately. VNA nurses made 4,392 visits to 1,254 influenza patients in the city, but there remained a critical nursing shortage. Mrs. Harry Mather, nursing director of the ARC, requested volunteer nurses' aides from the general public, stating ''they need have no experience, simply good health and ability to work long hours."[15] Although Kansas City (and St. Louis) would not desegregate until decades after the epidemic, and trained black nurses were rejected for service in World War I despite a desperate need, General Hospital requested and received much-appreciated service from black nurses during the height of the influenza crisis.[15]

Outcomes

Abundant available epidemiological data paint a clear, if grim, picture of influenza's toll in Missouri's two largest cities (Table 1). St. Louis reported 31,693 influenza cases and 2,883 deaths. In Kansas City, 11,431 cases of influenza and 1,724 deaths were reported.[19] The actual numbers of influenza cases undoubtedly were much higher, as many cases were not reported. Both St. Louis and Kansas City had higher rates of excess mortality than other areas of Missouri. Despite these dreadful mortality figures, the two cities fared relatively well in comparison to many other large metropolitan areas. In St. Louis the mortality rate ranked 32nd highest among 49 U. S. cities with populations above 100,000 and was the lowest of the 10 largest cities in the country; Kansas City had the 17th highest mortality rate (Pittsburgh, Pa., ranked first; Grand Rapids, Mi., had the lowest mortality).[17]

What factors explain the widely variable death rates among American cities in the 1918 epidemic? In hindsight through the lens of 21st century epidemiologic analysis, insight is gained by assessment of several metrics: time from the first reported cases to the peak of the epidemic;

overall excess mortality compared to baseline; excess mortality at the peak; and weekly mortality curves over the duration of the epidemic. Figure 5 shows the epidemic curves of St. Louis and Kansas City in comparison to Boston, a typical hard-hit eastern city which had the fifth highest mortality in the country. Boston experienced one dominant early autumn wave with an early peak and exceedingly high excess mortality. The epidemic curves in the two Missouri cities, which were comparable, had important distinctions from Boston: later onset of the epidemic; longer time from onset to peak; much lower peak mortality; and two autumn/winter waves with highest mortality in the last wave. Several factors accounted for these differences.

Cities that implemented what are now known as social distancing interventions earlier had much lower peak mortality rates than those which delayed action.[18] The flattened epidemic curves in St. Louis and Kansas City, as compared to Boston, indicate that control measures were effective and were implemented early enough to reduce mortality. In retrospect only a handful of the many "nonpharmaceutical interventions" used in 1918 worked: early closures of schools, churches, and theaters, and bans on public gatherings.[19] Each of these measures were enforced in both Missouri cities. The duration of implementation of nonpharmaceutical interventions also had a salutary effect on mortality. Both Missouri cities maintained social distancing policies longer than many other cities. The net result was that in hindsight, both St. Louis and Kansas City, despite the latter's political missteps, were among the four large U. S. cities, of 17 assessed, with the most effective interventions. In both cities disease transmission was 30-50% lower than expected.[19] Modern policy makers have used these findings to refine public health approaches for contemporary pandemic influenza preparedness.[17,18, 19]

Two other findings are notable. First, in both Missouri cities the higher second autumn/winter waves occurred after social distancing restrictions had been eased prematurely. Second, influenza mortality in Kansas City was consistently above that in St. Louis: from the onset of the epidemic in early October 1918 until its conclusion six months later, mortality rates were higher in Kansas City in 24 of 26 weeks.

In summary, from the vantage point of a century, we now recognize that social distancing actions taken by public health authorities in both St. Louis and Kansas City led to demonstrably reduced peak and overall excess influenza mortality rates. However, in both cities, premature easing of school closures and other epidemic control measures resulted in higher mortality in the second autumn/winter waves. History has given high marks to public health and volunteer organizational responses to 1918 influenza for both of Missouri's major cities, especially St. Louis, which benefitted from stronger leadership and a much less politicized public health approach than its sibling Kansas City.

Acknowledgments

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Continuing Obligations Following the Unexpected Death of a Physician: Things to Keep in Mind

by Wakaba Tessier, Wendy Keegan & Erica Ash

Introduction

Although the number of physician-owned group practices and solo practices is getting smaller, nationwide 57% of physicians still work for practices with less than ten providers and 16.5% of physicians are solo practitioners.[1] Especially in these smaller practices, the unexpected death of a physician can have significant effects on the practice's ability to care for patients. This article examines the ongoing obligations of practices immediately following a physician death, from both a group and solo practitioner perspective. In some instances, family members may need to step into the shoes of a group's administrator and take on the obligations set forth in this article, especially if the physician ran a solo practice and had minimal, or no, administrative staff.

Please note that this article is not intended to be an exhaustive list of the obligations one needs to undertake upon the sudden death of a physician. Rather, this article raises key issues and is meant to be read as general guidance.





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Notification

Upon the death of a physician, practices have obligations to notify certain regulatory agencies and business partners or vendors, which will likely vary given the type and size of the practice and its contractual obligations. Most importantly, practices must notify patients as soon as possible to facilitate continued patient care.

Patient Notification

The office should notify patients as soon as possible to support continuity of care for the deceased physician's patients.[2] As a first priority, the office staff should call patients with scheduled appointments so patients with immediate needs for a physician can find another healthcare provider. The office should also consider changing its answering message to alert patients calling the office that the physician's appointments have been cancelled and the physician will not be scheduling any new appointments. If another health care provider has agreed to provide patient care in the interim, the message should include such provider's contact information. If the practice uses an answering service, the office should inform the answering service of the same information.

The office should also send a letter to all of the deceased provider's active patients, which in Missouri is any patient who has had an appointment in the past seven years.[3] For example, the American Psychiatry Association ("APA") recommends that the office send this letter within forty-eight hours of receiving notification of the physician's death, which is consistent with the American Medical Association's Ethical Opinion 1.1.5.[4] The APA also recommends sending the letters via Registered Mail with a Return Receipt requested and retaining the return receipts in the patient record. Retaining the receipts ensures the practice has proof it sent notifications for any liability purposes.

Many medical associations provide example termination letters on their websites.[5] These examples contain the type of information that should be in a termination letter and are helpful starting points, as the specific information will vary depending on the type and size of the medical practice.

Patient notification letters typically should address at least the following issues.

For solo practices that are winding up, the letter should provide contact information for any physician who agrees to take over the deceased physician's short-term duties (e.g., answering post-surgical questions, providing prescription refills, etc.). To facilitate the transfer of care, practices that are winding up should also explain how the patient can find a new physician.[6] For example, patients can contact their insurance companies to get a list of providers in their coverage and plan area, do searches on the internet, look in phone books, and/or contact local medical associations for referrals. If the practice is not winding up, the letter can inform patients that they can find a new healthcare provider in any of the ways previously mentioned or continue care by any of the physicians within the practice.

The notice letter should also provide patients with four key pieces of information about their medical records. First, the letter should explain how patients may obtain copies of their medical records, either for themselves or for a successor medical provider. Because some patients may want their records sent to a new provider, the practice should attach a HIPAA compliant authorization to the letter so it may release the patient's records if the patient so chooses. Second, if after a certain date the records will be stored at a location other than the practice site, the letter should provide the contact information where patients can retrieve their medical records. Third, the letter should also outline any charges the patient will be responsible for with respect to copying and sending medical records. Missouri permits providers to charge a reasonable amount for copies. The amount cannot exceed "twenty-four dollars and eighty-five cents plus copying in the amount of fifty-seven cents per page for the cost of supplies and labor;"[7] however, this amount may change. Accordingly, practices should check the rate before charging patients. Finally, the letter should inform patients of the record retention policy, which is governed by state law, and that records not claimed within the specified time will be disposed of in accordance with the practice's record retention policy.

Notifying Agencies

The practice should also notify any state licensing boards, malpractice carriers, and third-party payors of a physician's death. Upon notification, it is likely that these entities will provide specific guidance on terminating any ongoing obligations with respect to the deceased physician. In addition, the practice should also notify the Drug Enforcement Administration (DEA) and any state controlled substance registration office in writing to have the DEA and state controlled substance registration, if applicable, retired.[8] If the deceased physician was a solo practitioner, the office will also need to dispose of any unused controlled substances and unused prescription pads (sometimes referred to as "Blanks"). The practice should consult with the local DEA office on procedures regarding unused inventory. The DEA's Diversion website has guidelines for disposing controlled substances and may provide further guidance.[9]

Patient Record Retention

Patient medical record retention could raise regulatory issues after a provider dies if the office fails to keep the records for the proper amount of time or in the proper manner.

Length of Retention

Missouri requires providers to keep records for at least seven years after the last service was provided.[10] Although the general statute does not specifically carve out an exception for minors,[11] the Missouri State Medical Association recommends "if the patient is a minor, you should plan on keeping the records at least until they reach nineteen years of age, or seven years since you have seen the patient[,]" whichever is longer.[12]

Manner of Retention

Though the duration of retention is the same for solo and group practitioners, the manner of retention will likely vary. Missouri regulations and HIPAA require that patients have access to their medical records and also that the records are kept private. Thus, if the deceased provider worked as part of a group, the group could retain the records with its other patient records. However, if the deceased provider worked as a solo practitioner, retaining the records could be more difficult. One option for the solo practitioner's office would be to store the records off site at a company that specializes in medical record retention. In the alternative, it could enter into a medical record custodial agreement with another practice.

Ongoing Liability Issues

Retaining medical records is a good practice because patients can sue the physician's estate for malpractice until the statute of limitations expires. Thus, beneficiaries may also want to check the physician's malpractice insurance to see what kind of policy the deceased provider had and decide if the coverage is sufficient. For example, if the physician had an Occurrence Policy, which provides coverage for any event that occurred during the policy

period,[13] no additional coverage would be necessary. Occurrence Policies provide the broadest coverage and, thus, are usually the most expensive. In the alternative, many physicians have Claims-Made Policies, which only cover claims reported during the policy period.[14] If the deceased physician had a Claims-Made Policy, the estate or practice may want to obtain additional insurance coverage. This additional coverage is often referred to as "Tail Coverage" or Extended Reporting Period ("ERP") Coverage and provides malpractice coverage for incidences that occurred during the original policy period but are reported after its expiration.[15] For an individual's policy, the deceased physician's insurer usually issues ERP coverage at no additional charge if the original coverage terminates due to death.[16] If the insurer does not issue free ERP coverage cost, the estate or practice may also usually purchase the coverage.[17]

While purchasing ERP coverage helps protect personal assets from malpractice liability, it is not cost effective or necessary to keep additional coverage forever because plaintiffs cannot bring lawsuits forever. Rather, plaintiffs must bring lawsuits within a certain period of time, called the "statute of limitations," or their claims are barred. Missouri has a two-year statute of limitations for medical malpractice claims; however, there are exceptions.[18] Patients can bring claims after two years if the patient is a minor or if the patient did not reasonably know she had a malpractice claim.[19] For example, if a physician performed surgery, the physician could be liable for malpractice claims for leaving a medical instrument inside the patient. In that case, the two-year statute of limitations would not start until the patient knew or should have known about the malpractice,[20] which could be much longer than two-years depending on when the patient discovers the object. Further, if the deceased physician treated minors, the physician could be liable for malpractice claims until the minors are twenty.[21] Ultimately, the physician's patient population and specialty will inform the need for Tail Coverage and the length of time for which it is reasonable to maintain.

Conclusion

The death of a physician can lead to uncertainty about the ongoing obligations of the medical practice. Further, those obligations can vary greatly depending on the size and type of practice. Awareness of these issues and some advanced planning can help to assure continuity of care for patients, and peace of mind for the practice and the deceased physician's estate. For more specific information about these obligations, you should consult with a licensed attorney who specializes in healthcare regulatory issues.

Helpful Resources

- The Missouri State Medical Association's website provides useful information about record retention in Missouri and is available at http://www.msma.org.
- For more information about record retention, visit Health Information & the Law at www.healthinfolaw.org.
- The DEA Diversion's website provides information about disposing of controlled substances and Blanks and is available at https://www.deadiversion.usdoj.gov/drugdisposal/index.html.
- For more information about obligations to patients, the AMA's Code of Medical Ethics is available online at https://www.ama-assn.org/delivering-care/medical-ethics.

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2. Am. Med. Ass'n, Code of Medical Ethics: 1.1.5 Terminating a Patient-Physician Relationship (2016) (hereinafter "Code of Medical Ethics: 1.1.5") (requiring that when a physician withdraws from a case, the physician must "(a) Notify the patient (or authorized decision maker) long enough in advance to permit the patient to secure another physician. (b) Facilitate transfer of care when appropriate.")
3. See Mo. Ann. Stat. § 334.097(2) (West 2018) ("Patient records remaining under the care, custody and control of the licensee shall be maintained by the licensee of the board, or the licensee's designee, for a minimum of seven years from the date of when the last professional service was provided.")
4. See id.; Am. Psychiatric Ass'n, Closing a Practice at Short Notice: What Every Psychiatrist and Their Family Should Know 3 (2007).
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9. For more guidance about how to properly dispose of controlled substances see Disposal of Controlled Substances by Registrants, 21 C.F.R. § 1317.05 (2018).
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21. Id.

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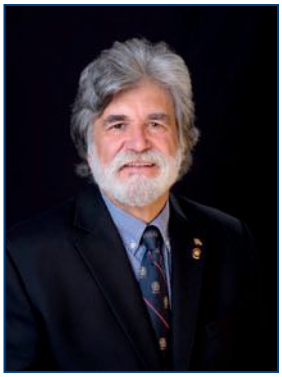
Quo Vadis?

by Joseph A. Corrado, MD

It is an honor to represent you as MSMA President in 2018-2019. I thought I'd enlighten you as to what's been going on. I must say, I didn't realize how difficult it would be to actively maintain a rural solo surgical practice and fulfill my presidential duties, but so far it has been terrific.

One of my goals was to represent MSMA at the contiguous state medical associations and get a pulse on what other societies face and feel. Since Missouri touches the most states, eight in all, that was hefty. So far, Donna, my wife, and I have been to five, quite a feat since some were on the same weekends.

As my first official act, we went to the Illinois State Medical Society's annual meeting on the outskirts of Chicago to honor the outgoing president Nestor Ramirez, MD, and see Kathryn Tyner MD, installed. Dr. Ramirez has an exciting story. He presented me with his recent book "When Pigs Fly," which chronicles his life, immigrating from his native Colombia, working as a country doctor in the Amazon forests. For entertainment he had a wonderful exhibition of Colombian Folk Dancing in full regalia and a banquet showcasing his native foods. Of note, they are also struggling to maintain membership, a little different since it's Chicago, than the rest of the state. They were wrestling with the question and voted to de-link their memberships between counties and the state in hopes it would encourage individual memberships in the counties that are struggling as well.



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The next weekend we visited the Iowa Medical Society in Des Moines, and were honored at their president's reception seeing President Joyce Vista-Wayne, MD, hand over the reins to Michael Romano, MD. Their membership had grown because their physician advocacy resulted in sweeping tort reform legislation in this state. The new president stressed how healthcare reimbursement in the U.S. has been going through its biggest change since Medicare in 1965, and that elected officials want and need to hear our views on the issues that matter to us. We at MSMA also feel that an organized state medical society is that vehicle. There was a wonderful talk on generational differences; it was focused on understanding the different thought processes between the different age groups. MSMA will offer this CME event at our 2019 Annual Convention.

After a long night drive, we made it to Oklahoma City for the OSMA inauguration of Jean Hausheer, MD. As Kevin Taubman, MD, relinquished his position, he noted that Dr. Hausheer had strong roots from training in Kansas City, Missouri, and considers herself a tiger. I was struck by the sparse attendance, but was invited by Jack Beller, MD, to sit in on their own OSMA Health Insurance meeting and I have brought that back for discussion and thought.

The following weekend we traveled to DeGray Lake Resort in Bismarck, Ark., to visit the Arkansas Medical Society. Let's just say the adage "You can't get there from here" has some credence. There, Amy Cahill, MD, installed Lee Archer, MD, as president, and we were cordially welcomed by Scott Ferguson, MD, then joined Jerry Harmon, MD, both on the AMA Board of Trustees. We listened to the hot topic of sexual harassment in the workplace, a timely issue, and how important it is for our protection to have policies in place.

We quickly bustled to Nashville to attend the Tennessee Medical Association annual gathering, as Nita Shumaker, MD, handed the reins to Matthew Mancini, MD. His goal was to make a measurable difference in the opioid abuse epidemic and to turn the tide on this crisis. They also are avidly looking at ways to supplement membership and not rely on dues dollars for the majority of their operating revenue. They develop physician services

(TMOPS) and prioritize partnerships for sources physicians regularly use with products at discounted rates.

Back again to Chicago and the AMA annual meeting in June; an eye-opening experience for those uninitiated, but there one understands just how important it is to be involved in organized medicine, and to see how everything we do at MSMA and at the AMA really does count. They are fighting to help physicians, no matter what specialty, in all issues affecting us, whether it's reimbursement, oppressive laws and mandates, or advocating for what's best for our patients. The highlight was to proudly stand on the podium with all 50 presidents behind our own David Barbe, MD, as he relinquished the power to Barbara McAneny, MD. Her message echoed my own, "Be proud and celebrate your achievement of becoming a physician." You are not just a provider. Insist on your title - you worked hard for it. Again, congratulations, David, on a phenomenal accomplishment and a great source of pride for us all.

Home again to connect with the Northeast Missouri Medical Society in Hannibal, then on to the Tri-County Medical Society in Washington, both very informative and cordial meetings. There I heard a wonderful view from a former Advanced Practice Nurse who now is a family practice physician. Her take was to recognize how much she didn't know, and how naive she and her supervising physician really were before she went to medical school and residency.

With our colleagues and staff to hear the same concerns, whether at the county level or at the national level, and proudly representing MSMA, I'm impressed at how many physicians are involved and feel strongly that all physicians need and should be members of organized medicine. Being a doctor requires a lot of work, it's not easy but there is no excuse, apathy is not an option. Trust me, if I can do it, anyone can.

On the horizon are the last three neighboring state conventions and greeting many of you at your local societies. Come, engage, and bring a physician friend. **MM**







Top, Dr. Corrado with AMA President Barbara McAneny, MD; with Oklahoma President Jean Hausheer, MD; and with Arkansas AMA Trustee Scott Ferguson, MD, and spouses.

Physician Advocacy: The AMA Annual Meeting 2018

by the Missouri Delegation to the AMA and compiled by Charles Van Way, III, MD

The AMA considers all matters of health as its charge. But every year, certain things are emphasized over others. At the 2018 Annual Meeting in Chicago, June 9-13, these were the opioid crisis, public health, firearm violence, medical education, insurance and finance, prescription drugs, and physician well-being.

The opioid crisis concerns all physicians. With considerable pressure from both state legislatures and medical organizations, physicians have collectively reduced opioid prescriptions by 20% over the last 2-3 years. But the death rate continues to rise. Several resolutions addressed this by condemning the companies making opioids, by educating physicians, by better training medical students and residents, and by encouraging drug companies to produce alternative non-addicting classes of pain killers. The problem is growing, and there was little consensus on how to deal with it.

A resolution addressed the problem of drug-assisted sexual assault by calling for mandatory drug testing of all victims. Drs. Rebecca Hierholzer of Missouri and Mark Miller from the Council on Science and Public Health educated the HOD about drug facilitated assault, especially about the inability of hospital and clinics to offer immediate testing due to lack of quick reliable assays and chain-of-custody issues. Occasionally, the HOD can become collectively enthusiastic about an appealing policy, without considering whether that policy is feasible. The well-intentioned resolution was not adopted.



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Perhaps the most popular issue at the meeting was control of firearm violence. The AMA has long supported gun control. Existing policies were strengthened by resolutions supporting prohibition of "assault-type" weapons, "bump" stocks, large capacity magazines, and armor-piercing bullets; mandatory registration of all firearm owners; and requiring that persons be licensed before they can purchase a semi-automatic firearm. This highly confrontive approach had a great deal of appeal to the delegates, who were focused on mass shootings, especially at schools.

Both a report from the AMA and a presentation on prevention of firearm violence took a public health-oriented approach. The 0.3% of deaths from mass shootings are highly publicized and distressing to all of us. But 59% of firearm deaths are suicides, and 39% interpersonal violence. To lower firearm deaths, these must be addressed. The panel presentation advocated collaboration among physicians, public health, hunting organizations, gun safety groups, and the general public. The AMA appears to be adopting a carrot and stick approach, calling for restrictive regulations while still advocating a collaborative approach.

Continuing with current political issues, the HOD adopted a resolution calling for a change in the current administration's policy of separating families of illegal immigrants, jailing the adults and placing the children elsewhere. This resolution was featured in newspaper articles across the country. As we all know, the policy has since been rescinded. But the issue remains, and implementation of new policies is "evolving." That's government-ese for "directionless and confused."

A resolution from Oklahoma called for physician education on human trafficking. A large percentage of victims come to the health care system, but very few are identified by physicians or hospital staff personnel. Human trafficking is a much larger legal and public health problem than most of us appreciate, and such education will have significant impact.

The AMA remains active in improving medical education. A report discussed the growing mismatch between places available for graduate medical education and



Missouri Delegates at the 2018 AMA Annual Meeting.

the number of physicians (MD and DO) being graduated. There are more first year jobs than there are graduates of US MD/DO schools, but much fewer than the total number of applicants. An increasing number of U.S. MD/DO graduates from U.S. and international schools are without positions following graduation. The report strongly advocated expanding graduate medical education to keep pace with expanding undergraduate medical education. Placement of graduates in GME should become one of the criteria by which medical schools are judged. The problem of graduates without residencies is severe, with perhaps 3,000 to 4,000 new MDs and DOs each year being unable to find jobs a training position.

Health insurance and health care financing continues to be a major concern. The cost of health insurance is unreasonably high. The financial strain of illness has become the most common trigger for individual bankruptcies. A report from the Council of Medical Services put part of the blame for recent increases on the repeal of the individual mandate. It recommended making premiums deductible up to 500% of the present limit, educating the public on health insurance, and establishing a federal reinsurance program. A resolution from Missouri called for evaluation of medical student education in health finance; this was referred for study, presumably by the Council on Medical Education.

Prescription drug shortages continue to plague the health care system. The AMA has already declared this a public health crisis. A resolution called for steps to be taken to minimize the impact of natural disasters on the drug supply. The possible role of pharmacy benefit managers in restricting the supply of drugs and increasing their cost was also discussed, Resolutions called for more control of pharmacy benefit managers, which are now given an anti-kickback "safe harbor" from oversight and regulation.

Continuing concerns about the electronic health record (EHR) resulted in a number of resolutions. One proposed requiring integration of prescription drug monitoring program with EHRs; this was referred for study, as it turns out to be a very complex technical issue. Other resolutions deal with requirements for interoperability and sharing of information, meaningful use requirements, integration of drug cost data, and education of students and residents in the use of EHRs. There was a Board of Trustees (BOT) report on "augmented intelligence" (AI), the new term for artificial intelligence. Several resolutions either dealt with AI or referred to it.

As always, there were a number of proposals concerning public health. Resolutions dealt with vaccination against papilloma virus. Resolutions on e-cigarettes called for effective regulation by the FDA, including listing of ingredients and national-level rules on things like access by minors.

The meeting of the Organization of State Medical Association Presidents (OSMAP) the day prior to the House of Delegates meeting was, as always, devoted to state issues. David Barbe, MD, spoke, as AMA president, of the current directions of the AMA. He included work-life balance, insurance issues, scope of practice issues, opioid use, and the always-critical issue of membership in the AMA. Other state-level issues included a movement for tort reform in Arkansas, a critical Wisconsin Supreme Court decision affecting caps on malpractice settlements, an attempt to impose medical price controls in California, and an opioid education program from Ohio. In Delaware, the medical society is beginning the use of blockchain technology to speed up prior authorization requests.

Several people from Missouri were in leadership roles. David Barbe, MD, finished his term as President of the AMA with this meeting. Dr. Barbe addressed the House of Delegates (HOD), emphasizing the importance of physician leadership. Edmond Cabbabe, MD, serves on the Council for Long Range Planning and Development. Jerry Kennett, MD, concluded eight years' service on the Council on Legislation. Charles Van Way, MD, continues to serve on the Steering Committee of OSMAP.

Barbara McAneny, MD, was inaugurated as the 173rd president of the AMA. An oncologist from New Mexico, Dr. McAneny has promoted innovative practice models, and has been a strong voice for care of the Hispanic and Native American populations in New Mexico.

Patrice Harris, MD, was elected to be President-Elect. A physician from Atlanta, Georgia, she has been Chair of the Board of Trustees, and has been a strong advocate for the care of underserved minorities. **MM**

Rising Leaders: Residents and Fellows at AMA Annual 2018

by Joanne Loethen, MD

Be driven, be committed, and lead medicine forward. These were messages residents and fellows from across the U.S. heard as they attended the 2018 Annual Meeting of the American Medical Association (AMA). The Resident and Fellow Section (RFS) held its section meeting in the days preceding the AMA House of Delegates. Fifty-nine first-time RFS attendees were present, many also serving as delegates from their state or specialty societies. The section heard from outgoing president, David Barbe, MD, who spoke to the impact AMA has had on ongoing public health crises of today - namely gun violence and opioid addiction. Dr. Barbe encouraged the continuation of a strong RFS voice within the AMA to help lead change in medicine. In a joint session with the Young Physician and Medical Student Sections, the RFS also heard from Surgeon General, Jerome M. Adams, MD, MPH, who echoed similar sentiments regarding early-career physicians being engaged in policy and public health issues to help move medicine forward in a positive direction. In a later speech to the AMA House of Delegates, Adams emphasized the importance for veteran AMA members to engage with younger members of their delegations to ensure sustainability of the organization.

As part of the RFS business meeting, action was taken on sixteen resolutions across a wide variety of issues. Nathaniel Barbe, DO, and Joanne Loethen, MD, served as delegates on behalf of Missouri's residents and fellows. Resolutions acted upon covered a variety of issues including:

- Opposition to the separation of children from parents at the U.S. border.
- Coverage for post-treatment reconstruction services of breast cancer patients.
- Alleviating restrictions to expand moonlighting opportunities for International Medical Graduates on J1 visas.
- Exploring how augmented intelligence and technological innovations can safely and effectively be integrated into the delivery of effective medical care.
- Studying the feasibility of a house-staff union or similar model that could serve to uphold appropriate working standards while ensuring uninterrupted patient care.
- Advocating coverage of additional imaging for women with dense breast tissue undergoing breast cancer screening.
- Promoting discussions of fertility preservation in pediatric and reproductive age cancer patients undergoing therapies that may affect long-term fertility.
- Improving the coordination of medical care for prisoners recently released to the community.
- Supporting a mandate for state newborn screening of critical congenital heart defects.
- Evaluating barriers to medical school matriculation for students with disabilities.

In closing business, the new RFS Chair, Colin Murphy MD, took the reins and the remainingRFS Governing Council was elected.

If you or someone you know is a resident or fellow interested in becoming more involved with the AMA or attending a national meeting, visit the AMA-RFS webpage at https://www.ama-assn.org/about/resident-and-fellow-section-rfs

Join us at the AMA Interim Meeting, November 8-14, 2018, in National Harbor, Md. This is just prior to the AMA Interim Meeting held November 10-14, 2018. **MM**



Joanne Loethen, MD, MSMA member since 2016 and Chair of the MSMA Resident and Fellow Section, is at the University of Missouri, Kansas City in Internal Medicine and Pediatrics
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YPS Report: The Role of Private Equity in Medicine

by Albert Hsu, MD & Nita Kohli, MD

One of the most interesting issues at the American Medical Association Annual Meeting is the encroachment of private equity in medicine. Corporate America is trying to figure out where to put their money, as the stock market is overheated, the interest rates are too low in banks, and many investors are turning to healthcare.

Approximately 14 percent of private equity acquisitions are now in healthcare, and these private equity groups often bundle multiple medical practices and then rapidly "flip" them. The largest dermatology group in the USA is now owned by a Canadian retirement fund, and while such practices may be great for revenue generation, there is a potential loss of healthcare dollars to non-healthcare entities that have little incentive to reinvest in their healthcare practices.

The potential threats by private equity ("If you don't sell to us, we will open 20 offices in your catchment area to compete against you"), and the profit-models of private equity firms may result in high-pressure RVU production guidelines, in which physician groups lose all autonomy and essentially become indentured servants.

Obvious concerns includd "profit over patients" in highly-leveraged private equity environments, as well as fears about when those firms go bankrupt (where doors are locked, records aren't retrieved, and patients are abandoned with no continuity of care).

While some decried the general increase in corporate ownership of physician practices today (with predatory practices, under-bids and subsidies, and playing fields skewed against risk-averse physicians), others pointed out the unique features of private equity, in which ownership "flips" frequently. An example was given of one dermatology group being owned by four different groups within an 18-month period!

Still others brought up the fact that some money behind these private equity groups may come from hospitals and Pharma and insurance companies – and that such inherent conflicts of interest may be masked by using private equity groups. Multiple physician specialties including dermatology, orthopedics, OB/Gyn, and radiation oncology indicated the urgent need for the AMA to draft model contract language for when private equity groups take over medical practices. A resolution on this issue was passed by the AMA, and we look forward to a report back next June.

Other advocacy and public policy issues that were addressed by the AMA-YPS include:

- Prohibiting retrospective ER coverage denial and returning to prudent layperson standard for emergency services
- Insulin affordability
- Physician burnout and wellness challenges
- Advancing gender equity in medicine and advancing the goal of equal pay for women in medicine
- Reducing disparities in obstetric outcomes, maternal morbidity, and prenatal care
- Clarifying federal enforcement of medical marijuana laws from the Department of Justice
- Integrating drug price information into EMRs
- Augmented intelligence in healthcare
- Legalization of interpharmacy transfer of electronic controlled substance prescriptions
- Maintenance of certification
- Economic credentialing
- Survivorship care plans
- Handling hazardous drugs
- Alcohol use and cancer
- Treating opioid use disorder

If you or someone you know is a young physician who may be interested in getting involved in the MSMA-YPS and/or AMA-YPS, contact MSMA Director of Marketing Stephen Foutes at stephen@msma.org or 800-869-6762, and/or visit the AMA-YPS webpage at https://www.ama-assn.org/yps-annual-overview. **MM**





Albert Hsu, MD, MSMA member since 2017 and Chair of the MSMA Young Physician Section, is a Reproductive Endocrinologist at the Missouri Center for Reproductive Medicine and Fertility in Columbia, Mo. Nita Kohli, MD, MPH, MSMA member since 2018, is the American College of Mohs Surgery representative to AMA-YPS and Dermatology Section Council. She is an Assistant Professor of Dermatology at Washington University, St. Louis, Mo.
Contact: scooberhsu@gmail.com

St. Louis Metropolitan Medical Society

Inspiring Member Physicians to Achieve Quality Medicine

As it has done for more than 180 years, the St. Louis Metropolitan Medical Society (SLMMS) continues to serve as the collective voice for physicians in the greater St. Louis area. In 2018, the Society is in its fifth year of a strategic plan focusing on key areas that support physician members and their practices in the rapidly changing world of medicine today.

SLMMS strategy is defined by its mission statement, "to support and inspire member physicians to achieve quality medicine through advocacy, communication and education." The Society continues to be guided by its vision statement, "physicians leading health care and building strong physician-patient relationships."

The leaders of SLMMS are instrumental in guiding the organization through times of tumult and change. J. Collins Corder, MD, 2017 SLMMS President, addressed this during his term. "We are a diverse group who advocate for each other and stand up for our patients in delivering the best of care in this time of uncertainty," said Corder. "Daily we are faced with a series of opportunities that are disguised as unsolvable problems. As physicians, we have been presented challenges from premedical, medical school and throughout our residency training as our mentors inspired us to be our best and shaped us to be part of this great profession. A dictum by which we as practitioners live is to 'always leave things better than we found them.' We are the agents of change as we work to move medicine forward in these changing times."



2017 President
J. Collins Corder, MD



2018 President
Christopher Swingle, DO

Physician Insurance Survey

Two years ago, SLMMS launched its first-ever physician-driven insurance survey, designed to capture physician assessment of insurance company performance. More than 300 doctors from throughout the St. Louis area responded, and the survey results "graded" insurance companies specifically on one of today's greatest sources of frustration in the medical practice – the process of obtaining prior authorizations and pre-certifications – and how it impacts the delivery of care. While the results indicated that overall grades for the insurance providers clustered near the midpoint or a "C" rating, a major conclusion was that physicians believe insurers are delaying and restricting much needed care for patients. Physicians commented that they "spend more time fighting insurance companies than fighting disease."

Seeing an opportunity to be impactful with sustained results over time, SLMMS is repeating the survey in 2018. The field research has just concluded, this year with 290 physician participants, and initially confirms that the divide of working with insurance companies is growing wider and physician frustration is increasing. The objective is to share these results with the business community and the media in order to direct much needed attention to improving processes that negatively impact the practice of medicine.

Prescription Drug Monitoring Program

Given the absence of a state-wide initiative, St. Louis County launched its Prescription Drug Monitoring Program in 2017, thanks to the efforts of SLMMS member and County Councilman Sam Page, MD. The Society was instrumental in its approval and supported its rollout to the medical community. Physicians applauded the program as a "physician-friendly and effective" tool. Less than one year later, the program has been embraced and adopted by more than 50 counties and municipalities across Missouri, and now covers three-fourths of the state population and nearly 90% of its health care providers. As it organically emerges as the state's PDMP, SLMMS looks forward with great anticipation to the day when it officially achieves that designation.

Opioid Symposium

In April 2018, SLMMS took another step in addressing the opioid epidemic by partnering with Clayton Behavioral and the Missouri State Targeted Response to the Opioid Crisis to present "What's My Role in Addressing the Opioid Crisis? – A Conference for Physicians Who Want to be Part of the Solution." More than 70 physicians from throughout the region participated in the half-day CME symposium. The keynote speakers identified the most promising medical and harm-reduction practices being used to decrease opioid-related morbidity and mortality, and a panel of four physicians shared practical tools for physicians, and how treatment fits into the continuum of care.



Physicians at the St. Louis April 2018 Opioid Symposium, from left: Drs. Sam Page, Douglas Pogue, Evan Schwarz, and Ravi Johar.

Issues Advocacy

Recognizing that advocacy is what members most value, SLMMS (joining with colleagues from across the state of Missouri) continues to project an active voice on key issues impacting the practice of medicine. In the past year, SLMMS has spoken out against restrictive insurance company policies that deny emergency room visits deemed unnecessary after the fact, and opposed a ruling that interfered with radiology coverage at hospital-based outpatient settings, both of which impact the physician's role as quarterback of the patient's health care team. More recently, SLMMS spoke out in the St. Louis media against the practice of balance billing in response to on-going coverage of the burden of expensive air ambulance charges being shifted to the patient. Key resolutions supported by SLMMS that were adopted by the Missouri State Medical Association this year addressed the need for creating needle exchange programs in Missouri, the funding of a Maternal Mortality Review Board, medical records custodial storage, and establishing a voluntary web-based opioid education program.

Community Outreach and Membership Growth

In his inaugural address this past January, 2018 SLMMS President Christopher A. Swingle, DO, addressed an increase in what he terms as the "atomization" of our nation. "There's a prevailing sense of disillusionment with formerly trusted institutions, and the feeling that community ties are fracturing," he stated. "To me, this is the overarching challenge that we face as physicians in organized medicine."

"It is extremely important to remember that there is only one forum that speaks for every St. Louis physician. There is no other place where the employed physician can talk with the entrepreneurial physician, or where the academic can interact with the private practitioner, or the retired doctor can mingle with the medical student except for the St. Louis Metropolitan Medical Society," he continued. "Each of us brings a unique set of talents in addition to the title of physician – this is a strength that we need to rediscover and reclaim."

To that end, Dr. Swingle has focused on building membership and strengthening SLMMS' profile in the community during his year as president. He has reached out to the St. Louis City and St. Louis County health departments and sat down with the deans and leaders of both St. Louis medical schools. He has encouraged members to think about what membership means to them, and in turn articulate that position to non-member colleagues.

SLMMS continues to connect with medical students and residents, with student liaisons from both local schools participating on the SLMMS Council. Grants from the Society's charitable foundation, the St. Louis Society for Medical and Scientific Education (SLSMSE), have supported the SlingHealth program at Washington University and the MedLaunch program at Saint Louis University. SLSMSE also supports other physician and community activities including the annual Hippocrates Society lecture, the Greater St. Louis Science Fair, World Food Day, the Missouri Physicians Health Program, and the SLMMS Alliance. The Alliance continues to play an integral part of fulfilling the SLMMS mission through community health education, charitable projects and legislative advocacy.

"SLMMS is a great society and an incredible network of talented physicians," said Swingle. "To create our future, we need to be the undisputed voice of medicine in our community, and need the support of all physicians to fulfill that mission." **MM**

MSMA Members in the News

Did you make the news? Submit your success story and photo to hwansing@msma.org.



Jin-Moo Lee, MD, PhD, (center) has been named the Norman J. Stupp Professor of Neurology at Washington University School of Medicine in St. Louis in recognition of his contributions to stroke research. Shown at his installation are (from left) John C. Morris, MD; David Holtzman, MD; David H. Perlmutter, MD, Dean and Executive Vice Chancellor for Medical Affairs; and Chancellor Mark S. Wrighton. Dr. Lee has been an MSMA member since 2007.



Congratulations, Craig Holzem, MD, on joining the team at Esse Health in Washington, Mo. MSMA appreciates your support as a member since 1981.



Young physician Tyler Krummenacher, MD, has supported the efforts of MSMA since 2006, and is now practicing at Missouri Baptist Sullivan Hospital.



MSMA commends Philip Kurle, MD, MSMA member since 2011, for being named Lake Regional Physician of the Year.



Candice Moore, MD, has been an MSMA member since 1977. We would like to congratulate her on joining Nevada Regional Medical Clinic to continue providing psychiatric care to the children in her community.

MM

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Aug 11	Determination of Death by Neurologic Criteria
Aug 17-18	Clinical Allergy for the Practicing Physician
Aug 23-24	12th Annual St. Louis Live Therapeutic Endoscopy Course
Sept 15	19th Annual St. Louis Critical Care Update
Sept 15	Update on the Management of Pituitary Tumors
Sept 21-22	Advances in Oncology & Hematology
Oct 13	Fetal Cardiac Screening
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USPSTF Update of Guidelines on Early Detection of Prostate Cancer

Prostate cancer is the most commonly diagnosed cancer in men in the United States, with an estimated 161,360 new cases and causing 26,730 deaths in 2017. Not all prostate cancers pose a threat to the life of the host, and most of the men over the age of 80, may harbor cancer cells in their prostates and many of them may not be even aware of the cancer. Most of the prostate cancers are slow-growing and take more than 10 years to reach a stage when they can threaten the host.

PSA, a simple blood test, became popular in 1980s as a screening device for prostate cancer and made major impact in the health care of elderly men. Before the introduction of PSA, most of the prostate cancers were diagnosed late when they were stage IV with metastatic disease, which were not curable and had high mortality. But since the advent of PSA, the prostate cancers are being detected early, are treatable and curable. PSA was acclaimed as the best tumor marker in the history of medicine.

Created in 1984, the United States Preventive Services Task Force (USPSTF) developed as an independent group of experts working with the analysis of evidence-based medicine in prevention of malignant and other health related issues. The USPSTF is made up of 16 volunteer members who came from the fields of preventive medicine and primary care.

Prostate, Lung, Colorectal and Ovarian Cancer Screening (PCLO) sponsored by NIH and completed in 2006 to determine the effect of cancer screening in men and women aged 55-74, did not show any improved P-ca specific mortality in PSA based screening. USPSTF issued a collaborative statement saying that PSA screening should be banned as it did not improve the mortality of prostate cancer, but only caused unnecessary prostate biopsies and cancer-related treatments including radical prostatectomies, and/or radiotherapy with associated complications like urinary incontinence and impotence with quality of life impediment and psychological stress to the patient and the family, not counting the economic burden involved in the treatment of the cancer.

However, after the recent evidence from the American Urologic Association and American Cancer Society, USPSTF revised its recommendations: Published in the *Journal of the American Medical Association* (JAMA), the USPSTF concluded that men aged 55-69 years or men with life expectancy of more than 10 years, should decide whether to undergo periodic PSA screening after discussion of the potential benefits and hazards with their clinician. According to USPSTF, there is a 'moderate benefit' of reducing P-ca related deaths with screening of men aged 55-69 years, more so in African American men and men with family history of prostate cancer. Such screening may prevent 1.3 P.ca deaths and three cases of metastatic disease per 1000 men.

The future of P.ca screening will likely remain PSA-based, but more scientific advances like Free PSA, PSA velocity, Multiparametric MRI and genomic tests etc may invade the horizon.

Sivaprasad D. Madduri, MD
MSMA Member since 1988
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Beating the Odds on Lifespan

In the January/February issue of *Missouri Medicine*, I described the evidence that caloric restriction is the single most promising path to lifespan extension and delay of age-associated disease and infirmity.[1] Dueling opinion pieces in the June 25, 2018, edition of the *Wall Street Journal* present contrasting views on the limits of human lifespan.[2] Brandon Milholland, PhD, posits an upper limit on human longevity of ca. 125 years. Joon Yun, MD, believes there is potential for a significantly longer human lifespan. While both pieces are provocative, they don't change the prospects for human lifespan extension as I discussed them in these pages.

The Gompertz function is a mathematical equation that posits the risk of dying rises exponentially with age, doubling roughly every eight years after the age of thirty in humans. Dr. Milholland believes that this iron law reflects age-dependent failure of multiple and diverse body systems. He writes: "Human aging is characterized by many things failing at the same time, which limits the effectiveness of most treatments at extending lifespan." Oliver Wendell Holmes anticipated this hypothesis of aging in his poem "The Deacon's Masterpiece or, the

Wonderful "One-hoss Shay": A Logical Story," where the Deacon's horse-drawn carriage fails when all the various parts age at the same rate and it goes to pieces all at once. To Dr. Milholland, any interventions to forestall human aging can only be incremental in the face of the 'staggering complexity' of age-related damage to cells, tissues, and organs. Indeed, caloric restriction acts through multiple pathways and mechanisms to attenuate the primary causes of age-related disease.

Yun sees potential to bend the Gompertz function curve through what he calls "bioresilience," the body's ability to respond to and compensate for stress. Dr. Yun posits a natural age-dependent decline in our ability to restore equilibrium after transient changes in blood pressure, blood glucose, or inflammation. If we could but exercise our response to stressors like temperature, diet, or inflammation, we could slow or arrest the physiological decline of aging. As I pointed out in these pages, the benefits of caloric restriction and exercise are thought to be examples of "hormesis," the chronic or intermittent exposure to low-grade negative stress that leads to long-term enhanced resilience.

Dr. Milholland asserts: "The problem is, aging isn't activated or lifespan limited by a genetic switch or dial." Yet there is clearly a genetic component to aging and lifespan. Consider the Greenland shark, the longest living vertebrate with a lifespan of at least 400 years.[3] Or the naked mole rat, which can live over thirty years while showing little or no sign of aging, while mice, which are similarly sized rodents, never live more than four years.[4] What are the genetic tricks these animals use to escape the Gompertz function?

Surprisingly, neither author mentions the transformative potential of stem cells and regenerative medicine. If we age because of degeneration of our cells, tissues, and organs, why can't that be reversed by regeneration through the renewable potential in our own body's stem cell populations? But until biomedical research unlocks the secrets of regeneration, caloric restriction still enjoys the most support as a lifespan-extending behavioral intervention.

In my 2013 *Missouri Medicine* review, "Telomeres, Cancer and Aging: Live Long and Prosper," I noted that the erosion of telomeres, the structures that cap both ends of each chromosome, is associated with aging and age-related stress.[5] The strategy of hormesis to drive bioresiliance and slow aging, as proposed by Dr. Yun, could be assessed using telomere length as a biomarker.

Herodotus (5th century BCE) described a people called the Macrobians who bathed in a fountain that made them long-lived.[6] Clearly, the lifespan of the fountain-of-youth legend can be measured in millennia, and the human dream of longevity seems eternal.

1. Eissenberg JC. Hungering for immortality. Missouri Med 2018;115;12-17.
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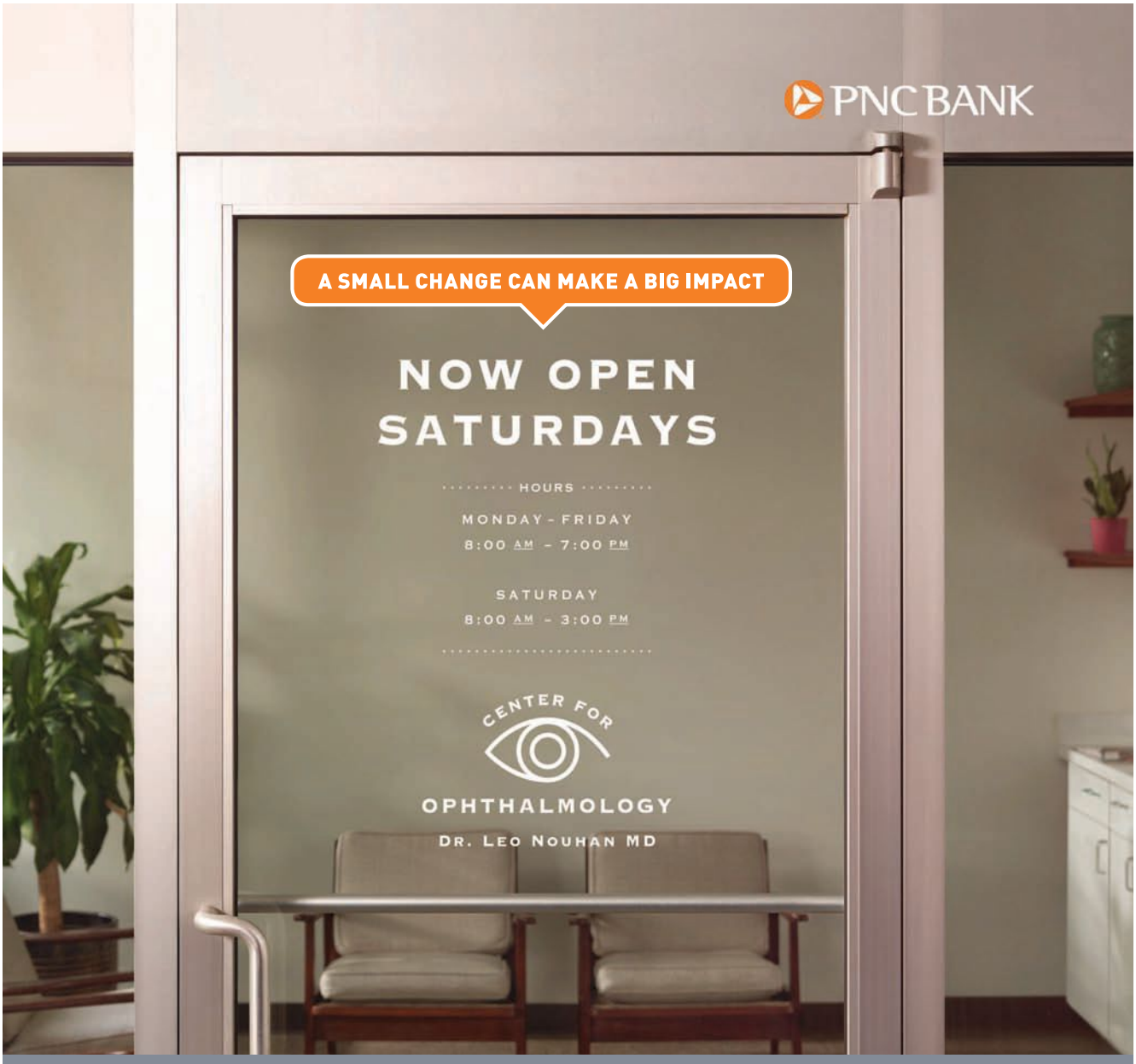
I recently had surgery for a small bowel obstruction. Through the emergency room, I was admitted to a Florida hospital. The physical exam consisted of listening to my heart, lungs, and abdomen. In the following four and half days, I had 14 x-rays, two CAT scans, and five blood tests. Meanwhile, I had a level 10 pain with each peristalsis. I was given small doses of morphine which did not relieve the pain entirely. The on-call night surgeon came by and did an abdominal exam and made the diagnosis of a Richter's pantaloon hernia as cause for the obstruction. I was taken to surgery for repair.

I mused, "If a patient came under my care, with the same history, I would do a complete physical and make the diagnosis. Then, do a flat and upright of the abdomen, a chest x-ray, EKG, blood tests, and off to surgery in one hour."

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Recent Recognitions Highlight Strengths of Innovative UMKC School of Medicine

by Mary Anne Jackson, MD

As the interim dean at the School of Medicine at the University of Missouri–Kansas City, I want to share some recent honors, accolades, and achievements of our students and faculty.

The opportunities offered and advantages of our innovative UMKC BA/MD program were recently featured in a Forbes magazine article by Kristen Moon, a college counselor who specializes in Ivy League and combined undergraduate and medical degree admissions. I want to underscore how I believe the UMKC School of Medicine has always been and continues to be ahead of the curve in creating a unique medical curriculum and culture. Our students have the opportunity for an accelerated program and the assurance of a medical school spot right out of high school. Starting their first year, each student is assigned to one of our docent teams, which provides the opportunity for earlier exposure to patient care, fosters small community learning, and encourages peer-to-peer teaching. A faculty physician who provides consistent mentorship and guides each student's personal and professional development leads each docent team. By embedding students, pharmacists, nurses, and medical librarians into each docent team, we ensure that students are actively engaged early on to understand the importance of team-based clinical care.



Mary Anne Jackson, MD, is Interim Dean, University of Missouri-Kansas City School of Medicine, and a professor of pediatrics in the Division of Infectious Diseases at Children's Mercy.
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Incorporating medical science and clinical skills with the liberal arts is another key to our program. The medical humanities curriculum weaves the arts, humanities and bioethics throughout the six-year program.

Students also have the opportunity to work with exceptional researchers, and more than 70% do so by graduation. UMKC School of Medicine researchers of note include Gary Sutkin, MD, associate dean of women's health and the Victor and Caroline Schutte Chair in Women's Health, who studies how key technological strategies and optimal communication in the operating room may promote an ideal learning environment, decrease surgical errors and improve patient outcomes. Karl Kador, PhD, is working on a novel approach to treat end-stage glaucoma and received $1.94 million in NIH funding to pursue this work. Mingui Fu, PhD, has funding from the American Heart Association to study the molecular basis of vascular inflammation.

Four students recently recognized for their research include Hunter Faris and Ravali Gummi, who both received top student research awards from the Missouri Chapter of the American College of Physicians — Faris for his poster on "Muscarinic Acetylcholine Receptors Inhibit Src Family Tyrosine Kinase Phosphorylation in the Rat Striatum," and Gummi for her poster on "Intracellular Calcium Channel Expression in Autoimmune Encephalomyelitis." Carley Oakley was recognized for being in the top 5% of TL1 recipients nationwide at the 2018 Clinical Science Translation Meeting in Washington.

In addition, for the fourth straight year, the National Institutes of Health has chosen a UMKC School of Medicine student for its Medical Research Scholars Program. Gurpreet Seehra of St. Louis was one of three-dozen students chosen by the NIH program for her academic excellence, creativity and interest in research. As a result, Ms. Seehra, who is interested in pediatric neurology, will return to UMKC for her final year of

medical school in fall 2019, after spending a research year at the NIH campus in Bethesda, Maryland. As Thomas Burklow, MD, director of the Medical Research Scholars Program, said, "The NIH Medical Research Scholars Program attracts the brightest talent from across the country. These scholars are the future leaders in American medicine."

Also in terms of faculty and student recognition, the School of Medicine's chapter of the Gold Humanism Honor Society was one of two established chapters nationwide to win a 2018 Distinguished Chapter Award. The award honors advancement in care and leadership initiatives that put patients first, sustaining a humanistic learning environment. There are 150 national medical school chapters, and a dozen or so residency programs that are part of the Gold Humanism Honor Society.

Led by Dr. Carol Stanford, our chapter was recognized for advancing ideas for National Patient Solidarity Week along with its involvement in the "Tell Me More" program, which promotes acknowledgement and respect for patients as individuals beyond their medical conditions.



UMKC medical students all are part of a team under the mentorship of a "docent" physician. Dr. David John supervises some members of his unit while staffing a clinic at Truman Medical Center.



Graduating members of the UMKC Gold Humanism Society, along with chapter sponsor Dr. Carol Stanford, showed off the banner recognizing their chapter as a national leader.

Anesthesiologist Assistant (AA) and Physician Assistant (PA) training programs at the UMKC School of Medicine also continue to incorporate physician leadership and expertise into the training of our students. Faculty members have helped develop the didactic curriculum and serve as clinical preceptors for the students. The first AA class began in 2008 and the first PA class in 2014. To date, 100% of the 80 AA graduates and 52 PA graduates have achieved board certification, and nearly 80% are practicing in Missouri or Kansas.

Lastly, efforts to support medical student wellness continue at medical schools across the country, and the UMKC School of Medicine has been in the vanguard. There is increasing appreciation for the scope and impact of burnout, experienced by nearly 50% of students nationwide, even before they have professionally entered the field. Many factors can lead to burnout, so programmatic solutions are critical. At UMKC, our fulltime wellness program coordinator, Niloofar Shahmohammadi, in 2016 implemented a robust program that has a particular focus on first-year students. To help them make the transition into medical school, this innovative program uses short, focused "Wellness Check-Ins" at prescribed times after the students' arrival. The check-ins assess how students are coping and help identify those in need of follow-up or other services. Results from an anonymous survey that evaluated the effectiveness and value of this program were presented to the Association of American Medical Colleges last year and confirmed that student check-ins were associated with an increased sense of belonging, increased perception of their ability to succeed, increased confidence and more willingness to use campus resources as needed. Since the AAMC presentation, our program has received email requests and phone calls from staff at other schools asking for help and suggestions in implementing a similar check-in process with their students.

As these initiatives and honors illustrate, our innovative programs, supportive atmosphere and dedicated faculty and students all help distinguish the UMKC School of Medicine. The school serves our city, state and region while producing national and international leaders. And it produces graduates with both the medical training and the caring outlook necessary to be not only expert clinicians, but also skilled educators and cutting edge researchers. **MM**

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Pediatric Medicine Nurtures, Heals, and Impacts the Future

by Douglas C. Rivard, DO

The field of pediatric radiology has continued to grow on the foundations set in place by Dr. John Caffey and his successors and now encompasses all areas of medical imaging.

There is significance in the way we, as a society and community of medical providers, care for our pediatric patients. Not only can we nurture and heal our most vulnerable population, we also have the opportunity to impact our future. These values are shared among all physicians, but are especially ingrained in physicians caring for pediatric patients. Pediatric radiologists, a subset of pediatric specialists, aid in the diagnosis, planning and treatment of sick kids and are afforded multiple challenges and rewards in doing so.

The practice of pediatric radiology is considered to have started in 1929 when Dr. John Caffey, a pediatrician who coincidentally trained at one point in St Louis at Barnes Hospital, was assigned to take over radiology at Babies Hospital in New York. He went on to be a prolific publisher and academician. In 1945 he published the first pediatric radiology textbook titled Caffey's Pediatric Diagnostic Imaging. The textbook is still in print to this day, with the 13th edition due later this year. The field of pediatric radiology has continued to grow on the foundations set in place by Dr. Caffey and his successors and now encompasses all areas of medical imaging.



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Diagnostic pediatric radiologists are adept at all imaging modalities including plain film, fluoroscopy, ultrasound, CT, MRI and nuclear medicine, and they use these modalities to image all organ systems. Pediatric interventional radiologists perform minimally invasive procedures including vascular access, biopsies and drains, tumor ablations and vascular malformation sclerosis that often times can save a child a surgical procedure in the operating room. Pediatric radiologists have additional fellowship training in imaging children of all ages and the diseases unique to the pediatric population. Continued robust research in pediatric imaging has led to tailored imaging studies and protocols that result in excellent diagnostic yield for all pediatric diseases with decreased radiation doses, decreased lengths of exam, and fewer cases performed with general anesthesia. With the help of child life and anesthesia physicians and nurses, a complex difficult study can be done with relative ease.

Please enjoy this issue of *Missouri Medicine* that is centered on pediatric imaging. In it you will find articles on some specific advances made in the field by the pediatric radiology faculty at Children's Mercy Hospital and the University of Missouri-Kansas City School of Medicine. The articles represent a broad cross section of content and expertise ranging from presurgical imaging and multidisciplinary planning for pediatric epilepsy, imaging of pediatric musculoskeletal injuries, cardiovascular imaging, and pediatric interventional radiology. Finally, two articles outline some of our current endeavors, with emphasis on 3D printing to aid planning and management of pediatric surgical patients, and digital tomosynthesis for pediatric airway imaging. **MM**

Digital Tomosynthesis Applications in Pediatric Orthopedic Imaging: A Case Series

by Sherwin Chan, MD

In this small case series, we have shown that digital tomosynthesis can excel in answering specific pediatric orthopedic questions.



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Abstract

Digital tomosynthesis (DTS) is an emerging technology that provides cross-sectional, three-dimensional imaging similar to computed tomography (CT) at a fraction of the radiation dose and cost. In this article, we describe multiple cases where our pediatric orthopedic surgeons have used DTS imaging to help in clinical management of fracture healing.

Introduction

There has been a longstanding interest in reducing radiation dose through the American College of Radiology (ACR) Image Gently campaign in an effort to reduce the number of radiation induced cancers, while still maintaining diagnostic quality exams for clinicians to appropriately manage their patients. [1-3] In pediatric radiology, the main contribution of radiation dose comes from computed tomography (CT) scans.[4] CT has proven incredibly useful and will likely remain the workhorse for cross-sectional imaging for complex problems in the foreseeable future.[5] However, as technologies advance, there has been an interest in reducing the number of CT scans overall, while still maintaining diagnostic accuracy and one of the efforts has been in tomosynthesis.

Tomosynthesis is decades-old technology that is regaining prominence due to recent technical innovations.[6, 7] The new iteration named digital tomosynthesis (DTS) is able to provide cross-sectional, three-dimensional imaging like CT at a fraction of the radiation dose and cost. This technology fills an imaging sweet spot between radiographs and CT. DTS is a radiographic technique that produces cross-sectional images with similar in-plane resolution to radiography.[8] DTS utilizes a standard x-ray tube, a flat-panel detector overlaid with an anti-scatter grid, and a motorized tube crane to move the x-ray tube. A reconstruction algorithm allows for production of multiple cross-sectional images at a much lower dose than that of CT. In the chest, DTS dose is approximately 5% of CT and about twice the dose of a two-view chest computed radiography (CR). The typical DTS dose ranges from 0.27 mGy to 0.31mGy depending on the patient's age and size.[8, 9]

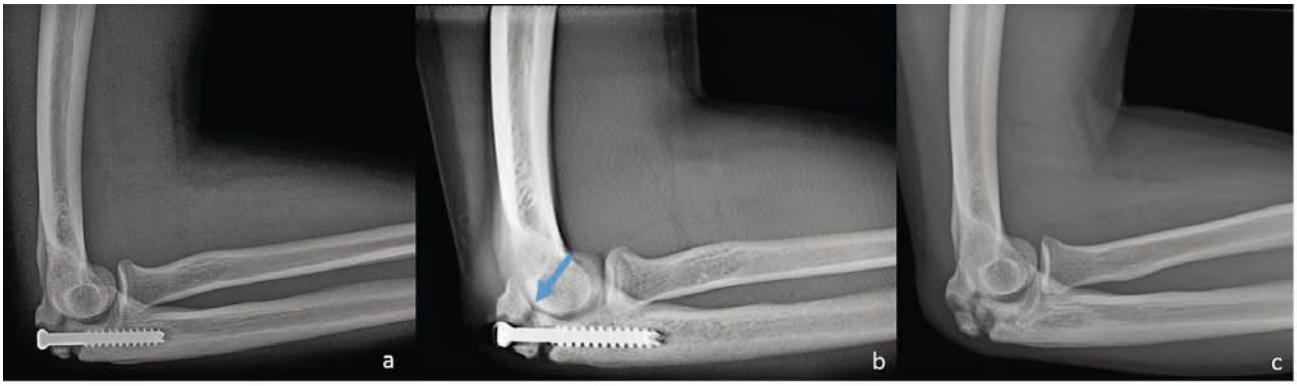


Figure 1. 15-year-old male with history of right olecranon stress fracture was treated with screw fixation. His course was complicated by a post-operative infection. (a) Lateral radiograph of the elbow demonstrates a screw across an olecranon fracture. (b) A selected slice from a digital tomosynthesis exam demonstrates a bony bridge between the proximal fracture fragments (arrow). (c) Lateral radiograph of the elbow two months after the initial radiographs demonstrates healing bony bridging of the olecranon fracture after screw removal.

DTS is gaining acceptance in adult imaging and has been studied mostly for breast and lung cancer screening applications where patients undergo repeated rounds of imaging.[10-13] DTS has also been studied in the setting of fracture healing and orthopedic hardware.[14-18] In pediatric populations, DTS has only been used to screen and stage cystic fibrosis.[19] However, this technology has not been widely studied in pediatric imaging and we believe that this technology holds great promise in this arena.

Regulatory Overview

Several DTS systems are FDA-approved for general diagnostic imaging (chest, bone and abdomen) under the 510(k) pathway.[20-22] Approval under the 510(k) pathway means that the FDA has determined that a new medical device is equivalent (defined as the device achieves the same results as a predicate device and the FDA agrees it is safe) to an already FDA approved medical device. FDA approval means that physicians can use the device for the approved indications.

The ACR has also come out with guidance on how to bill chest, upper extremity, lower extremity and spine DTS exams. They recommend using CPT code 76100, Radiologic examination, single plane body section (e.g. tomography), other than with urography.[23]

Children's Mercy Hospital Implementation

Children's Mercy currently has GE DTS equipment in four of our imaging locations; and our radiologists, radiologic technologists and orthopedic surgery department underwent training on how to obtain and post-process the images.

Pediatric Case Studies

Case 1

A 15-year-old male with history of right olecranon stress fracture treated with screw fixation and local bone graft presented for follow up. His course was complicated by a postoperative infection and subsequent surgical debridement of the infection ten days after initial surgery. He was on appropriate antibiotics and was doing well without significant pain around the fracture site. The orthopedic surgeon wanted to know if there was enough healing around the hardware that it could be removed.

The initial radiograph (Figure 1a) was interpreted as "… No increased callus is appreciated on the lateral projection at the fracture site when compared with the most recent x-ray."

DTS imaging of the elbow was performed the same day to get a more detailed evaluation of healing. The DTS images (Figure 1b) showed bridging of the bone around the screw. The



Figure 2. 15-year-old male who presents for a 6-month follow-up of his left forearm fractures. (a) Frontal radiograph of the forearm demonstrates a healing radial diaphysis fracture (white arrow) and a persistent lucent fracture line spanning the width of an ulnar diaphysis fracture (blue arrow). (b) A selected slice from a digital tomosynthesis exam demonstrates a bony bridge between the two fragments of the ulnar fracture (blue arrow). (c) A follow up frontal radiograph of the forearm demonstrates both the radial and ulnar fractures are healing with bony bridging across both fractures with no persistent fracture lines.

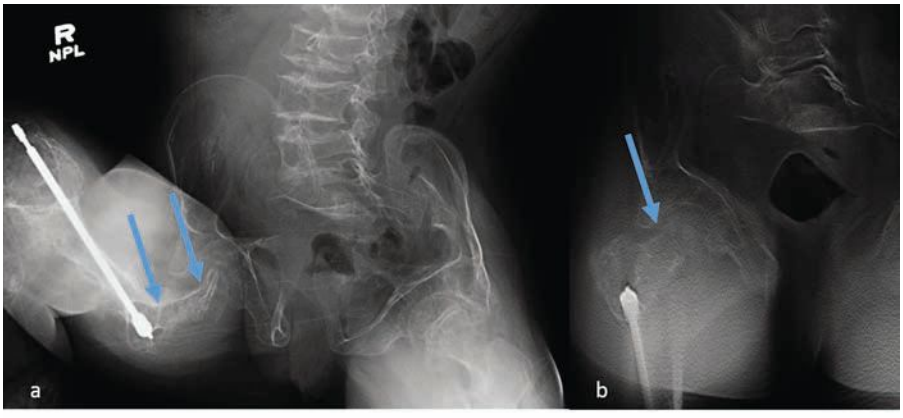


Figure 3. 13-year-old female with a history of osteogenesis imperfecta presents with right hip pain after a wheelchair injury. (a) Frontal radiograph of the pelvis is suspicious for femoral neck fracture because of contour deformity in the femoral neck (arrows). There is also diffuse bony demineralization making interpretation more challenging. (b) A selected slice from a digital tomosynthesis exam demonstrates that the femoral neck cortex in question is intact (arrow).

orthopedist then felt comfortable enough with the demonstrated degree of healing to remove the infected screw two weeks after these exams. At a follow up visit three months later, the patient was doing well and participating in weight training without any new complaints and an additional radiograph showed moderate bony callus bridging the previous fracture site (Figure 1c).

Case 2

A 15-year-old male presented for a six-month follow-up evaluation of left forearm fractures.

The initial radiograph (Figure 2a) was interpreted as "...radial fracture appears to be healing well with signs of remodeling and minimal remaining lucency. The ulnar fracture continues to have a significant amount of periosteal reaction, some signs of remodeling, but there is also a fair amount of residual lucency noted causing suspicion for delayed union versus nonunion."

Because of the concern for fracture non-union, the orthopedist then ordered DTS imaging of the forearm the same day. The DTS images (Figure 2b) demonstrated healing across the fracture, prompting a decision to start a bone stimulator and re-examine in one month with radiographs. The radiographs performed a month later (Figure 2c) showed a less distinct fracture line consistent with a healing fracture with no concern for non-union.

Case 3

A 13-year-old female with a past medical history of osteogenesis imperfecta presented to the emergency department with pain in the right hip after a wheelchair injury. The patient was in her wheelchair in the back of the school bus and the driver slammed on the brakes causing her chest to hit her knees. Radiographs on this patient were difficult to interpret due to her bony demineralization.

The initial radiograph (Figure 3a) was interpreted as "Probable fracture of the right femoral neck with shortening and collapse on

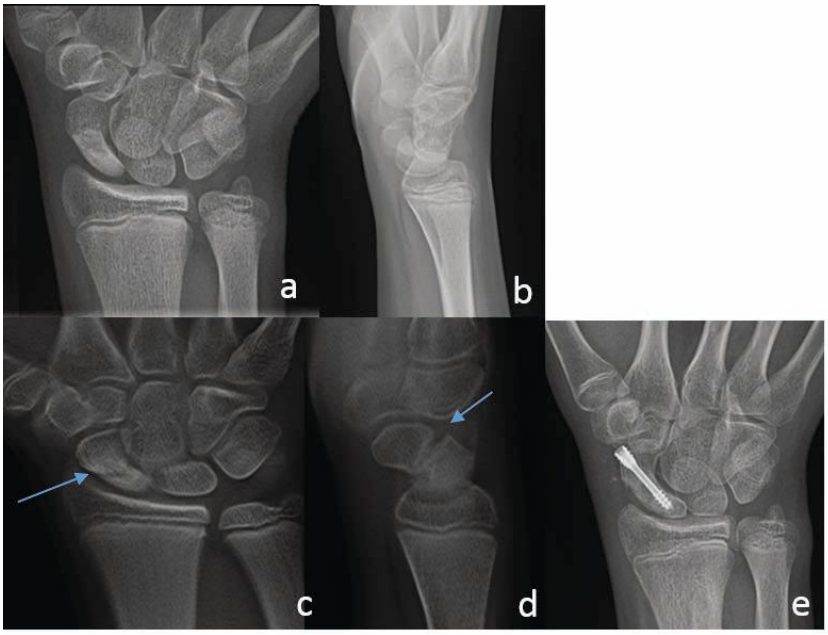


Figure 4. 13-year-old male presents with right wrist pain three months after a rollover motor vehicle accident. Frontal (a) and lateral (b) radiographs of the right wrist demonstrates a nondisplaced scaphoid waist fracture with some sclerosis around the fracture line. No discrete fracture line lucency is imaged. Selected slices from a frontal (c) and lateral (d) digital tomosynthesis exam of the wrist demonstrate a 3 mm gap between the two fragments of the scaphoid fracture indicating non-union. (e) A follow up frontal radiograph of the wrist demonstrates a screw across the scaphoid fracture with no avascular necrosis or remaining lucent fracture line.

the frontal view. This could be further evaluated with CT if clinically indicated." The orthopedic team was consulted and recommended a DTS to further evaluate (Figure 3b). The DTS was interpreted as "Tomographic images demonstrate diffuse osteopenia and chronic deformity related to osteogenesis imperfecta. Though there is contour irregularity of the femoral neck, it appears chronic in nature. No cortical offset or acute fracture line is seen." The patient was then discharged from the emergency department and followed up in orthopedic clinic in one month. At the one month follow up, repeat radiographs of the right femur did not show any evidence of new bone formation or healing fracture.

Case 4

A 13-year-old male with history of ejection during a rollover motor vehicle collision while riding in the trunk of a car presented three months later with right wrist pain.

Wrist radiographs were obtained which showed a non-displaced scaphoid mid-waist fracture. The images were interpreted as "Findings suggestive of healing scaphoid fracture." The orthopedist placed the patient into a thumb spica cast for the next four weeks with plans to follow up for further evaluation of this fracture with hand specialist.

At the visit with the hand specialist, radiographs (Figure 4a, b) were obtained which were interpreted as "... there is similar alignment of scaphoid fracture fragments with progressive healing. The proximal half of the scaphoid demonstrates increasing sclerosis. The previously noted subchondral cystic changes have resolved." The orthopedist was suspicious for fracture non-union and wanted a more detailed evaluation with DTS. The DTS (Figure 4c, d) showed "fracture through the scaphoid waist. There is palmar angulation of the distal fracture fragment with distraction of approximately 3 mm at the superior medial aspect of the fracture. The fracture margins are sclerotic. No osseous bridging is identified. There is subtle sclerosis of the proximal pole which may suggest avascular necrosis."

After the DTS results, the orthopedist decided that the fracture requires surgical fixation, likely with bone graft from the distal radius with possible insertion of a compression screw. After surgery, the patient did well and was discharged from clinic after radiographs showed good healing (Figure 4e).

Discussion

The above examples are just a few of the cases where our radiologists and clinicians feel DTS has added value to our care of children. In these four

cases, DTS proved useful in answering a specific clinical question about fractures after radiographs were inconclusive.

DTS has a large advantage over radiographs because DTS is a cross-sectional imaging modality that can diminish the blurring in radiographs contributed by overlying structures. DTS also has some advantages over CT, the most obvious being lower ionizing radiation dose and lower cost. Another advantage is that DTS is integrated with radiographic equipment and this equipment is often physically located much closer to the orthopedic clinic area than CT, and is often much more available. Additionally, two of our patients had metallic orthopedic hardware located close to the region in question that would have caused beam-hardening artifact if a CT was performed in that region, limiting evaluation of the adjacent structures.

In this small case series, we have shown that DTS can excel in answering specific pediatric orthopedic questions. More study is needed to fully investigate whether DTS has a bigger role in pediatric orthopedic imaging and to define the clinical questions for which DTS excels. The cases that we have presented could form a basis for further systematic evaluation of this new imaging modality.

Disclosure

Children's Mercy Hospital has received a research grant from GE Healthcare to work on optimizing GE imaging protocols for pediatric imaging that was active from 2015 to 2016. The authors had full control of the data and the information submitted for publication. None of the authors are employees of or consultants for the sponsor.

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Imaging the Pediatric Athlete: Acute and Stress Skeletal Injuries

by Brian Dunoski, MD

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Imaging diagnosis of sports injuries in children presents several challenges due to the appearance and susceptibilities of the developing skeleton.



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Abstract

Sports-related traumatic injuries in children have increased in tandem with participation in higher level activities. The developing musculoskeletal structures in children are susceptible to unique injuries that vary with location and the stage of skeletal maturation. The imaging evaluation of sports injuries in children presents several unique challenges. The purpose of this article is to educate the reader on injuries unique to the skeletally immature athlete with focus on their imaging evaluation and diagnosis.

Introduction

Sports-related traumatic injuries in children have increased in tandem with participation in higher level activities. The CDC states "more than 2.6 million children 0-19 years old are treated in the emergency department each year for sports and recreation-related injuries," a figure which does not include those children treated in the outpatient setting.[1] Though there is overlap between skeletal injuries sustained in children and adults, the developing musculoskeletal structures in children are susceptible to unique injuries that vary with location and the stage of skeletal maturation.

The pediatric skeleton is in constant flux as it grows primarily through the process of enchondral bone formation, in which compression and traction epiphyses are especially susceptible to injury due to the relatively fragile cartilaginous physes.[2] Ligaments, muscles, and tendons elongate secondary to this bone growth, resulting in strength and flexibility imbalances that further predispose children participating in high level athletic activities to injury. Additionally, the joint capsule and associated ligaments have been estimated to be two to five times stronger than the growth plate.[3]

The imaging evaluation of sports injuries in children presents several unique challenges. Until skeletal maturity, the imaging appearance of the bones is constantly changing. Despite years of subspecialty training, seasoned pediatric radiologists require consultation with colleagues and refer to imaging atlases of anatomic or developmental variations. Even then, differentiating anatomic or developmental variation from pathology is often problematic. Though ultrasound, CT and MRI are helpful adjuncts to radiographs, knowing when to proceed to these more advanced (and expensive) imaging modalities can be equally challenging.

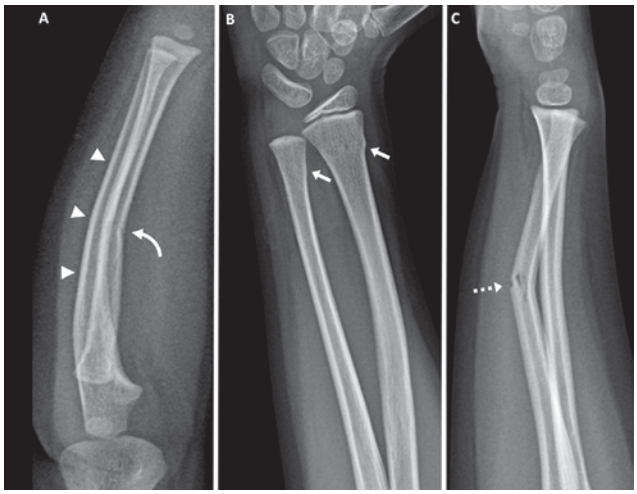


Figure 1. Radiographs of forearm fractures in young children.
A. Non-displaced transverse fracture of the radius (curved arrow) with plastic bowing deformity of the ulna (arrow heads).
B. Buckle fractures of the distal radius and ulna metaphyses (solid arrows).
C. Greenstick fracture of the ulna diaphysis (dashed arrow).

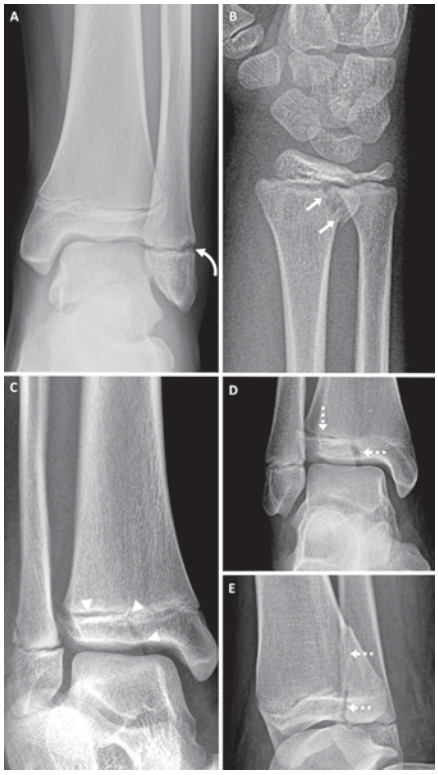


Figure 2. Radiographs of Salter Harris (SH) fractures.
A. SH I fracture shows widening of the distal fibula physis (curved arrow)
B. SH II fracture through the distal radius metaphysis and physis (arrows)
C. SH III fracture (Juvenile Tillaux) through the distal tibia epiphysis and physis (arrow heads)
D, E. SH IV fracture (Triplane). Dashed arrows show the fracture defect extending through the physis and epiphysis on the AP view and through the metaphysis , physis and epiphysis on the lateral view.

Fractures

Incomplete fractures occur due to the relative flexibility of a child's bones, often seen in the forearm after a child attempts to break their fall on outstretched hands (Figure 1). Many incomplete fractures may be subtle; for instance, plastic bowing fractures present with only a smooth curved deformity of the bone. This type of fracture may require a comparison view of the unaffected extremity for confirmation in equivocal cases. Buckle fractures present with slight bulging of the cortical contour and may only be radiographically evident on a single view. Greenstick fractures are more readily diagnosed as a lucent fracture defect that does not extend entirely through the bone, often with some degree of angular deformity .

Fractures of the growth plate are categorized by the Salter Harris classification system depending on their involvement of the adjacent metaphysis and epiphysis (Figure 2). Type I fractures disrupt only the growth plate; they may be radiographically occult or present with mild physis widening. Type II fractures, which extend through both the physis and its adjacent metaphysis, are the most common Salter Harris fracture encountered. Type III fractures disrupt the adjacent epiphysis, as seen in juvenile Tillaux fractures of the ankle. Salter Harris Type IV fractures involve both the adjoining metaphysis and epiphysis as with Triplane fractures of the ankle. Salter Harris Type V fractures are crush injuries of the growth plate and are very rarely encountered.

Radiographs are generally sufficient for the diagnosis and follow-up of the majority of fractures in children. Salter-Harris fractures, especially those that involve the epiphysis and joint articular surface, may benefit from further evaluation by CT or MRI when radiographs are inconclusive or further information is needed for definitive orthopedic intervention.

Overuse Injuries

Trueta and Amato demonstrated that disruption of metaphyseal vascular supply halted the normal process of enchondral bone formation, resulting in persistence of hypertrophic chondrocytes that did not undergo apoptosis and ossify.[4] Laor et al. later proposed that the physis widening seen on imaging studies in children with chronic repetitive stress injuries are the manifestation of the same metaphyseal microvascular injury.[5]

Overuse injuries at compression and traction epiphyses tend to occur in specific locations as a consequence of the repetitive stresses encountered while participating in sporting activities (Figure 3). In throwing athletes, overuse injuries are most commonly sustained in the proximal humeral physis and the medial epicondyle of the humerus, termed Little Leaguer's shoulder and elbow, respectively. [6,7] The extreme weight-bearing activities experienced in gymnastics tend to damage distal radius physis, resulting in the so-called "Gymnast's wrist." [8] Though the various muscle attachments at the apophyses of the pelvis and proximal femurs are not uncommon sites of overuse injuries, more commonly seen are those overuse injuries involving the extensor mechanism of the knee (e.g., Sinding-Larsen-Johanson and Osgood-Schlatter diseases). [9,10]

The findings of overuse injuries are often readily evident on radiographs. One may see growth plate widening as the imaging manifestation of persistent hypertrophic chondrocytes, which may be eccentric to the side of maximal load (e.g., the medial compartment of the knee joint). "Fragmented" ossification pattern of epiphyses and apophyses may also be present; however, given considerable "normal variation" of ossification patterns, this finding does not always indicate overuse injury. It should be interpreted in conjunction with the presence of ossification center displacement, soft tissue swelling and the clinical presentation of the child. A comparison x-ray of the unaffected body part can be useful in equivocal cases, where a single view generally suffices and spares the patient radiation dose.

MRI is the preferred cross-sectional imaging examination for its ability to demonstrate the anatomy of the growth plate. Overuse injuries are depicted by widening of the physeal cartilage, which is usually more hyperintense than normal on T2-weighted sequences. There is typically edema-like signal in the adjacent bone marrow. The zone of provisional calcification, normally seen as a T1 and T2 hypointense line on the metaphyseal side of the physis, is often disrupted in the area of injury. The adjacent soft tissues often appear edematous to varying degrees. In contrast to Salter Harris type I fractures, which also present with physeal widening, there is no fracture through the cartilage with chronic repetitive physis injuries.[5]



Figure 3. Chronic repetitive injuries.
A. Osgood-Schlatter. Though fragmented ossification of the tibial tuberosity (arrowheads) may be normal, the presence of overlying soft tissue swelling (curved arrow) and history of point tenderness confirm diagnosis.
B. Sinding-Larsen-Johansson. Radiograph for anterior knee pain shows fragmentation of the patellar apex (dashed circle) with mild pre-patellar soft tissue swelling.
C. Gymnast wrist. Widening of the distal radius physis with irregular mineralization of the adjacent metaphysis (dashed arrows) from strenuous upper extremity weight-bearing exercises.
D. Little League Shoulder. Normal radiographs (not shown) prompted further MR imaging evaluation, revealing abnormal fluid-signal centered on the proximal humerus physis (black arrows) and small joint effusion in the axillary pouch (asterisk).
E. Physis stress injury at the knee. There is increased signal and widening of the distal femoral growth plate (open arrow) due to persistence of physeal cartilage and indistinct appearance of the normal low signal zone of provisional calcification on the metaphyseal side of the widened physis.
F. Little League Elbow. Coronal fluid-sensitive MR image shows edema within and about the medial epicondyle (arrows).

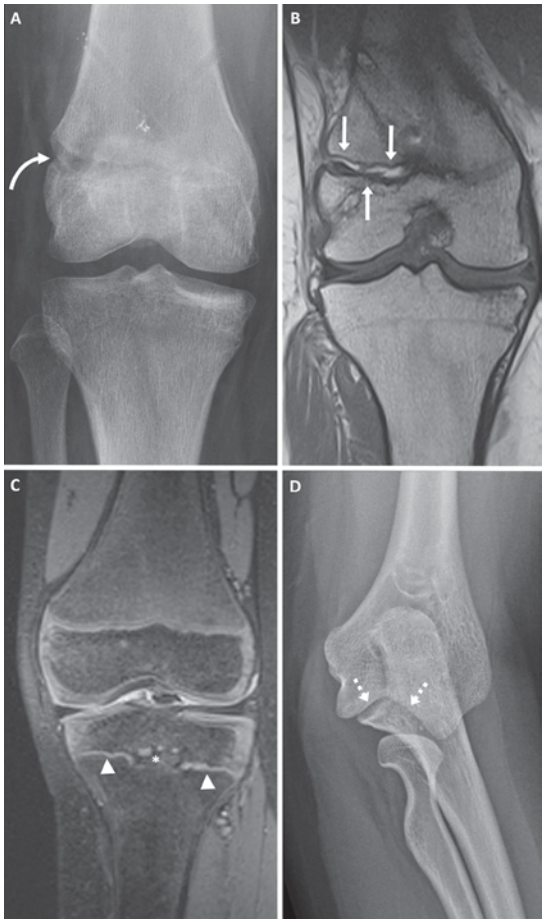


Figure 4. Complications of Salter Harris Fractures
A, B. Soft tissue entrapment. 6 months after internal fixation of distal femur Salter Harris II fracture, there is persistent lucency along the lateral aspect of the distal femoral physis (curved white arrow). Subsequent MRI shows fat and fibrous tissue separating the metaphysic and epiphysis at the site of previous physis disruption (arrows).
C. Physis bar. Fat-saturated 3D spoiled gradient sequence juxtaposes low signal osseous bridge (asterisk) across intermediate signal physis cartilage (arrow heads).
D. Fishtail deformity. Concavity between the capitellum and trochlea (dashed arrows) represents growth disturbance following fracture of the distal humerus.

Complications of Physis Injuries

Physis injury disrupts normal enchondral bone formation in several ways. When left untreated, overuse injuries can result in asymmetric decreased bone elongation on the affected side, resulting in angular deformities (Figure 4).[5,7] Premature growth plate fusion also arrests longitudinal bone growth with a fixed osseous bridge across the physis. Small or peripheral bridges across the growth plate result in asymmetric longitudinal growth and thus angular deformity of the affected bone. Larger or complete osseous bridges result in generalized bone shortening and thus limb length asymmetry. Though premature physis fusion may be readily evident on radiographs, comparison images of the unaffected side are useful to gauge asymmetry in physis width and morphology, especially in children nearing skeletal maturity. Fat-saturated 3D spoiled-gradient MR sequences are especially helpful as they juxtapose bright-signal cartilage with low-signal physeal bar. Small voxel size allows for multiplanar reformatted images, facilitating determination of the size of the physeal bar in relation to the total physis cross-sectional area that will ultimately guide orthopedic intervention.[11]

Soft tissue or periosteum may become entrapped within the fracture defect, resulting in non-reducible fracture, persistent physis widening or fracture non-union. Though MRI illustrates the entrapped tissue between fracture fragments, diagnosis can be challenging due to similar hypointense signal intensity of periosteum and the adjacent zone of provisional calcification.[12]

Uncommonly seen are regional growth disturbances due to microvascular injury impairing enchondral bone formation as seen with the so-called "fishtail deformity" of the elbow. [13]

Osteochondral Lesions

The etiology for juvenile osteochondral lesions (OCL) remains unclear, probably resulting from a combination of chronic repetitive injury, ischemia, and genetic factors.[14] Much like overuse injuries at the primary physis, disruption of the secondary physis seen with pediatric OCL on MR imaging may indicate similar pathophysiology.[15] Though OCL are readily visible on radiographs, MRI is required to evaluate the integrity of the overlying cartilage and assess for features suggesting unstable lesion that ultimately guides orthopedic intervention (Figure 5). It is important to note that OCL research is an area of rapidly emerging science, which includes a large consortium of orthopedic surgeons, sports medicine doctors and radiologists working together to develop better diagnostic tools and criteria and improve treatment of OCL.[16]

Kijowski et al documented the differences in imaging criteria for instability between pediatric and adult OCL. They found that the imaging features of instability in adult OCL were non-specific in skeletally immature individuals. For example, cysts were only indicated instability if

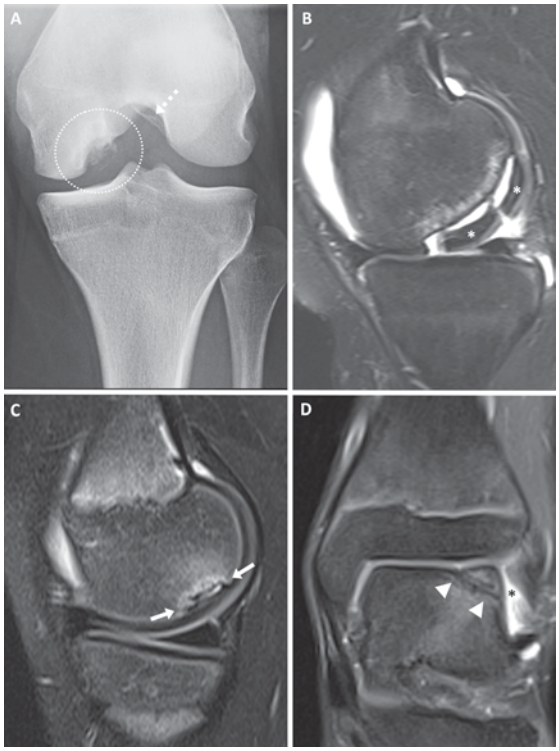


Figure 5. Osteochondral lesions
A. Radiograph shows scalloped lucent lesion in the medial femoral condyle with underlying sclerotic bone (dashed circle). Note displaced intra-articular body in the femoral notch (dashed arrow).
B. Sagittal fluid-sensitive MR image of the same child in (A) shows large unstable osteochondral fragments (white asterisks) separated from the medial femoral condyle.
C. Sagittal fluid-sensitive MR image demonstrates the so-called "oreo cookie" appearance of an unstable OCL in the medial femoral condyle (arrows) with abnormal contour of the subchondral bone plate, a rim of fluid with hypointense underlying perimeter and subjacent marrow edema.
D. Coronal fluid-sensitive MR image shows a medial talar dome OCL with linear hypointense signal flanking intermediate signal tissue that it is darker than adjacent joint fluid (black asterisk), suggesting fibrovascular tissue and potentially instability.

multiple or larger than 5 mm in diameter. More reliable MR features indicating instability of a pediatric OCL included "a rim of fluid signal intensity, multiple breaks in the subchondral bone plate on T2-weighted MR images, and a second outer rim of low T2 signal intensity."[17]

Research by Zbojniewicz et al. correlated MR imaging of pediatric OCL with histopathological specimens. They found abundant fibrovascular tissue in either round cyst-like or linear diffuse hyperintense signal configurations at the cartilage-bone interface and the subchondral bone. This fibrovascular tissue had similar MR appearance to sites of fracture non-union and could be differentiated from fluid or edema on fat-suppressed T1-weighted gradient-echo sequences. Additionally, the presence of T2-hyperintense signal bound by deep and superficial hypointense signal (similar to an "Oreo cookie") may indicate OCL separation from bone prior to instability evident at the cartilage surface.[18]

Conclusion

Imaging diagnosis of sports injuries in children presents several challenges due to the appearance and susceptibilities of the developing skeleton. Though many injuries are straight forward, ongoing research continues to expand our understanding of sports injuries in children, changing our imaging approach and improving diagnosis and subsequent therapeutic outcomes.

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Disclosure

None reported. **MM**

Advances in Pediatric Cardiovascular Imaging

by Erin Opfer, DO & Sanket Shah, MD

Both CT and MRI offer non-invasive methods of imaging the type and severity of a number of congenital heart conditions.





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Abstract

Cardiac imaging plays a key role in the accurate diagnosis of pediatric congenital heart disease (CHD). Echocardiography and catheter angiography are traditionally used to delineate cardiac anatomy. CT and MRI imaging offer a non-invasive way to image cardiovascular anatomy which can be used in conjunction with echocardiography for the diagnosis and treatment planning for CHD. These modalities can depict the morphology and relationship to surrounding structures better than echocardiography, especially in complex congenital defects.

Introduction

The incidence of congenital heart disease (CHD) is approximately 4-12 in 1000 live births.[1,2] Hemodynamic derangements from congenital heart defects range from mild to severe depending on the structures involved and their effects on cardiovascular physiology. Mild defects such as a small ventricular septal defect or atrial septal defect may go undetected for years. Whereas more complex defects, such as tetralogy of Fallot or transposition of the great arteries, often are detected prenatally or in the neonatal period. Early and accurate diagnosis of CHD can help clinicians decide management strategies and improve outcomes in patients with CHD[3-4]. Initial diagnostic imaging of CHD has primarily been with transthoracic echocardiogram. However, advancements in CT and MRI imaging techniques have made these modalities useful adjuncts in the imaging of complex heart defects. These advanced imaging techniques can provide better depiction of the anatomy and can be useful in preoperative planning and postoperative management of patients with CHD defects[5].

Echocardiography

Echocardiography (cardiac ultrasound) has been the standard first line imaging for suspected CHD for decades. The advantages of echocardiography include accessibility, portability, as well as no radiation and usually no sedation. It provides an excellent depiction of intracardiac and valvular anatomy, cardiac function, and hemodynamics.[6] Transthoracic echocardiograms (echo) are commonly performed to screen for and follow up on cardiac diseases

Echocardiographgy provides several different image types and measurements from M-mode, gray scale, color Doppler, strain and 3D images.6,7 The cardiology office usually performs the examination and results are quickly available to clinicians. Patients are required to remain still for 30-45 minutes during the examination. As a result, infants are often difficult to image due to motion or poor cooperation. Sedation may be required in such instances. If

a more detailed assessment is needed, a transesophageal echocardiogram may be performed. Transesophageal echocardiography is more commonly used in the operating room for preoperative planning and intraprocedure assessment.[8]

Newer technologies such as Tissue Doppler, myocardial strain assessment and 3D echo has expanded the use of echo as a diagnostic tool. 3D images add to the presurgical assessment, particularly in cases of complex intracardiac anomalies, septal defects and valvular anatomy[8,9] (Figure1). Tissue Doppler and ventricular strain measurement methods have aided in the assessment of myocardial contractility and evaluation of ventricular function, although MRI remains the most accurate for ventricular function assessment.[7-8,10] Fetal Echocardiography can also be used for the prenatal diagnosis of congenital heart disease. Early detection can improve overall survival rates and allow for perinatal planning.[11]

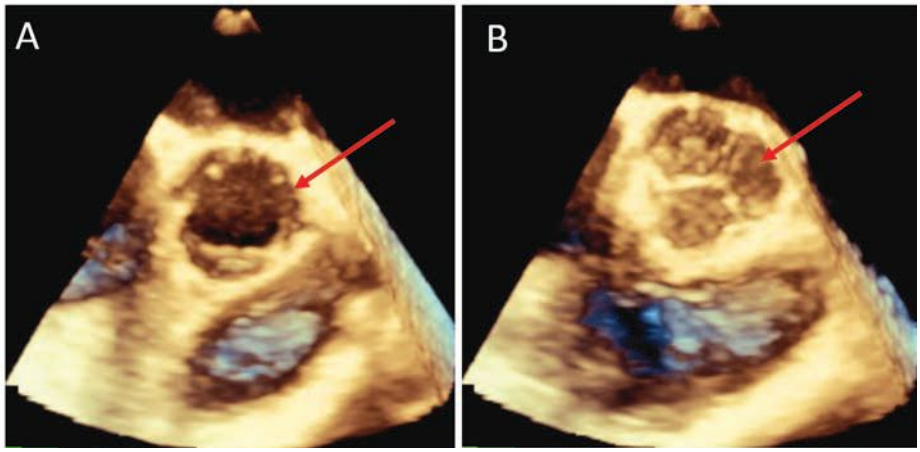


Figure 1. Three dimensional echocardiogram images show excellent resolution of an open (A) and closed (B) aortic valve.

Despite its advantages for assessment of cardiac anatomy and function, echocardiography does have limitations. Poor acoustic windows due to physical conditions (ie: obesity, scoliosis, pectus) can limit the imaging evaluation. Pulmonary venous anatomy and aortic arch anatomy can typically be evaluated with echo, but detailed anatomy of the extracardiac vascular structures may be better depicted with cross sectional imaging such as CT or MRI. Echo is also not as accurate at evaluating ventricular volumes, especially the right ventricle which can be important in patients with RV dysfunction.[12] MRI remains the gold standard for assessment of ventricular function.

Computed Tomography

Computed Tomography (CT) has proven to be a useful adjunct to catheter angiography and echo in the assessment of CHD in children. Complex congenital defects often involve the extracardiac vascular structures which are better delineated with CT rather than echo. CT angiography offers a noninvasive alternative to traditional catheter based angiography for visualization of the vascular anatomy. CT imaging is also a quicker and less expensive technology.13

Patient preparation for a CT angiography examination depends on the anatomic or clinical indication. CT usually requires no sedation, unlike MRI which requires sedation due to the longer examination time. However, sedation is sometimes necessary in young children and when detailed intracardiac or coronary anatomy is required.[14]

Intravenous iodinated contrast is necessary to opacify the vascular structures. The usual contrast volume is 1-2 ml/kg in pediatric patients.[14] The route of intravenous contrast administration can depend on the anatomy to be evaluated, but most commonly is administered in an upper extremity peripheral vein. Contrast bolus tracking or timing boluses can be used to ensure appropriate opacification of the vascular anatomy.[5,14]

CT radiation doses have been a concern in the pediatric population. However, due to new multidetector and dual source CT technology, temporal resolution has improved resulting in faster scans and reduced CT doses. Doses for prospective ECG gated CT scans range from 1-3 mSv in adults and to 0.2-0.7 mSv in newborns and infants.[15,16] Comparatively, doses for retrospective ECG gated CT scan can range from 2-6 mSv.[15-17] The improvement in spatial and temporal resolution on newer generation CT scanners has also improved image quality. Dose reduction techniques can also be used to further reduce the overall dose, such as lower pitch, higher tube current and tube current modulation and decreasing the acquisition window.[5,14,17]

CT angiography examinations can be performed with or without Electrocardiography (ECG) gating depending on the congenital defect to be imaged. Non ECG gated CT

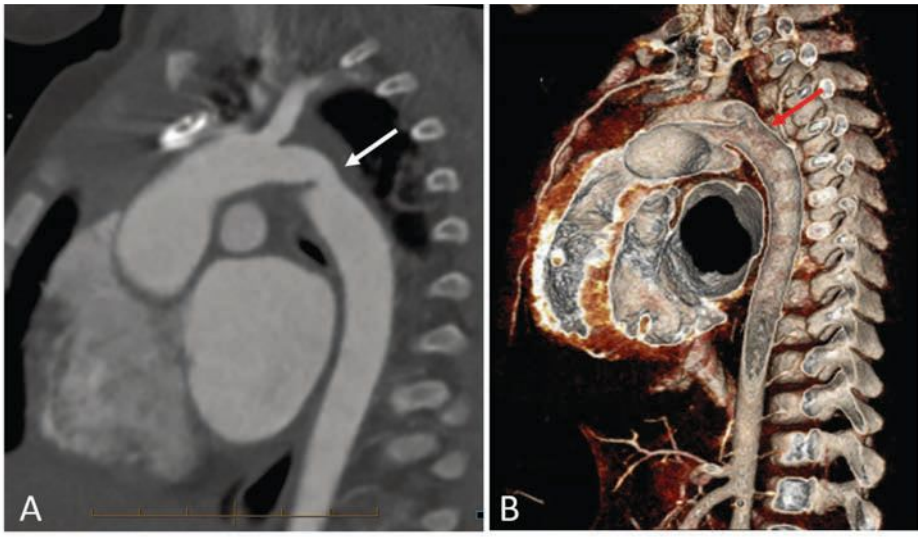


Figure 2. (A) Sagittal oblique CT images of a 15 month old for arch evaluation. Mild hypoplasia of the distal transverse arch and narrowing of the juxtaductal arch consistent with coarctation. Patient also had a patent ductus arteriosus. (B) 3 dimensional images show area of arch narrowing and relation to the patient's PDA.

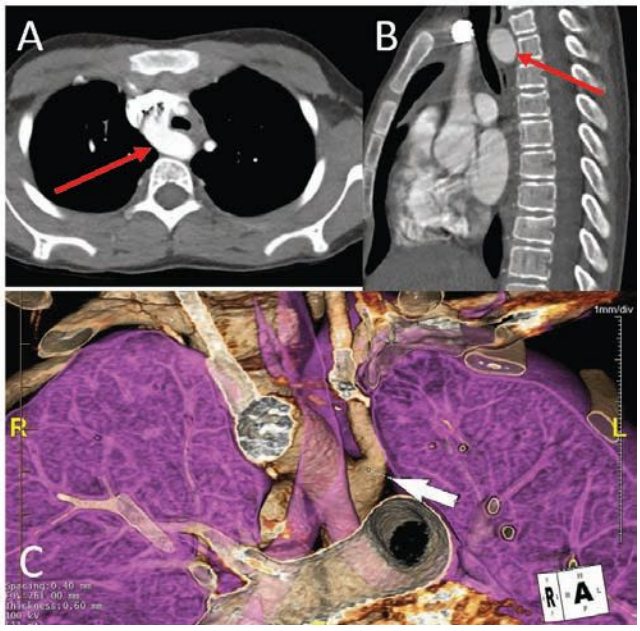


Figure 3. Axial (A) and sagittal (B) CT angiography demonstrates a right sided aortic arch with posterior compression on the trachea. (C) 3D reformatted image shows the relationship of the trachea and right sided aortic arch.

examinations are mainly used for the evaluation of major arteries and veins, such as pulmonary arteries or veins, aortic arch or evaluation of vascular ring. Assessment of the vessel relationships, connections and size can be accurately assessed with little motion degradation of the images (Figure 2). These exams are usually and preferably done without sedation or breath hold. Relationships of the airways to the vascular structures and airway compression can also be an important clinical piece of information that can be obtained from these studies. The airways and vessels can be evaluated with reformatted multiplanar images or 3D reformatted images (Figure 3). Dynamic airway CT evaluations can also be performed to further assess the degree of compression by the vascular structures in question.[15]

ECG gated studies have reduced artifact associated with cardiac motion and are most useful for evaluation of intracardiac and coronary anatomy. For optimal image quality one of the prime requisite for these studies is little to no patient motion; therefore breath holds are preferred, and sedation is often required in young children. ECG Gating techniques can be prospective or retrospective.

Prospective ECG gated CT scans are obtained data during a set interval of the cardiac cycle, in contrast to retrospective gated studies which obtain data throughout the entire cardiac cycle.5, 15,16 For this reason, prospective studies are lower in radiation dose compared to retrospective studies and therefore preferable. During a prospectively gated examination, data is usually obtained during the portion of the cardiac cycle where the heart is most at rest. This changes depending on the patient's heart rate. In patients with a lower heart rate (<75 bpm), images are obtained in end diastole (70-80% of the R-R interval). In patients with higher heart rates, data is usually obtained at end systole (30-40% of the RR interval).16 Since data is only obtained from a fixed time point during prospective studies, functional data cannot be obtained. Prospective imaging can also be limited in patients with variable, irregular or rapid heart rates. In these cases, a retrospective examination can be performed. Functional data can be processed from these studies since the data is obtained throughout the cardiac cycle. At our center, most functional CT studies are done secondary to patient's inability to undergo MRI (for eg. implanted cardac pacemaker or defibrillator).

The CT angiography images can be further evaluated with the help of various post processing and reformatting techniques. Newer CT scanners produce isotropic data sets that can be reconstructed into many multiplanar reformatted [MPR] and 3D reformatted images. (Figure 4) MPR images can assist in the accurate orthogonal measurements of vessel diameter/size. 3D reformats are helpful in preoperative visualization of the anatomy[18] and can also be printed on 3D printers to allow surgeons a physical model of the structures before entering the operating room.[19]

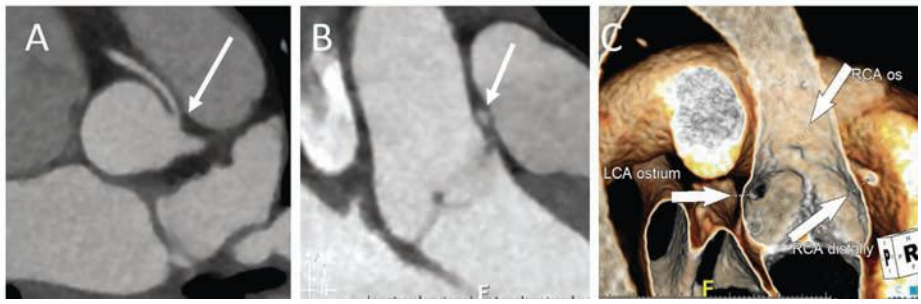


Figure 4. (A) Axial image from a gated cardiac CT shows an anomalous right coronary artery arising off the left aorta and coursing intra-arterial between the aorta and main pulmonary artery. (B and C) Multiplanar reconstructed images show the takeoff of the RCA is superior to the commissure between the right and left coronary cusps. The RCA origin is ovoid and has an acute angled take off

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has been used with increasing frequency in the preoperative and postoperative evaluation of CHD. MRI offers an additional noninvasive way to visualize both the anatomy and physiology without radiation exposure, and is commonly used for evaluation of cardiac function and vascular flow data which can aid in directing treatment. Cardiac MR (CMR) is frequently performed for the assessment of intracardiac shunts and preoperative assessment in valvular disease.[20] Postoperative evaluation for patients with tetralogy of Fallot, aortic arch interventions, transposition of the great vessels and single ventricle physiology are also common indications for cardiac MRI (CMR). In addition to preoperative and postoperative assessment of CHD, MRI is highly recommended to be used to evaluate cardiac tumors, myocarditis, and cardiomyopathies.[20-21]

Cardiac MRI examinations can be long studies which can take 1-2 hours to perform depending on the anatomy to be evaluated. Typically sedation is required for children under the age of 7-8 years of age and is performed by an experienced cardiac anesthesiologist.[20,22-24] It is very helpful to have an ongoing discussion between the imaging team and the anesthesiologist about imaging goals, duration of the study, breath-holds required and hemodynamic changes that may occur during the test. Infants under the age of 3-6 months usually do not require sedation. These examinations are typically focused exams to answer a specific clinical question and tend to be shorter in length than studies performed on older children.[21] The examinations on neonates and infants can be performed after feeding and swaddling the child.[25] Many pediatric centers have child life specialist programs which help evaluate the children prior to the study. The child life specialist explains the procedure and answer questions from the child and parents. They will usually show the patient a MRI simulation with a model or video prior to the examination. Many MRI scanners in pediatric centers also have audio visual equipment which allows the children to watch a movie of their choice during the non-sedated examination. These interventions can reduce the number of patients needing sedation for MRI examinations.[26]

Cardiac MRI studies are performed on both 1.5 Tesla and 3 Tesla field strength magnets. Each magnet has advantages and disadvantages. The higher field strength 3 Tesla magnets have a high signal to noise ratio which improves definition between the myocardium and blood pool. You can also get higher spatial resolution images with the same scan time and contrast resolution because of the higher signal present. However, the higher field strength also has more magnetic susceptibility artifacts and field inhomogeneity than the 1.5T magnets which can degrade the images[27]. Some of these effects can be mitigated by the choice of imaging sequences that are used. For example, gradient echo sequences are less susceptible to field inhomogeneity than steady state free precession (SSFP) sequences and can be used when imaging with a 3T magnet.[27]

Imaging of the cardiac structures entails multiple imaging planes and sequences which each assess different aspects of the anatomy and physiology. Most studies begin with non-gated bright blood steady state free procession (SSFP) images and black blood single shot fast spine echo images to obtain a general view of the anatomy. These initial images are then used to plan imaging planes for targeted imaging sequences. Cinegraphic ECG gated SSFP images are then obtained of the heart in various projections, such as short axis, 4 chamber and 2 chamber views. The cine images are obtained over the course of the cardiac cycle and can be used for assessment cardiac function and ventricular size/volu mes.[20-21] Specialized left and right ventricular outflow tract views can also be performed depending on the anatomy. Velocity encoded phase contrast sequences can be performed when the assessment of flow within vessels is needed. This can be important in determining valvular function and information regarding the blood flow velocity and volumes can be obtained. Regurgitant fractions and gradients across the cardiac valves can be calculated which can be helpful in determining timing of valve replacement or repair surgeries. Differential flow to the pulmonary arteries and systemic to pulmonary blood flow (Qp:Qs) for shunt assessment can also be calculated from the velocity encoded sequences.[20-23]

The need for intravenous contrast agents in cardiac MRI depends on the indication. Contrast agents can be used to better delineate the vascular structures, assess for perfusion, and determine presence of delayed enhancement. When contrast is necessary, the most commonly used agent is a gadolinium based contrast agent (GBCA). Gadolinum is considered a safe intravascular contrast agent with low adverse event profile.[28] It is used for contrast enhanced MR angiograms which can give excellent depiction of the vascular anatomy and dimensions. Assessment of delayed enhancement with

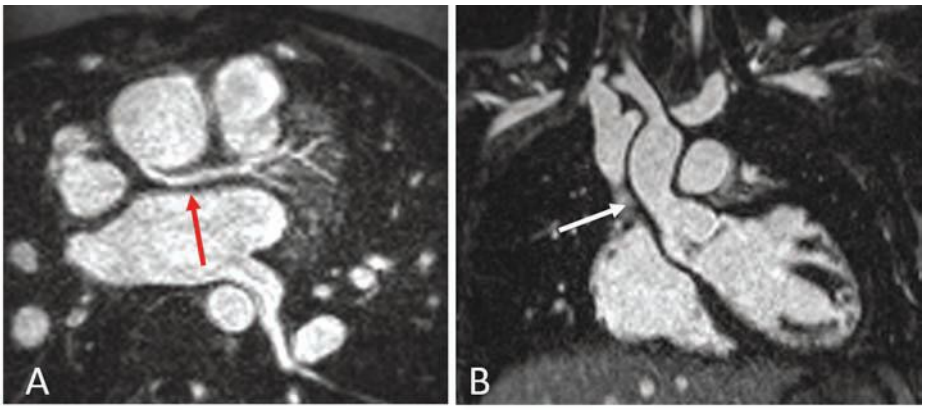


Figure 5. Examples of Cardiac MRI with use of Ferumoxytol as a contrast agent. (A) Shows a slightly posterior [benign variant] origin of the left coronary origin in detail on contrast MRI. (B) Excellent contrast enhancement of the ascending aorta which can be used for evaluation of vessel size and anatomy.

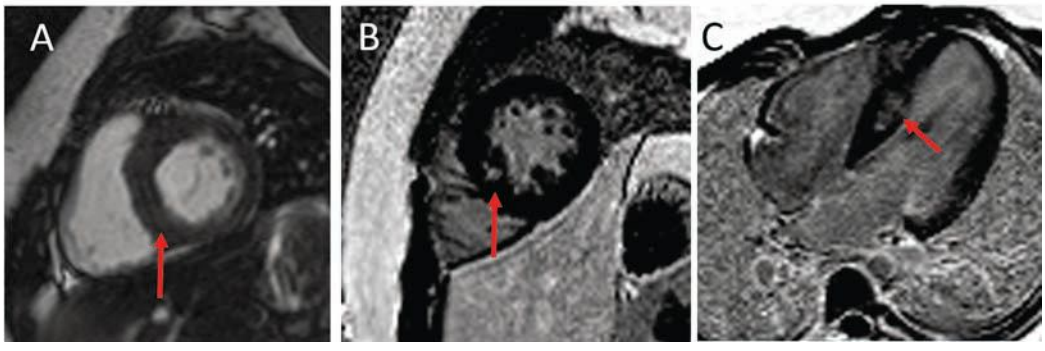


Figure 6. 8-year-old with hypertrophic cardiomyopathy. MRI images in short axis (A) shows asymmetric thickening of the septal wall with patchy mid-septal delayed post contrast enhancement (B and C) consistent with fibrosis [red arrows].

GBCAs can detect the presence of scar or fibrosis which can impact the management of patient with conditions such as hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia, and myocarditis[29] (Figure 5).

However, GBCAs are not safe for use in patients with poor renal function.[30] In cases which a GBCA cannot be used, newer non-gadolinium based alternative agents have been used with increasing acceptance. Ferumoxytol is one such agent that has been used as an alternative for MRA. Ferumoxytol is an ultrasmall superparamagnetic iron oxide particle used in the treatment of iron deficiency anemia. Secondary to its long intravascular half-life and high T1 relaxivity, it can be used with a diaphragm navigated 3D whole heart sequences to give excellent visualization of the vascular structures on MRI[31-32] (Figure 6).

After the acquisition of the CMR data is complete, the images are post processed with software that can generate physiologic data similar to echocardiogram. MRI is the reference standard for the assessment of ventricular function.[33] Endocardial and epicardial contours are usually traced on the short axis cine images for assessment of cardiac function, mass and volumes. MR angiographic data can be processed using various multiplanar and maximum intensity projections creating two dimensional and 3D images of the vasculature. Volume and surface rendered images of the anatomic structures can produce 3D images that can be used by surgeons in the planning of complex surgical procedures.

Future Advances

Many additional advances in pediatric cardiac imaging have recently been developed and investigated. MRI 4D flow assessment is an emerging technology which can assess multidirectional vascular flow patterns and hemodynamics. This information can be helpful in the management and evaluation of patient s with such conditions as bicuspid aortic valves and post Fontan pathways.[34] As a result of the development of higher resolution MRI and CT scanners, 3D printing technology can be used to produce complex cardiac models and virtual/augmented reality visualization of the cardiac structures.[19] This 3D technology can be useful in the preoperative assessment and can allow surgeons to even practice surgery prior to the operation.[19]

Conclusion

Although echocardiogram has been the first line screening imaging modality for congenital heart disease for decades, advances in CT and MRI have made them useful adjuncts in the imaging evaluation in CHD patients. Sometimes multiple modalities are needed to fully evaluate the cardiac structures involved in complex congenital heart lesions. Both CT and MRI offer non-invasive methods of imaging the severity of a number of congenital heart conditions. The decision between choosing modalities for the evaluation of CHD depends on the clinical indication to be answered. CT is best used when high spatial resolution is necessary, as in evaluation of coronary arteries. However, CMR can provide functional and physiologic data along with excellent anatomic images. These are complementary modalities to angiography and echocardiography in the diagnostic assessment and management of patient with complex CHD.

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Disclosure

None reported. **MM**

Pediatric Interventional Radiology: Blurring the Lines Between Specialties

by Douglas C. Rivard, DO & Brenton D. Reading, MD

The field of pediatric interventional radiology has flourished over the past decades due to the increasing development of imaging equipment, smaller devices, and technical innovations lending themselves to caring for the smallest patients.





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Abstract

Medical imaging has transformed the ease and speed of patient care with provision of detailed evaluation of anatomic structures and disease processes. Interventional radiology uses imaging guided techniques to further diagnose or treat diseases with minimally invasive methods. These techniques are particularly helpful in treating pediatric patients.

Introduction

The discovery of X-ray production and detection in 1895 by Wilhelm Rontgen marked the advent of the field of medical imaging. In the subsequent century, medical imaging advances would result in ever more sophisticated imaging techniques and insights that have had immeasurable impact for the collective benefit to patients. The magnitude of this benefit is substantiated by the fact that numerous scientists have been awarded Nobel Prizes for their contributions to the field of medical imaging over the past century.

Interventional radiology (IR) is a radiology subspecialty that involves the use of imaging methods such as x-ray, ultrasound, CT scans, and other innovative methods to diagnose and treat diseases involving almost every organ system. Interventional radiologists are trained both in diagnostic radiology and in the minimally invasive techniques using these imaging modalities for delivery of medications and devices in the most innovative fashion with unprecedented precision. It is obvious how minimally invasive techniques are beneficial to patients, and perhaps even more so for pediatric patients owing to their small size and desire to achieve therapies with the least possible disruption to growing patients. In this manuscript, we will briefly review the history of interventional radiology and highlight some of the contemporary ways IR is applied in innovative ways for pediatric patients.

After Rontgen's X-ray discovery, the first angiogram of a cadaver arm was performed one year later in 1896. While the methods, including the use of mercury sulfide, lime and petroleum, seem crude by today's standards, the value of such imaging modalities was evident to early medical professionals. Various other imaging techniques ensued over the next few decades including attempts to image the central nervous system by injecting air into the ventricles followed by radiographs to examine the brain for gross structural abnormalities and asymmetry of the ventricles which might suggest an intracranial mass. Not until 1927 was the first successful angiogram performed on a live human patient. Dr. Egas Moniz, a Portuguese physician, performed and documented the first angiogram of the cerebral vasculature performed with rudimentary contrast agents

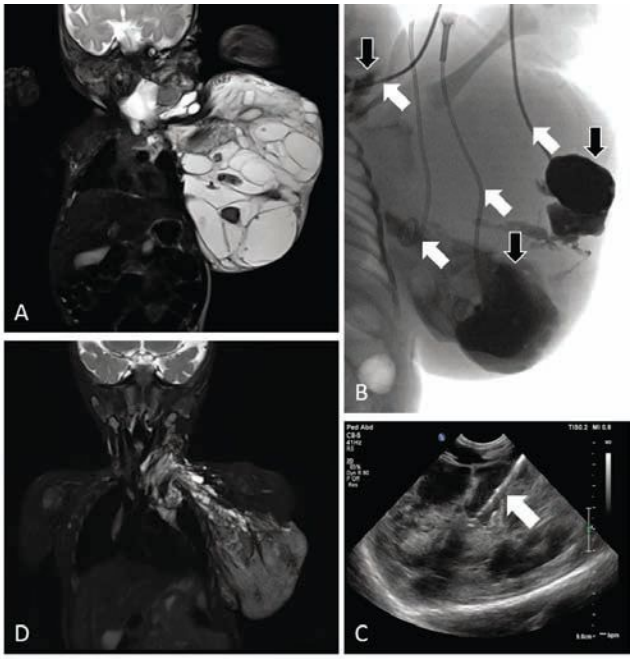


Figure 1. Newborn male with left axillary lymphatic malformation. A. T2 MR imaging in neonatal period demonstrates a large multilocular cystic lesion in the left axilla with predominantly high signal and heterogeneous areas of low signal suggesting hemorrhage. B. Flouroscopic image from initial sclerotherapy treatment demonstrates multiple drains (white arrows) with contrast (black arrows) in loculated cystic areas. Sclerotherapy was performed through the drains. C. Ultrasound Image from initial sclerotherapy demonstrates a needle (white arrow) advancing into the loculated cystic mass. D. T2 MR imaging 14 months post multiple sclerotherapy treatments demonstrates decreased cystic areas with residual scar tissue which was subsequently removed at surgical debulking.

and direct carotid cut downs to access the arteries for injection.[1] After that time others went on to continue advancing the role of angiography and predictably multiple innovations arose in the next decades leading to techniques such as pulmonary, vena cava angiography, and the Seldinger technique for less traumatic access to vessels for subsequent angiography or intervention such as angioplasty or stent placement.

In the 1960s, a visionary radiologist and angiographer, Dr. Charles Dotter, imagined using the angiography catheter as a surgical instrument. In an address he delivered in Europe to a group of multinational radiologists, he described a future state where the catheter could be used as a delivery device for balloons, stents, medications, and other devices.[2] His vision was very prescient and sparked the next 50 years of development of the specialty of interventional radiology. During this time, there were concurrent advances in the design and manufacture of devices and catheters leading to ever-smaller devices and catheters. Then, in the mid-1980s, several pediatric radiologists began utilizing these imaged guided minimally invasive techniques in children with success.[3] Today, the field of pediatric IR is growing and being utilized increasingly for our smallest patients with success in all organ systems.

Interventional Radiology Uses

IR physicians use their skill and training in imaging and imaged guided therapy to perform numerous diagnostic and therapeutic procedures. The most commonly performed IR cases involve placing needles, wires, and catheters under imaging guidance with ultrasound, fluoroscopy, and CT into organ systems and body cavities such as the vascular system, gastrointestinal tract, genitourinary system, biliary tract, peritoneum, pleural space, thecal space, and other fluid collections/abscesses for the purposes of medication administration, nutritional support, diagnostic imaging, laboratory sampling, and therapeutic treatment. In comparison to adult IR, most of these common procedures require only minor variations in technique and equipment to accommodate the smaller size and more delicate tissues of pediatric patients. However, there are other IR procedures that are more specific to pediatric practice based on the unique physiology of the pediatric patient. Additionally, pediatric IR cases also encompass treatment of a larger proportion of congenital lesions as compared to adults.

Sclerotherapy of vascular malformations (congenital malformations of lymphatic vessels, veins, and arteries) while not specific to pediatrics, is most commonly performed early in life. Lymphatic malformations contain serous fluid with varying amounts of internal hemorrhage and are often treated with drainage or aspiration and injection of sclerosant agents such as doxycycline or bleomycin (Figure 1). Venous malformations on the other hand are not aspirated and are generally injected with foamed sotradecol. Precise placement of the proper sclerosant agent is essential especially if the malformation is in a critical area such as in the orbit or near the airway. High flow malformations that involve connections to arterial supply are most commonly treated with precise navigation of a catheter or needle to inject ethanol or embolic agents to occlude the nidus. Following sclerotherapy, the vascular malformation often increases in size for a week or two due to inflammation. Follow-up is planned in a few months to give the lesion time to scar down and allow time for new or untreated areas to develop. Larger or more complex vascular malformations frequently require multiple treatments.[4]

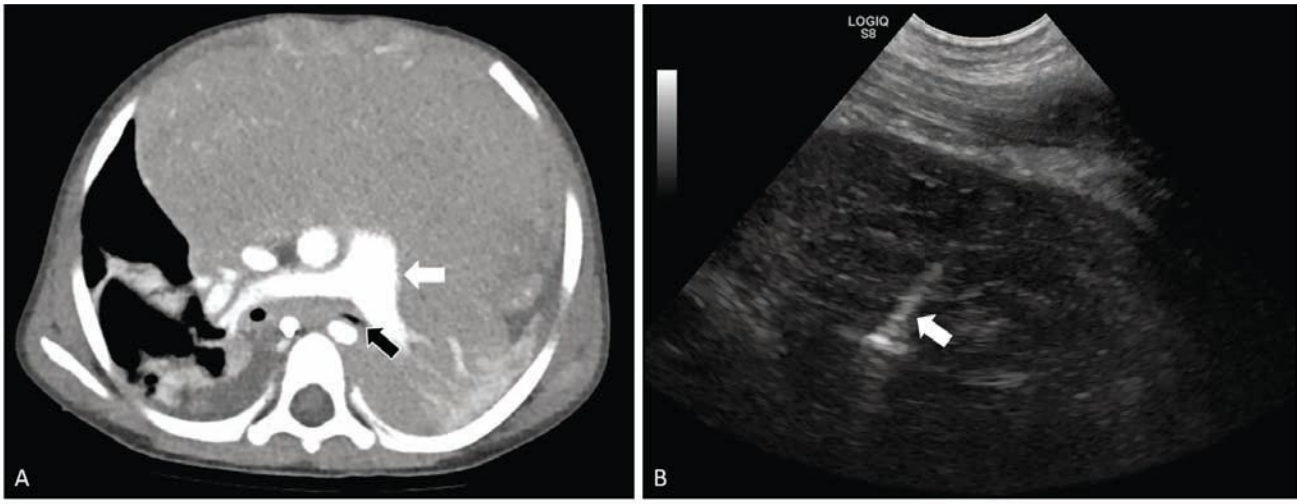


Figure 2. Three year-old female with lymphoma resulting in anterior mediastinal mass. A. CT of the chest demonstrates a large anterior mediastinal mass resulting in mass effect on the major mediastinal vessels (white arrow) and mass effect on the left mainstem bronchus (black arrow). B. Ultrasound image from biopsy with minimal sedation to decrease risk of cardiopulmonary compromise demonstrates the biopsy needle (white arrow) within the mediastinal mass.

In addition to congenital lesions, lymphatic collections may also be acquired due to disruption of lymphatic channels, most commonly following thoracic surgery for congenital cardiac anomalies. Lymphatic leaks are notoriously difficult to stop and the first step in treatment is defining the location of the leak. Recent advancements in fluoroscopic and MR lymphangiography provide excellent detail of the lymphatic system and often define the location of a leak. In some cases where the leak arises from small diffuse lymphatic channels, fluoroscopic lymphangiography with lipiodol may even be therapeutic as the viscous and mildly sclerotic contrast agent can occlude small lymphatic channels. Alternatively, after the leak is located, it can be occluded with glue or coils through a catheter placed percutaneously into the thoracic duct. In cases where the duct is too small to cannulate, imaging can help guide an open surgical closure.[5]

There is an ever-increasing role of the pediatric IR physician in the treatment of children with malignancies. This ranges from image guided biopsy procedures to procure necessary tissue for diagnosis to more advanced direct tumor therapies. Pediatric IR physicians also play an important role by placing vascular access devices in children such as PICCs, tunneled lines, and port catheters for oncology therapy. Pediatric types of cancer such as lymphoma also present unique challenges with opportunities for IR intervention. Lymphoma commonly results in mediastinal adenopathy which given the limited space of a child's chest and pliable tissues may result in mass effect causing airway or mediastinal vessel compression. This presents a challenging clinical scenario in which a diagnostic biopsy is needed prior to treatment and yet treatment would be helpful in decreasing the mass effect to facilitate safer biopsy. These challenging cases require a multidisciplinary approach with IR, Hematology/Oncology, Critical Care, Surgery, Pathology, and Anesthesia. Often, biopsy is safely performed prior to treatment with ultrasound guidance, local anesthetic, and minimal sedation (Figure 2).

Metastatic disease in pediatrics has traditionally been treated with chemotherapy or surgery. However, percutaneous ablation and transarterial chemoembolization which are becoming more common in adult oncology are now being employed in cases of inoperative pediatric metastatic disease. In addition, nonmalignant lesions such as osteoid osteoma and pheochromocytoma may be treated with percutaneous thermal ablation resulting in decreased hospitalization and faster recovery (Figure 3). In the future, the indications for ablation and catheter directed chemoembolization in pediatric oncology will likely increase.

Drainage of infectious or malignant fluid collections is another area that Pediatric IR physicians also contribute to pediatric care with minimally invasive, imaged guided techniques. Ultrasound is frequently employed as the preferred imaging modality to place needles and drains in children as it permits real time precise guidance without using radiation. Abscesses and other fluid collections

are routinely drained percutaneously using these techniques sparing surgical intervention for many children (Figure 4). The treatment of parapneumonic effusion or empyema is one such example that has undergone a shift in treatment paradigm from surgical debridement with video assisted thoracoscopy (VATS) to image guided chest tube placement with intrapleural infusion of fibrinolytics such as tissue plasminogen activator. This approach has resulted in excellent results and now is the preferred treatment approach at our institution with success rates approaching 90% obviating the need for surgery.[6]

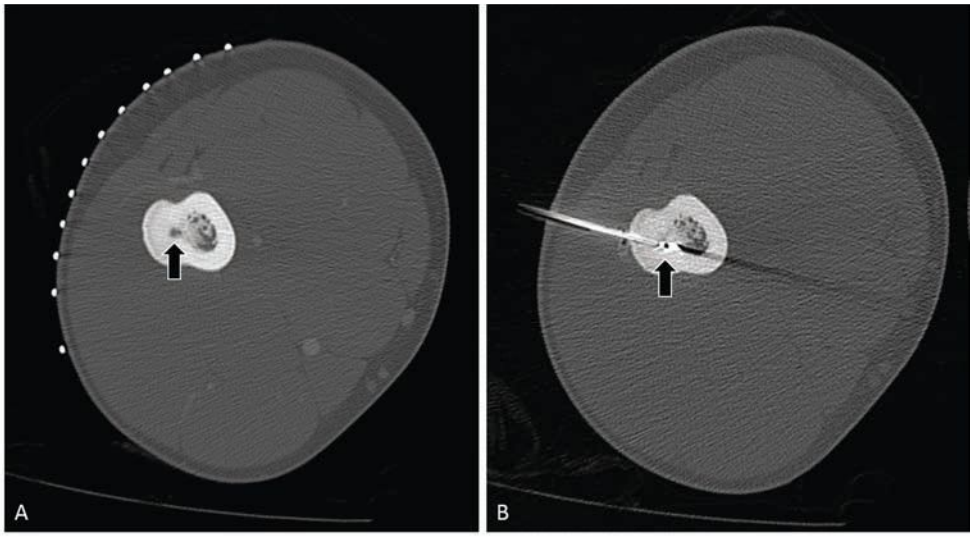


Figure 3. 14 year-old male with right femoral osteoid osteoma. A. Axial CT image with a grid to prepare for treatment demonstrates an osteoid osteoma with cortical sclerosis and central lucent nidus (black arrow). B. CT image with radiofrequency ablation probe in place demonstrates the tip positioned appropriately for treatment across the central nidus (black arrow).

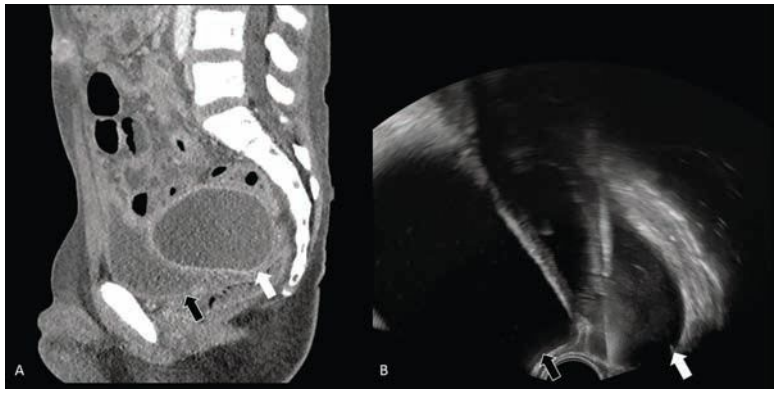


Figure 4. 13 year-old male with pelvic abscess post perforated appendicitis. A. Sagittal CT image shows a rim enhancing pelvic abscess (white arrow) posterior to the urinary bladder (black arrow). B. Sagittal ultrasound image during transrectal drainage demonstrates a needle and guidewire in the abscess (white arrow) posterior to the urinary bladder (black arrow).

Conclusion

In summary, the field of pediatric interventional radiology has flourished over the past decades due to the increasing development of imaging equipment, smaller devices, and technical innovations lending themselves to caring for the smallest patients. As is evident from this brief overview, the IR scope of practice overlaps with nearly every other specialty in the hospital providing unique opportunities for collaboration. With shorter treatment times, less invasive approaches, and frequent ability to treat and discharge in the same day, IR consults will undoubtedly continue to have growing impact in delivery of efficient, value added patient centered care to pediatric patients with complex medical diseases.

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Disclosure

None reported.

MM

Pre-Surgical Planning: Multimodality Imaging to Optimize Outcomes in Pediatric Epilepsy Surgery

by Timothy P. Zinkus, MD

A multidisciplinary epilepsy conference is the ideal setting to integrate information from the patient's diagnostic radiology workup with information obtained from the remainder of the patient's clinical assessment.



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Abstract

Neuroimaging is an important component of the pre-surgical planning for pediatric epilepsy. High-resolution structural magnetic resonance images are combined with advanced structural and functional imaging techniques to better define the surgical lesion and decrease morbidity postoperatively. The combination of neuroimaging, electroencephalography (EEG), and neuropsychiatric testing in a multidisciplinary epilepsy conference setting is essential for determining a plan for surgical management.

Magnetic Resonance Imaging

The foundational imaging modality for the diagnostic workup of epilepsy is magnetic resonance imaging (MRI). A dedicated epilepsy protocol is recommended which is generally tailored towards a higher-resolution assessment of the cerebral cortex and associated signal abnormalities. Imaging resolution of the brain can be optimized with the use both a higher field strength 3T magnet and a multichannel head coil such as 32 or 64 channel.[1] A whole brain isotropic T1 weighted sequence in generally the mainstay for providing structural or anatomic detail of the brain (Figure 1A). The detection of signal abnormalities in the brain may also be increased with the use of a thin section T2 axial sequence (Figure 1B) or an isotropic fluid attenuated inversion recovery (FLAIR) sequence. Isotropic sequences are an essential part of the imaging protocol because they are commonly used for surgical navigation. The sequences are also useful for co-registration with other structural and functional imaging techniques. Because of the high propensity of mesial temporal sclerosis in childhood epilepsy, dedicated thin section coronal T2 and T2 FLAIR sequences angled perpendicular to the hippocampi are very useful sequences as this orientation provides improved visualization of the hippocampal morphology. Susceptibility weighted imaging (SWI) is a useful sequence since it is sensitive for the detection of hemosiderin and calcification. Diffusion tensor imaging (DTI) is also useful for both the detection of diffusion signal abnormalities and for the post processing of white matter fiber tracts.

Diffusion Tensor Imaging

Diffusion Tensor Imaging (DTI) is an MRI sequence that assesses both the magnitude and direction of the microscopic motion of water molecules. The directional information of white matter tracts obtained through DTI allows for the three-dimensional (3-D) reconstruction of fiber tracts. Through post-processing, 3-D fiber tracts can be reconstructed and fused to the structural isotropic T1 sequence for more precise anatomic localization (Figure 2). White matter structural information can be obtained that is not visible on traditional sequences. The proximity of an epileptogenic focus to the fiber tract can be delineated for surgical planning and to help predict morbidity. For example, fiber tracking of the optic radiations in patients with anterior lobe epilepsy has been show to assist

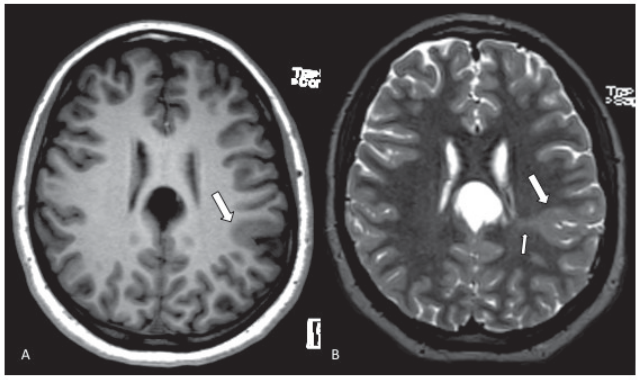


Figure 1. Axial isotropic T1 **(A)** sequence demonstrating abnormal thickened cortex in the left frontoparietal region (arrow). Axial isotropic T2 **(B)** sequence showing abnormal T2 signal extending from the thickened cortex to deep white matter (arrow).

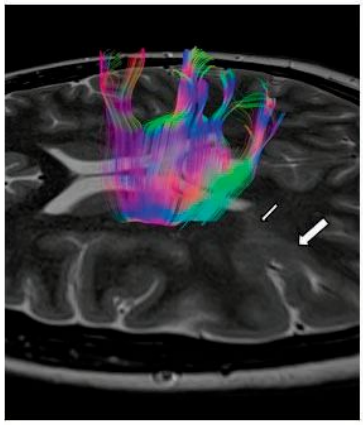


Figure 2. Tractography fused to axial isotropic T2 sequence demonstrating proximity of the corticospinal tracts (color) to the thickened cortex and deep white matter lesion (arrow).

with the prediction of postoperative visual field deficits. [2] Additional parameters which may be evaluated with DTI include white matter fractional anisotropy (FA) and mean diffusivity (MD). FA and MD measurements have been shown to correlate with memory and language impairments in temporal lobe epilepsy which may help predict neuropsychological status in patients with epilepsy. [3]

Functional MRI

Functional MRI (fMRI) is a noninvasive means to help identify eloquent cortex for pre-surgical planning. The most commonly used technique for fMRI is blood oxygen level dependent (BOLD) imaging. The principle of this technique is that increased cerebral blood flow corresponds to areas of increased neuronal activity. Areas of increased neuronal activity are generated during fMRI through a stimulus delivery or paradigm. Commonly used paradigms for pre-surgical planning include motor, sensory, speech, and visual (Figure 3A, 3B. The implementation of the paradigms in the pediatric setting can be challenging since the patient must not only be awake and cooperative during the exam but also relatively motionless. Stimulus delivery may be accomplished through specialized equipment including DVD goggles or flat screen television with a mirror mounted on the MRI head coil. Depending on the paradigm, patient responses to the stimuli may also be recorded with MRI compatible response pads. The BOLD imaging sequence is very susceptible to patient motion and dental hardware so proper patient screening prior to the exam is essential. One of the more common uses for fMRI for epilepsy pre-surgical planning is language lateralization in which fMRI has be shown to help predict post-operative language deficits.[4]

A more traditional radiologic examination for language lateralization is the Intracarotid Sodium Amybarbital Procedure or Wada Test. During a Wada test, a femoral arterial puncture is performed and after an abbreviated cerebral angiogram, intra-arterial sodium amybarbital is administered via each internal carotid artery. Both language and memory testing is usually performed by a neurologist and/or neuropsychologist during the Wada test in which a cooperative patient is given various tasks. In the pediatric setting, it may be difficult to perform a Wada test considering the more invasive nature of the exam and the need for a cooperative patient. Functional MRI may be the best option in this context considering how various studies have shown good correlation for language lateralization between the more invasive Wada test and fMRI.[5] Functional MRI has also been shown to reliably delineate the proximity of eloquent motor cortex to a surgical lesion and therefore improve surgical outcome. [6] This may mitigate the need for more invasive intraoperative cortical stimulation.

Fluorodeoxyglucose Positron Emission Tomography

Fluorodeoxyglucose positron emission tomography (FDG-PET) is utilized to assess glucose uptake in the brain. The brain normally demonstrates avid FDG uptake as normal metabolically active neuronal cells readily utilize glucose. The FDG isotope is injected intravenously and after an approximate thirty-minute uptake time, imaging is performed on the PET scanner. If sedation is necessary for the examination, it is preferentially administered after the isotope uptake is completed as sedation can affect glucose uptake in the brain. The patient is monitored with EEG during the isotope uptake and scan to monitor for the presence or absence of seizure activity. In the absence of seizure activity, a seizure focus tends to be hypometabolic which manifests as decreased FDG uptake. One context in which FDG-PET has been proven useful is the diagnostic evaluation of seizures in the setting of a normal brain MRI. An FDG-PET directed "second read" of an MRI has been

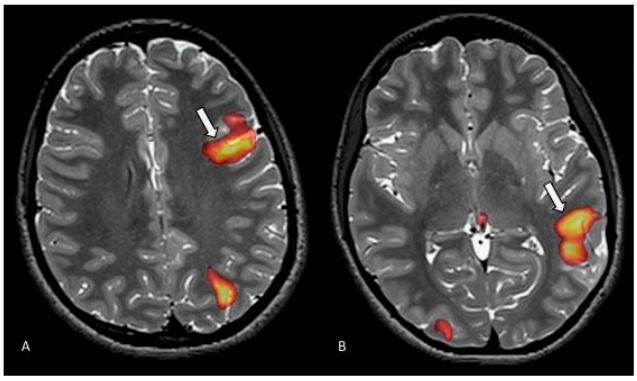


Figure 3. fMRI language paradigm fused to axial isotropic T2 sequence demonstrating left hemisphere language dominance with activations corresponding to Broca's **(A)** and Wernicke's **(B)** areas.

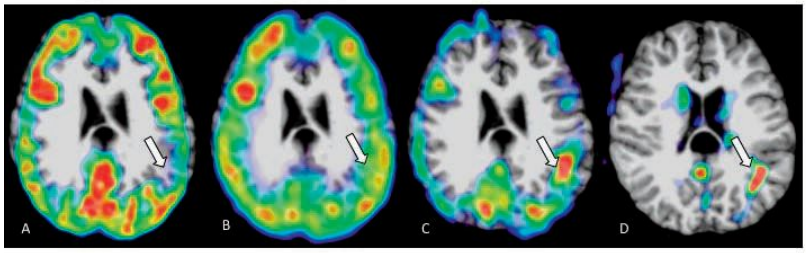


Figure 4. FDG-PET **(A)** fused to axial isotropic T1 sequence demonstrating an area of hypometabolic activity in the left frontoparietal region corresponding to abnormal cortical thickening. *
SPECT images fused to axial isotropic T1 sequence: interictal **(B)**, ictal **(C)**, and subtracted **(D)** images highlight an area of increased perfusion in the left frontoparietal region. *
* Postprocessed PET and SPECT images are courtesy of Dr. Lalit Bansal

proven helpful in the detection of seizure foci such as subtle cortical malformations. [7] Detection is only further improved by post-processing techniques whereby the structural MRI is fused to the FDG-PET scan, providing better correlation of the abnormal structure on MRI to the abnormal function on the FDG-PET scan (Figure 4A).

Single Photon Emission Computed Tomography

Single Photon Emission Computed Tomography (SPECT) is an imaging technique utilized to assess brain perfusion. A radioisotope which can cross the blood brain barrier is injected intravenously. The distribution of this isotope in the brain represents brain perfusion and correspondingly neuronal activity. Both ictal and interictal imaging is typically performed with this technique. For ictal imaging, the patient is admitted to the epilepsy monitoring unit and taken off seizure medications. Over a three day admission, the patient is actively monitored by the bedside and with EEG. If a seizure event occurs the radioisotope, which is ready for injection at the bedside, is injected within as close proximity to the seizure event as possible. During ictal isotope uptake, a seizure focus tends to be hyperperfused. Interictal imaging is also performed during this admission. Ictal (Figure 4B) and interictal (Figure 4C) images may be post processed to produce a subtracted image series (Figure 4D) which may further highlight an area of abnormal brain perfusion. The use of this ictal-interictal subtraction technique with fusion to MRI has been proven to assist in the detection of a seizure focus.[8]

Multidisciplinary Epilepsy Conference

A multidisciplinary epilepsy conference is the ideal setting to integrate information from the patient's diagnostic radiology workup with information obtained from the remainder of the patient's clinical assessment. [9] The information gained from the structural and functional diagnostic imaging techniques discussed above are of even greater value when considered in the context of the patent's clinical evaluation. Clinical information presented from the epileptologists regarding seizure semiology and from neuropsychiatric testing may be effectively integrated with diagnostic studies through this multidisciplinary team setting into a cohesive management plan. The presentation of the information in this cohesive manner assists with further neurosurgical preoperative planning with the overall goal of optimizing the patient's postoperative outcome.

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Disclosure

None reported.

MM

Emerging Technology and Applications of 3D Printing in the Medical Field

by Neil J Mardis, DO

As teaching or diagnostic aids, 3D models offer a new and unique approach to traditional medicine, supplementing and enhancing existing modalities.



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Abstract

3D printing technology evolved in the 1980s, but has made great strides in the last decade from both a cost and accessibility standpoint. While most printers are employed for commercial uses, medical 3D printing is a growing application which serves to aid physicians in the diagnosis, therapeutic planning, and potentially the treatment of patients with complex diseases. In this article we will delineate the types of printers available to the consumer, the various materials which can be utilized, and potential applications of 3D models in the healthcare field.

Types of 3D Printers

There are many styles of 3D printers, each with their own advantages and drawbacks. It is important to consider institutional goals and expected model usage when purchasing a printer. The following is a review of the more common commercially available printers and their potential applications to medical modeling. Printers can be divided into two basic groups, additive and reductive processes. Additive machines deposit layer upon layer of material, progressively building the model into a 3-dimensional shape. In a reductive process, the printer begins with a block of material which it progressively cuts away to reveal the final shape. Most commercially feasible printers for medical applications utilize additive techniques.

Fused deposition modeling (FDM) printers, commonly referred to as material extrusion printers, are among the most common additive types of 3D printers. These printers are relatively inexpensive, typically ranging between $2500 and $20,000. High-quality reliable printers are available at the low end of this price range and are a viable means to begin medical 3D printing. Many FDM machines are capable of printing in a variety of materials such as ABS, PLA, TPE/TPU, nylon, dissolvable material, and polypropylene to name a few (see materials discussion below). FDM style printers feed a spooled filament into a hot nozzle which melts and extrudes the material in the X-Y plane producing a layer of printed material before the nozzle raises or the print bed lowers and a new layer is deposited (Figure 1). The advantages of this style of printer are the relatively low cost of the printer itself, low material cost, readily available filament and replacement parts, and the ease of installation and use. Due to the nature of the machines, very high-resolution prints may be difficult, print times for complicated anatomical structures may be long, and material and color choices may be limited.

Another type of 3D printer is the stereolithography (SLA) style printer. This additive machine, which was introduced in the mid-1980s, uses an

ultraviolet laser to draw layers into a photopolymer resin bath. As each layer is hardened, the printer bed descends and a subsequent layer is built. Digital light processing (DLP) printers operate in a similar manner, substituting the laser with a light source similar to that of a projector to harden the resin. Compared to SLA, the DLP light source is cheaper to produce and maintain. Both methods of printing can create high quality prints with smooth surfaces, however resin-based models may be brittle and the material costs are greater than those conventionally used in FDM printing.

Polyjet printers also utilize photopolymers for high resolution modeling. In contrast to SLA/DLP printers which progressively harden layers of a model in a bath of resin, the polyjet printer sprays photopolymer material through a nozzle much like an inkjet printer. This polymer is hardened with an ultraviolet light allowing for extremely high spatial resolution. In addition to a high level of anatomic detail, the polyjet printer can produce models of various colors, textures, and densities not easily achievable by FDM, SLA, or DLP printers (Figure 2). The cost of polyjet printers is substantially higher than the previous machines and the size and architectural requirements of the machine must be considered.

Three more additive type printers include the selective laser sintering (SLS), selective laser melting (SLM), and electron beam melting (EBM) printers. These machines are similar to SLA/DLP printers, substituting a powder for the resin bath. Sintering heats the material up enough to fuse it while retaining porosity. Melting heats, the material further, making it into a homogenous part. While these printers can produce models in materials not available on the above-mentioned machines, such as ceramics and various metals and alloys, their size and cost may be prohibitive for many healthcare institutions.

Reductive printers are also available including laminated object manufacturing (LOM) machines. With this technology, thin layers of material (paper, plastic, metal) are glued together and then cut away with a thin blade or laser. More layers can then be laid down and the process repeated to complete the model. The potential benefit of this technology is the variety of materials which can be utilized. Some of these materials are very inexpensive and easily recycled, such as paper. LOM printers tend to be very large and expensive which could limit institutional usage at this time.

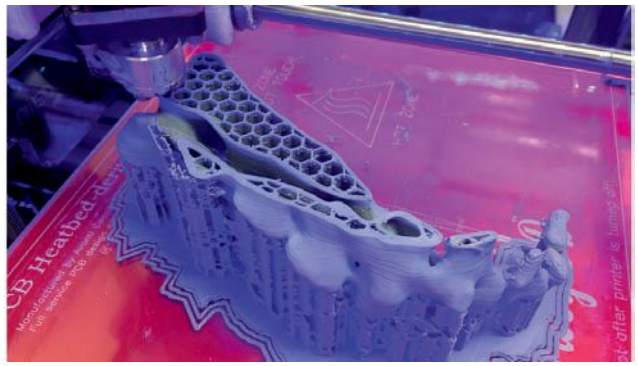


Figure 1. A model of a sacrum being printed on an FDM machine. The model is printed in thin layers (0.1–0.4 mm) as the printer bed slowly descends. The hexagons inside the model serve as support material to provide internal stability. Exterior support material can be removed when printing is complete.



Figure 2. Two models of an infant skull. The model on the left was printed on a polyjet machine. The righthand model was printed on an FDM machine. Print lines are visible in the FDM print and the model is less sturdy. Additionally, the polyjet model has a higher degree of fine detail.

The Printing Process

FDM printers serve as a cost-effective means of establishing a medical 3D printing lab. Their ease of use, smaller size, low cost filament, and commercial availability makes them ideal for physicians interested in entering the arena of 3D printing. Understanding the basic functioning of an FDM printer is particularly useful even if a more complex and expensive printer is contemplated. As stated previously, FDM printers are additive machines, laying down layers of filament which is fed from spools into a heated nozzle. Many printers allow the user to control the temperature of the nozzle, facilitating the use of various filaments with differing melting points. Most FDM printers move the nozzle

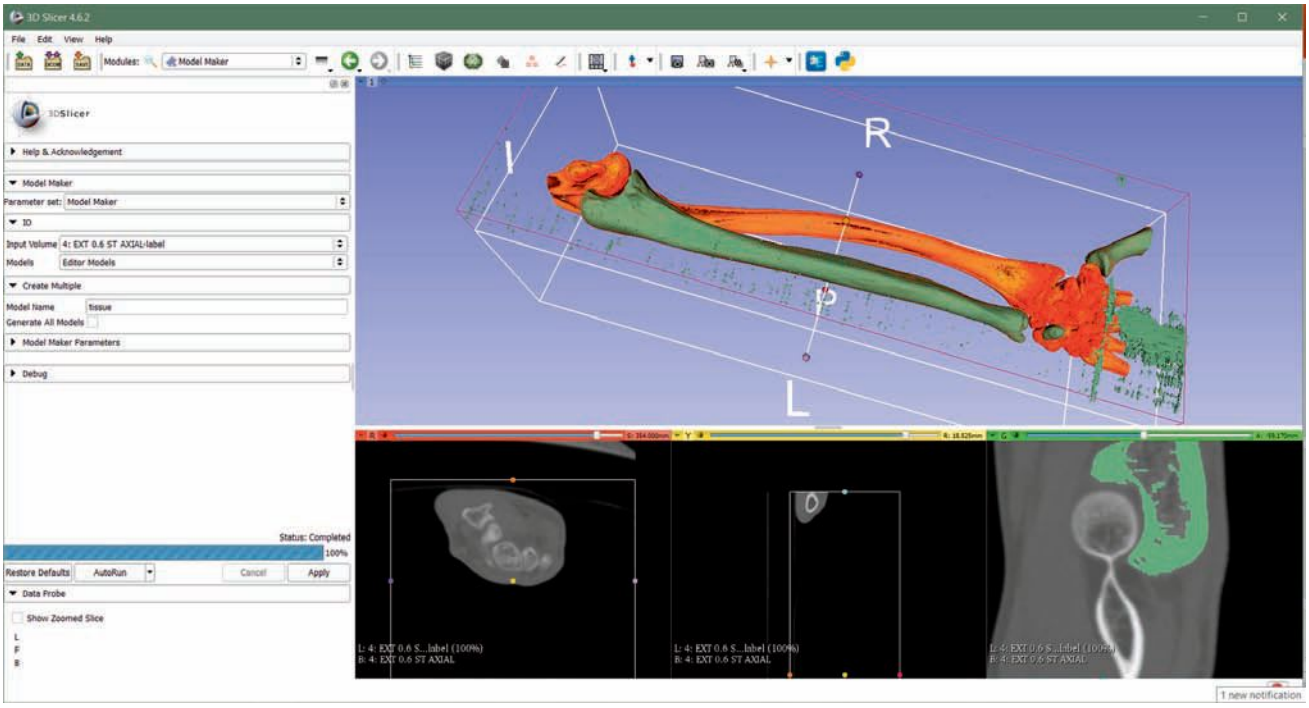


Figure 3. The ulna is segmented from a CT of the forearm in the open source software program 3D Slicer (www.slicer.org).

in the X-Y plane, "drawing" a layer of molten material onto the printer bed. After a layer is completed, the bed descends or the nozzle raises and a subsequent layer is deposited onto the prior. The printer bed is the flat surface, often glass, which the model is built on. Some printers allow the user to heat the print bed to improve adhesion of certain filaments. Utilizing an adhesion agent improves the bond between the initial layers of the model and the bed. There are many adhesion agents available, many of which are liquids or glues that are painted onto the bed prior to printing. While a model can be printed directly onto the bed, often times the use of a raft will improve print success rate. A raft is a thin layer of material conforming to the silhouette of the model which is laid down first, serving as a strong base to hold the model in place as it prints. This raft can be removed from the model after the printing is complete. In addition to a raft, support material is often critical to printing success. Support material may consist of columns, rows, grids, or solid portions of material which is deposited to buttress overhanging edges of the model during the printing process. The support can be the same filament as the primary model or, in a multi-nozzle printer with the capability of extruding more than one material during a single print, can be a dissolvable or easily manually removed substance. Other factors to consider while printing a model are print speed (i.e. how fast the nozzle moves in the X-Y plane), amount of infill (support material inside the model which serves as an internal scaffolding), and layer thickness.

3D Print Materials

Various materials are available for 3D printing including hard plastics, flexible nylon and thermoplastic polymers, dissolvable supports, ceramics, paper, and metal alloys. For clinical medical 3D printing, most users will find hard plastics and flexible materials most useful. The most common filaments utilized by FDM printers are ABS and PLA. ABS (acrylonitrile butadiene styrene) is a widely available option which produces hard plastic models which are durable and relatively inexpensive. ABS is commonly employed to make sporting equipment and protective headgear, in the automotive industry for trim and bumpers, and in the manufacturing of toys such as Lego™. The benefits of ABS include not only durability and low cost, but also dissolvability with acetone. Acetone is a powerful solvent and when applied to the surface of an ABS model will mask the

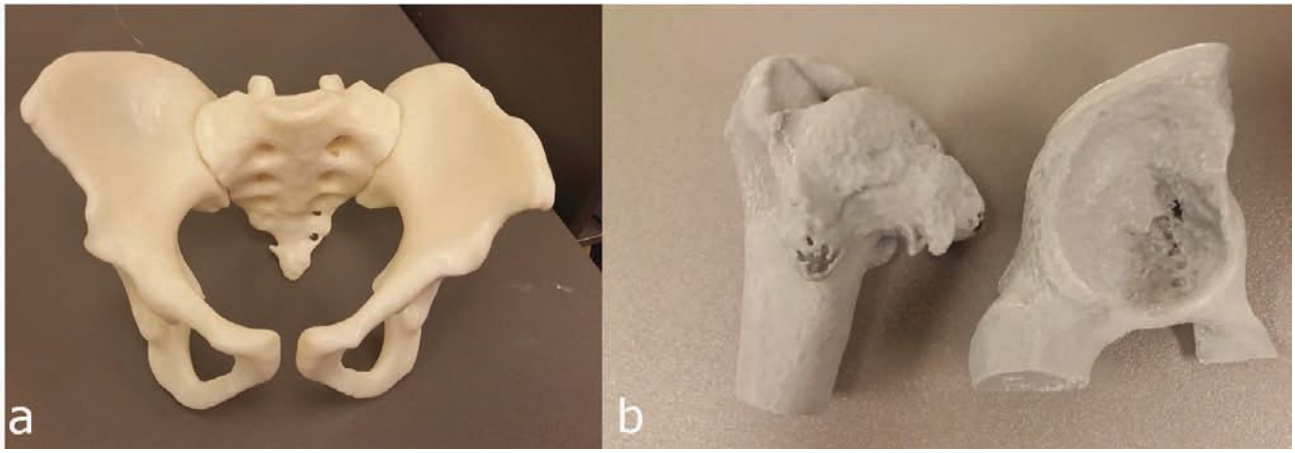


Figure 4. a) Full pelvic model printed on an FDM machine. Model was utilized by an orthopedic surgeon to mold a fixation plate preoperatively. b) Proximal femur and acetabulum of a patient with Perthes. Size of osseous spurs was better appreciated on the 3D model and changed the surgical approach.

print layers rendering a smoother model. Additionally, when a complex or large anatomic structure is printed in multiple sections, the application of acetone allows the pieces to be fused together into a seemingly singular model. ABS requires a heated bed for adherence, therefore not all printers can accommodate this filament.

Polylactic acid (PLA) shares many attributes with ABS including durability and low cost. PLA is a thermoplastic like ABS, however it is made from renewable sources such as corn starch, tapioca root, and sugarcane. While slightly weaker and less flexible than ABS, PLA can be utilized by a greater number of printers due to its lower melting point and lack of requirement of a heated bed for adhesion. PLA does expand when heated so clogging of the nozzle may be more frequent than encountered with ABS. Fusing multiple printed parts is also more difficult with PLA, which is less soluble in acetone, often requiring glues to adhere models.

Depending on the specifications of the FDM printer, other materials such as nylon or thermoplastic elastomers (TPE) may also be options. Nylon filament has more flexibility than ABS and PLA, however is more prone to warpage and will absorb water if not properly stored. This material is more difficult to print than conventional filaments but can produce structurally solid yet pliable models useful in the construction of orthotics or braces. TPE is a soft rubbery material with exceptional elastic properties. Additionally, TPE has good layer-to-layer adhesion, resulting in durable models. For the purposes of medical printing, TPE provides a material which can be easily be deformed, cut, or fixed with screws and hardware by a referring physician. The profound layer-to-layer adherence precludes using TPE as the support material for a TPE model as the supports cannot be easily removed from the primary structure. A dual-head printer capable of extruding TPE from the primary nozzle and a dissolvable support material such as high impact polystyrene (HIPS) from a secondary nozzle will allow for constructing models in this unique filament.

3D Printing in Healthcare

The potential of 3D printers in healthcare is vast. Models can be printed for teaching and educational purposes, as diagnostic aids, for treatment planning, or for therapeutic means. Computer aided tomography (CT) scans provide high resolution images ideal for the construction of 3D models. The high contrast of bone to soft tissue along with the ease and availability of submillimeter reformats make ENT, craniofacial, and orthopedic applications ideal for FDM printing. Individual bones can be segmented and modeled (Figure 3) from a standard CT with thin section reconstructions ($<$1 mm). Organ and soft tissue prints from CT data or models constructed from MRI exams are possible, but require a greater amount of preprocessing.

As teaching and educational models, 3D prints convey a wealth of information which may be difficult to express in a standard anatomic drawing or a two-

dimensional image such as a radiograph or CT/MRI slice. Complex anatomy can be shown to patients and their families by the referring physicians in a very tangible means which is less abstract to nonmedically trained individuals then conventional imaging studies. Elements of often intricate disease processes, surgical options, and expected outcomes can be discussed in a manner more approachable to patients and their family members.[1]

For medical students and residents, models can serve as valuable teaching aids. Models of normal anatomy can be utilized early in medical education similar to conventional skeletons in the anatomy lab and library. The relatively low cost of 3D printed models compared to commercially available models make them a viable option for budget conscious departments. For example, a model of a full pelvis which might cost hundreds of dollars from a third-party seller can be printed for twenty to thirty dollars with a conventional FDM style printer. As students and residents progress in their training, 3D printed models of anatomy which varies from the norm or is deformed or altered by pathologic processes can be incorporated.[2] Commercial availability of models such as these is limited and specific models can be tailored to fit the instructor's and student's needs. Likewise, patients who have been followed with serial exams offer an important means for trainees to study disease progression over time. Residents in surgical programs can benefit from studying models pre and post treatment and can even learn specific surgical techniques practicing on a model first.

Attending physicians may use 3D models as diagnostic aids and for treatment planning. Careful examination of a 3D model may yield clinical insight not as easily achieved with conventional imaging methods (Figure 4). Surgical specialist are particularly tactile individuals who are adept at diagnosing and planning treatment based on hands-on information.[3,4] A 3D model supplements the physical exam, allowing the physician to manipulate internal anatomy, evaluating pathology in a method not achievable with computer-based imaging.[5] Models can also be used to preplan surgical techniques.[6,7] Multiple surgical approaches can be tested prior to going into the operative room. Hardware can also be measured and custom contoured to an individual patient's anatomy, saving valuable OR and anesthesia time.[8] Models can be placed in a sterile



Figure 5. Two models printed for research purposes. The model on the left is a metacarpal used to evaluate different pinning techniques for fracture fixation. On the right is a pediatric trachea phantom used to study foreign body obstruction with tomography.



Figure 6. A custom ankle foot orthotic printed in nylon/thermoplastic elastomer. Orthotic was tailored to the patient's foot and lower leg length, width, and circumference. The use of nylon/TPE provides stability and durability while retaining some degree of flexibility.

bag and taken into the operative room for continued reference during complex surgical procedures, often allowing the surgeon to refer to anatomic structures or regions not easily visualized from conventional surgical approaches.

In addition to treatment planning, 3D printers offer a new tool to supplement research endeavors. Models can be constructed to evaluate new surgical approaches or validate existing techniques. Research projects which are not feasible with living subjects can be simulated with identical 3D models (Figure 5). Three-dimensional models can also be built for customized calibration phantoms for radiography, ultrasound, CT, or MRI usage.[9]

As a therapeutic tool, 3D printers offer a unique means to customize orthotics, prosthetics, and braces to individual patient needs.[10,11,12] While some knowledge of computer aided design software is necessary, it is possible for a physician to create a highly specific treatment option for his or her patient in a variety of sizes and materials. Orthotics and can be created quickly and inexpensively based on exact patient measurements and requirements (Figure 6). This is particularly useful in patients who are rapidly growing or in disease processes that evolve over time. In areas of the country or world which have limited access to commercial prosthetics and orthotics, a desktop 3D printer offers otherwise impractical or impossible therapeutic options.

Conclusion

Many types of 3D printers are commercially available. As this technology rapidly evolves, prices for these machines continues to decrease. Physicians and institutions interested in adding 3D models to their patient care or teaching programs can do so with limited initial investment. The expanding range of printing materials allows for virtually unlimited applications in the healthcare field. As teaching or diagnostic aids, 3D models offer a new and unique approach to traditional medicine, supplementing and enhancing existing modalities. The ease of generating durable medical goods highly customized to individual patient needs lends the opportunity to improve patient care and even provide care to patients previously underserved. While currently the construction of 3D models is not billable to Medicare/Medicaid or standard insurance companies, as the technology is adopted more frequently into standard practice this will likely change. Along with other emerging technologies such as virtual reality, 3D printing offers the potential to significantly change existing standards of teaching, diagnosis, and treatment of complex medical conditions.

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Disclosure

None reported. **MM**

Exposure to Ticks and their Pathogens in Northeast Missouri

by Deborah A. Hudman, MS

Results from these surveys indicate that exposure to ticks is common and ehrlichiosis infections are likely underdiagnosed while Rocky Mountain spotted fever and Lyme disease are likely overdiagnosed.



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Abstract

While the prevalence of human pathogens has been quantified in ticks in Adair County, Missouri, the prevalence of residents acquiring tick-borne diseases and seeking medical treatment has not. A public survey (n=109) revealed that 96% of respondents reported finding attached ticks on their person; of these, 38% developed symptoms post tick bite; of these, 55% reported consultation with a health care provider. Overall, 89% of practitioners surveyed had treated at least one patient for tick-borne disease. Rocky Mountain spotted fever and Lyme disease were the most common illnesses diagnosed, however, the only confirmed cases reported by Missouri Department of Health and Senior Services from 2013-2017 were ehrlichiosis. Results from these surveys indicate that exposure to ticks is common and ehrlichiosis infections are likely underdiagnosed while Rocky Mountain spotted fever and Lyme disease are likely overdiagnosed.

Introduction

Land managers, farmers, and people who recreate outdoors have an increased risk of tick exposure and thus an increased risk of infection with tick-borne pathogens. Three tick species are present in Northeast Missouri: the lone star tick, *Amblyomma americanum*, (Linnaeus, 1758), American dog tick, *Dermacentor variabilis* (Say, 1821), and the blacklegged tick, *Ixodes scapularis* (Say, 1821). The lone star tick is the most prevalent species.[1-2] Due to the abundance of this tick and its propensity to feed on humans, pathogens transmitted by lone star ticks pose an important threat to human health. Lone star ticks transmit the etiological agents which cause ehrlichiosis, Heartland virus, Southern tick-associated rash illness (STARI), tularemia, and their bites have been associated with Alpha-gal allergy or mammalian meat allergy.[3-5] In addition, there is some evidence that lone star ticks may have a role in spotted fever group (SFG) rickettsiae like diseases.[6-8] In Adair County, 436 adult lone star ticks demonstrated infection rates of 6% for *Borrelia lonestari*, 19% for *Ehrlichia chaffeensis*, 3% for *Ehrlichia ewingii*, 36% for *Rickettsia amblyommatis*, and 1% for *Rickettsia montanensis*.[9] Briefly, *B. lonestari* and *R. amblyommatis* have been implicated, but not definitively proven, as putative agents of STARI which is a Lyme disease-like illness.[10-11] E*hrlichia chaffeensis* and *E. ewingii* are the causative agents of ehrlichiosis which ranges from influenza-like symptoms in its mildest form to an occasionally fatal course. Both *R. amblyommatis* and *R. montanensis* have been implicated in the SFG rickettsiae like diseases.[6-8]

Mapping the public health threat of tick-borne diseases (TBDs) requires quantification of not only the density of infected host-seeking ticks but also the rate of human exposure to these ticks. The purpose of this study was to

Table 1. Residents of Northeast Missouri self-report annual exposure to and average number of ticks removed from persons

	Have seen a tick on their person	Have had an attached tick to their person		Average number of ticks removed per year from their person
Response	(n=109)	(n=109)	Response	(n=105)
			1-5	63 (60%)
Yes	106 (97%)	105 (96%)	6-10	24 (23%)
No	3 (3%)	4 (4%)	11-25	8 (8%)
Not Sure	0	0	26-100	10 (9%)

Table 2. Residents in Northeast, Missouri who self-report symptoms post tick bite, visited healthcare, and were treated for those symptoms

	Rash	(n=22)	(n=8)	flu-like symptoms	(n=6)	(n=4)	Both rash and flu	(n=12)	(n=10)
Response	(n=104)	visited healthcare	received treatment	(n=104)	visited healthcare	received treatment	(n=104)	visited healthcare	received treatment
Yes	22 (21%)	8 (36%)	4 (50%)	6 (6%)	4 (67%)	2 (50%)	12 (12%)	10 (83%)	7 (70%)
No	77 (74%)	14 (64%)	3 (38%)	86 (83%)	2 (33%)	2 (50%)	92 (88%)	2 (17%)	2 (20%)
Not sure	5 (5%)	0	1 (12%)	12 (11%)	0	0	0	0	1 (10%)

collect data on: a) the frequency of tick encounters in people who work outdoors in Adair County; b) the frequency of treatment of TBDs in clinics within Adair County; and c) the reported numbers of TBDs for Adair County by the Missouri Department of Health & Senior Services. It is known that many TBDs are widely underreported in the United States.[12-13] This study was designed to identify if people are actively seeking treatment for TBDs, if TBDs are being diagnosed in medical clinics, and provide a more accurate assessment and better understanding of the prevalence of these diseases in a highly endemic county.



Figure 1. *Amblyomma americanum* female tick (left) and male tick (right)
Photo credit: Kelly Rogers, ATSU photographer

Materials and Methods

Public Survey

Public exposure to ticks and the potential to acquire TBDs was assessed by a nine question survey. The survey was distributed to employees of the Missouri Department of Conservation and USDA National Resource Conservation Service who routinely work outside. In addition, surveys were distributed to people who attended the Agricultural fair that occurred in Adair County (February 3rd, 2018) to include the local farmers. A total of 109 responses were obtained. Areas covered by the survey included: experiences with ticks; concerns about contracting TBDs; visits made to health care professionals due to tick bites. It was calculated that for a population of 20,000, a confidence level of 95%, and with 109 responses that the margin of error is 9.40%. No personal data were collected and so the ATSU IRB committee found this study to be exempt under Section 45CFR46.101(b)(2).

Clinician Survey

Four separate primary care clinics with approximately 25 health care providers in Adair County were contacted to fill out a six-question survey to determine how often they see patients with suspected TBDs, types of TBDs treated, if any, and if a blood sample is routinely sent off to screen for TBDs. A total of 9 responses were collected for a 36% response rate. No personal or medical data was collected and so the ATSU institutional review board (IRB) found this study to be exempt under Section 45CFR46.101(b)(2).

Database Query

The past five years of tick-borne reported diseases for Adair County, Missouri 2013-2017 were obtained from the

Missouri Department of Health and Senior Services (DHSS), Bureau of Reportable Disease Informatics, Missouri Health Surveillance Information System.

Results

Public Survey

Tick bites are common in Adair County; 97% of all respondents report seeing a tick on their person and 96% report finding a tick attached to their body (Table 1). On average, 60% report that they remove 1-5 attached ticks per year, 23% remove 6-10 attached ticks per year, 8% remove 11-25 attached ticks per year, and 9% remove 26-100 attached ticks per year (Table 1). Thirty-eight percent of people reported developing a rash, influenza-like symptoms, or both following a tick bite (Table 2). Of those 38% who developed symptoms after a tick bite only slightly more than half (55%) sought medical attention and of those 59% were treated for TBDs (Table 2). If an individual developed a rash from a tick bite they were not as likely to seek medical attention (36%) when compared to individuals that developed influenza-like symptoms (67%) or had both rash and influenza-like symptoms (83%) (Table 2).

Sixty-one percent of the respondents stated that they always perform tick checks after spending time outdoors, 28% stated that they performed tick checks most of the time, 10% stated they sometimes perform tick checks, and only 1% stated that they almost never perform a tick check (data not shown). When asked how concerned they were about tick bites, 48% stated they were very concerned, 47% stated not very concerned, 4% stated they were not concerned at all, and 1% did not answer the question (data not shown). The level of concern about tick bites seems directly proportional to the number of individuals who had symptoms associated with a tick bite. The individuals that were not concerned at all about tick bites never experienced any symptoms post tick bite while 27% of the not very concerned group and 44% of the very concerned group had experienced symptoms post tick bite.

Clinician Survey

Of the nine survey results, only one health care provider had not treated a patient in the past year for tick bites (Table 3). Four of the health care providers had treated eleven or more patients each for tick bites in the past year (Table 3). Five of the providers had treated for Lyme disease, six for Rocky Mountain spotted fever (RMSF), and one for ehrlichiosis in this past year (Table 3). Most providers (78%) send a blood sample to a diagnostic lab when they suspect their patient is presenting clinically with a TBD (Table 3).

Database Query

For the past five years there were a total of 6 confirmed cases of *E. chaffeensis* and one confirmed case of *E. ewingii*. In addition, there was one probable case of *E. chaffeensis*, one probable ehrlichiosis/anaplasmosis undetermined, 16 probable RMSF, and one probable tularemia case in the past five years. A grand total of 26 probable and confirmed cases of TBDs in Adair County from 2013-2017 was reported (Table 4). Probable and confirmed cases are each characterized by clinically compatible illness. A probable case may have laboratory results that are consistent with the diagnosis but such results are not necessary. Confirmed cases have a fourfold or greater increase in antibody titer, polymerase chain reaction assay, or pathogen isolation in cellular culture.

Discussion

It has been indicated that a low human population density, a high white-tailed deer density, and greater proportions of deciduous forest cover were all positively correlated with elevated incidence of ehrlichiosis in the state of Missouri.[14] Adair County, which is located in Northeast Missouri, had a population of 25,607 (45 persons/mi^2) as of the 2010 census.[15] The white-tailed deer density is 18/mi^2 and 28% of the county is forested.[16] With an abundance of lone star ticks and white-tailed deer, a 22% infection rate in adult ticks with the pathogens that cause ehrlichiosis, and a rural population that includes 822 farms, it seems likely that ehrlichiosis would be a common diagnosis.[17] However, from the past five years (2013-2017) there have only been seven confirmed cases of ehrlichiosis (DHSS). This data implies that ehrlichiosis may be asymptomatic, underreported, or being misdiagnosed.

Ehrlichiosis presents clinically most often as fever, chills, headache, malaise, myalgia, and nausea, and fewer than 30% of adult patients present with a rash.[18] With 38% of all respondents developing symptoms post tick bite, whatever the TBDs may be, they are not asymptomatic. In addition, six percent of the respondents developed influenza-like symptoms with no concurrent rash and 12% developed a rash with influenza-like symptoms, which both would be symptomatically consistent with ehrlichiosis and thus make them probable cases.

Another possible explanation for the lower-than-expected number of reported ehrlichiosis cases is that 45% of those individuals that present symptoms post tick bite are not seeking medical attention, thus accounting for large numbers of unreported infections. As the infection tends to manifest as a generalized influenza-like illness, infected individuals may be less likely to visit a doctor unless more severe symptoms emerge. However, 78% of all respondents

Table 3. Estimates, by health care professionals, of number of patients treated for tick-borne diseases in the past year in Adair County, Missouri

# of patients		# of diseases treated		# of blood samples screened for tick-borne diseases	
Response	(n=9)	Response		Response	
None	1 (11%)	Lyme Disease	5	Never	0
1-5	3 (34%)	RMSF	6	Every time I suspect a tick-borne disease	7
6-10	1 (11%)	Ehrlichiosis	1	Only when the patient has insurance to cover the costs	2
11-25	2 (22%)	Tularemia	0	Only when the patient requests it	0
26-100	2 (22%)	STARI	0	Only when I am confident it is a tick-borne disease	3
		None of these	1		

did seek medical attention if they presented with influenza-like symptoms, which they self-reported was associated with a tick bite. Data from this study implies that ehrlichiosis is not asymptomatic, but it is likely under-recognized.

Misdiagnosis is another factor that may explain the lower-than-expected probable or confirmed cases of ehrlichiosis. In Adair County, in the past year alone, 9 clinicians reported that they treated 12 patients for TBDs, but only one was treated for ehrlichiosis while RMSF was diagnosed six times. The majority of health care providers (78%) stated that when they suspect their patient is presenting with a TBD, they send a blood sample to be screened under a "tick panel". In general, these tick panels test for RMSF IgG and IgM, ehrlichiosis, Lyme disease, and Tularemia antibodies. If a sample returns to the clinic as a positive for RMSF then RMSF will be the final diagnosis. Sixty-seven percent of the doctors surveyed stated that they never obtain a second blood sample from the patient to confirm the diagnosis unless the patient is still ill and 22% stated they never obtain a second blood sample. As a result, these RMSF cases are not confirmed because they cannot demonstrate a fourfold titer increase and may well represent false positive diagnoses because of the high background seropositivity for RMSF. It has been demonstrated that SFG rickettsiae like diseases with titers as high as 256 are not uncommon in children due to previous infections from tick bites which certainly meets the case definition for probable RMSF.[19] DHSS did not report one confirmed case of RMSF in the past five years even though it is the most prevalent TBD reported by local health care professionals.

Rickettsia ricketsii, the etiological agent of RMSF, was not detected in any of the 309 *D. variabilis* (American dog) ticks sampled in Adair County over two consecutive years.[2,9] The absence of *R. rickettsii* detection in American dog ticks and lone star ticks which were screened with polymerase chain reaction is suggestive that RMSF is being misdiagnosed. It has been suggested that the cross-reactivity of antibodies of other SFG rickettsiae, such as *R. amblyommatis*, may explain these positive results from tick panels when *R. ricketsii* appears to not be prevalent in the tick population.[20] In the 436 individual adult lone star ticks tested in 2015, *R. amblyommatis* demonstrated an infection rate of 36% and in the 189 individual American dog ticks screened four percent were infected.[9] This data may support the notion that *R. amblyommatis* is associated with clinical illness or in the very least masking the results of an ehrlichiosis infection.[21]

In this study, 12 cases of TBDs were diagnosed by health care providers in Adair County during 2017. That is nearly half of what DHSS reports in the county for the past five years. It would be unreasonable to speculate as to why four clinics would be reporting higher numbers of TBDs than DHSS as these findings are subject to several limitations. For example, all data collected were self-reported, potentially subject to recall bias, and not independently validated. Further, some of the survey questions to which clinicians and the public responded are subject to variable interpretation, and there is no way to confirm that all the patients seen in the clinics or all individuals who completed a survey reside in Adair County. The reports from DHSS, however, have been confirmed to be Adair County residents and this may explain, to some degree, why DHSS reports lower numbers than the clinics who may be attending to patients from surrounding counties.

It is important to note that five of those 12 TBDs were diagnosed as Lyme disease. To date, there is still great uncertainty regarding the occurrence of Lyme disease in Missouri. *Borrelia burgdorferi sensu lato* (s.l.) was first reported to be isolated and cultivated from Missouri in 1995 from ticks that had been feeding on cottontail rabbits (*Sylvilagus floridanus*).[22] However *Borrelia burgdorferi sensu stricto* (s.s.), the cause of Lyme disease, has not been reported in Missouri ticks.

Table 4. Tick-borne reported diseases and conditions, Adair County, Missouri 2013-2017, Missouri Department of Health and Senior Services. Numbers reflect reported cases that meet the Centers for Disease Control and Prevention's definition of a probable or confirmed case.

Condition	2013		2014		2015		2016		2017	
	Confirmed	Probable	Confirmed	Probable	Confirmed	Probable	Confirmed	Probable	Confirmed	Probable
Ehrlichia chaffeensis	2	0	1	0	0	0	2	1	1	0
Ehrlichia ewingii	0	0	0	0	1	0	0	0	0	0
Ehrlichiosis/ Anaplasmosis undetermined	0	0	0	1	0	0	0	0	0	0
Rocky Mountain Spotted Fever	0	2	0	4	0	3	0	2	0	5
Tularemia	0	0	0	0	0	1	0	0	0	0

Nor has *B. burgdorferi* (s.l.) yet been isolated from any patient in Missouri showing symptoms consistent with Lyme disease.[23] Data obtained here suggests that Lyme disease is continuing to be over-diagnosed in Missouri.

From 2008-2012 Missouri had the second highest reported incidence rate of *E. chaffeensis,* and was tied for the highest incidence rate of *E. ewingii*.[24] Given the preponderance of lone star ticks, its aggressive predilection for biting humans, clinicians in this region should maintain ehrlichiosis high in the differential diagnosis for tick-borne disease. In nearly 30,000 ticks examined for human pathogens in Adair County, *R. rickettsii* was never once detected, while *E. chaffeensis* and *E. ehrlichia* are very prevalent in the tick populations. In addition, the only confirmed cases for the past five years in Adair County have been for ehrlichiosis. This data implies that infections with *E. chaffeensis* and *E. ewingii* are under-recognized, at least in Adair County, if not throughout a larger portion of Missouri.

This information serves to contribute to a more accurate picture of the overall burden of TBDs in Adair County and highlights the need for better understanding in our community about what diseases are present, in particular ehrlichiosis, how those diseases present clinically, and when people should seek treatment if at all possible.

Acknowledgments

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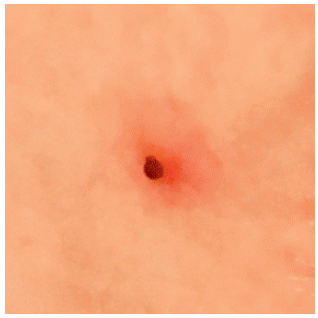
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EDITOR'S NOTE

Buying Some Piece of Mind if You Get 'Ticked-off'

by John C. Hagan, III, MD, Editor

Few things creep me out anymore. But finding a tick embedded in my dermis sets off all kinds of alarm bells. My wife is a master-gardener and our home sits on over a quarter acre lot that she has lovingly and skillfully turned into a show garden. I have no botanical talents but do qualify as unskilled manual laborer. I am enthusiastic and have passable skills in weeding, mowing, spraying, clipping, and raking. I'm always careful to check for ticks after a session of yard work.



Lone Star Tick embedded four days.

After an especially long and dirty session of winter clean-up in May of this year, I noted itching and irritation under my left lateral malleolus an area I could not visualize. Over a couple of days, this got much worse and I asked another person, who prefers to remain nameless, to look at this area and was told there was a small scab and some redness. After four days I could not wear my left shoe comfortably. I used my iPhone to photograph the area. I perceived the 'scab" to be an embedded tick feasting on my O positive blood (see photo). I did some deft surgery using a mirror and jeweler's forceps and removed the tick in one piece.

Since the tick had been embedded for over 100 hours, I was quite concerned about contracting a tick-borne illness. The examined tick had a partial blood meal but was difficult to identify. So, I emailed Deborah A. Hudman, MS, who authored the adjacent article. This is her second manuscript on diseases vectored by Missouri ticks. I also emailed Eden M. Esguerra, MD, our *Missouri Medicine* Infectious Disease specialist. After this conference of experts, I began doxycycline twice/daily and sent the entire tick to TickReport (www.tickreport.com) for identification and DNA/RNA pathogen testing.

TickReport is a commercial service of the University of Massachusetts' Laboratory of Medical Zoology. For a fee ranging from a low of $40 to a high of $200 within 72 hours they will: identify tick species and life stage, feeding status, send high resolution photomicrographs, and a report on up to 23 DNA and RNA tests for pathogens. Not being one to scrimp on peace of mind, I parted with $200, not covered by insurance, to hopefully have 23 'happy news' tests in three days. As promised within that time frame, I was emailed a very detailed report finding all 23 DNA/RNA tests were negative for pathogens, and a very detailed microphotograph of my lately deceased nemesis. It was a 'partially fed, nymph stage Lone Star Tick.' With this report in hand, I stopped the antibiotics after four days and felt much relieved. Two weeks later, after another extended garden session in 90-degree weather, I noted a rash on my stomach and legs. Being a physician, and always quick to accept the worst possible outcome, without the TickReport testing I'm sure I would have concluded I had a tick-borne disease. With it I was able to surmise it was a heat rash with some contact dermatitis to the brand-new tick-repellant clothing I was wearing for the first (and last) time.

For physicians' practices or if you personally become a tick entrée this TickReport service is something to be aware of and consider. **MM**

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Disclosure

None reported. **MM**

Sleep Medicine: Single Series

Sleep Medicine: Restless Legs Syndrome

by Pradeep C. Bollu, MD, Anudeep Yelam, MD & Mahesh M. Thakkar, PhD

Restless legs syndrome is one of the most common movement disorders characterized by an irresistible, often uncomfortable, urge to move the legs.



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Abstract

Restless Legs Syndrome is a highly prevalent sensorimotor disorder characterized by urge to move the legs due to discomfort that primarily happens in the evening or at nights. Although the exact pathophysiology remains unclear, brain iron deficiency and altered dopaminergic function appears to play an important role in the pathogenesis of this condition. This disorder affects women more frequently and is associated with significant morbidity.

Introduction

Restless legs syndrome/Willis Ekbom disease (RLS/WED) is a complex sensorimotor disorder with a high degree of clinical variability. This disease is associated with an uncontrollable urge to move due to painful and uncomfortable sensations in the legs. Rarely, the symptoms can be experienced in the arms and in the trunk. RLS is very commonly associated with periodic limb movements in sleep. The principal abnormality in RLS appears to be dopamine deficiency and brain iron dysregulation. In the last few years, multiple candidate genes have been discovered that increase the risk of RLS. Secondary causes of RLS should always be excluded when evaluating patients with symptoms of RLS. Dopaminergic therapies are the mainstay treatment for RLS though their prolonged use is associated with augmentation. This article provides a clinically useful overview of the disease, pathophysiology, the differential diagnoses and treatment strategies.

History of the disease

The disease was first described by the English physician Sir Thomas Willis in 1672 where he emphasized that people with RLS experience sleep disruption and limb movements. The term 'fidgets in the legs' has also been used as early as the early nineteenth century. Wittmaack, a German neurologist labelled it 'anxietas tibiarum' which was also used by Beard, Bing and Oppenheim in their writings. They considered this a form of hysteria or a sign of neurosis[1]. Almost three centuries after its initial description by Willis, a Swedish neurologist, Karl-Axel Ekbom coined the term "Restless Legs" and provided a comprehensive report of this condition in his doctoral thesis, *Restless legs: Clinical study of hitherto overlooked disease*[2]. Ekbom based his thesis on 34 personal observations and favored vascular cause and even recommended vasodilators as prime therapy[1]. He observed that the disease has proclivity to affect women and described the familial tendency seen in some cases. Ekbom's work was largely ignored until it was rediscovered by Arthur S. Walters and Wayne A. Hening in the 1980s. Periodic limb movements in sleep (PLMS) were first recognized by Symonds in 1953 and were recorded on a polysomnogram by Lugaresi et

al. in 1965. This polysomnographic documentation of PLMS was a crucial step in supporting the organic nature of RLS. The first RLS diagnostic criteria were established in 1995 and revised in 2003. In 2013, the Restless Legs Syndrome foundation renamed itself the 'Willis-Ekbom Disease Foundation' and encouraged the use of the name Willis Ekbom disease.

Epidemiology

Once thought to be a rare disorder, RLS is now considered a common condition, with considerable clinical variability. The prevalence of RLS varies between different regions. Over 50 population-based prevalence studies have shown that RLS affects approximately 5-10% of European and North American adults with about 2-3% experiencing moderate to severe symptoms. However, they indicate a lower prevalence of the disease in Africa and Asia and among Hispanics. The overall pediatric prevalence is 2-4% in the United States. Based on a population-based survey, the prevalence of RLS was 3% between ages 18 and 29, 10% between ages 30 and 79 and 19% in people older than 80 years of age. The mean age of onset is during the third or the fourth decade[3].

Clinical Features of Restless Legs syndrome

The core feature of this disorder is uncomfortable and irresistible need or urge to move the legs with accompanying unpleasant and sometimes, painful sensation in the legs. These symptoms may extend beyond the legs and involve arms or the trunk. Rest typically brings on the symptoms while movement relieves them. In children, these symptoms are frequently misdiagnosed as growing pains. Early onset RLS (<45 years at onset) usually starts with intermittent symptoms and progresses slowly. Late onset RLS is usually stable at onset or rapidly progresses over five years to a stable pattern. The symptoms in RLS can be unilateral or bilateral. Up to half the people with RLS complain about restlessness in the arms as well. Typically, this happens as the disease worsens in severity. RLS is typically associated with semi rhythmic leg movements during sleep that are referred to as 'Periodic Limb Movements in Sleep' (PLMS). These symptoms of RLS can profoundly affect sleep resulting in insomnia, daytime fatigue, reduced concentration and mood problems (Figure 1).

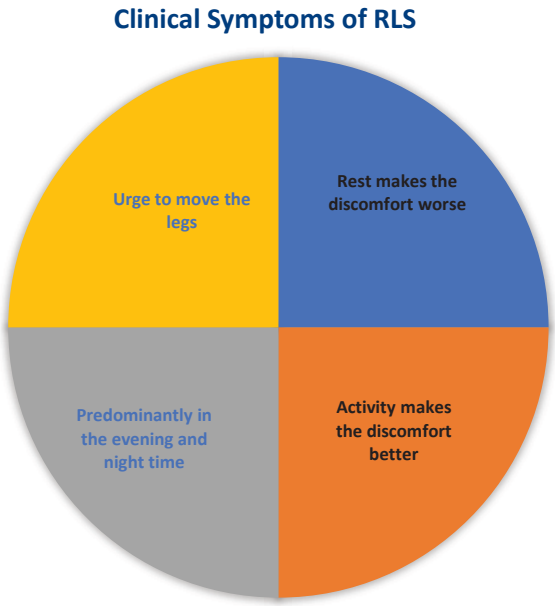


Figure 1. Core Clinical symptoms of Restless legs syndrome

Pathophysiology of RLS

Ekbom, in 1945 postulated that microvascular alterations in the leg might be the cause the symptoms of RLS. He proposed chronic venous insufficiency as a potential mechanism in his original disease description. However, with the advent of dopaminergic drugs, the research focus shifted towards analyzing the regulation of brain dopamine. Based on the current research, we discuss the pathophysiological mechanisms that might be operating in the pathogenesis of the disease.

Iron Dysregulation

Clinically, iron deficiency is based on the bone marrow iron concentration with hemoglobin and other serum measures developed to correlate with bone marrow iron levels. Iron homeostasis is organ specific. In the brain, the iron homeostasis is regionally regulated, based on the local cellular energy demand and its accessibility from the blood brain barrier. Low brain iron, despite having normal levels of peripheral iron is the best-established neurobiological abnormality in RLS. Cerebrospinal fluid (CSF) ferritin is lower in patients with RLS than controls. Multiple studies have shown that lower ferritin is associated with increased severity of the disease. Two studies found a reduction in CSF ferritin, along with an increase in transferrin, in RLS patients

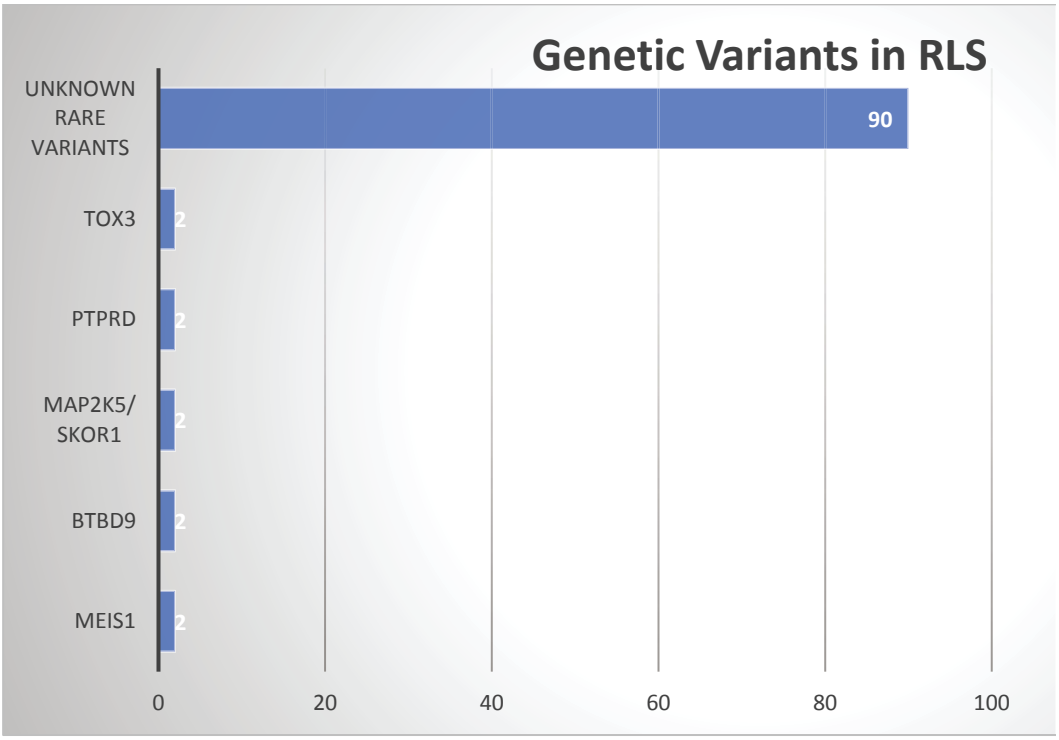


Figure 2: Genes implicated in RLS pathogenesis. The most common genetic variants account for only 10% while 90% are rare or unknown.

even though the serum ferritin and transferrin levels did not differ significantly from healthy controls. Diet induced brain iron deficiency in rodents represents a well-accepted pathophysiological model of RLS.

Dopaminergic Dysfunction

Dopaminergic dysfunction has been thought to be strongly associated with RLS since the symptoms of RLS respond well to dopaminergic medications. Similarly, dopamine antagonists worsen RLS symptoms. Brains of RLS patients show an increased dopamine production along with increased dopaminergic activity. However, there is a reduction in the dopamine D2 receptors and dopamine transporters in the striatum suggesting inadequate dopaminergic stimulation.

Role of Glutamate and Adenosine

When the brain iron is experimentally reduced, an increase in glutaminergic activity can be seen. Based on an MR spectroscopic study, a similar increase in glutaminergic activity has been noted in RLS patients. Drugs that decrease glutaminergic activity like NMDA receptor antagonists and $\alpha 2\delta$ ligands reduce the sensory symptoms of RLS.

Adenosine Hypothesis

Recent studies have shown that brain iron deficiency in rodents is associated with a hypoadenosinergic state with downregulation of adenosine A1 receptors in the striatum and cortex[4]. This hypo-adenosinergic state may provide a mechanism to explain PLMS secondary to hypersensitivity of cortico-striate terminals[5]. Similarly, the hyperarousal in RLS may also be due to the downregulation of the A1 receptors in the cortex, basal forebrain or hypothalamus[4,6].

Genetics of RLS

RLS is a classical complex genetic disorder in which common and rare genetic variants contribute to the phenotype. A population based survey in Canada reported concordance rates of RLS to be 54% in monozygotic twins and 19% in dizygotic twins demonstrating a substantial genetic contribution in RLS[7]. Genome Wide Association Studies (GWAS) made it easier to identify genetic variants associated

with increased risk of RLS. For RLS, GWAS performed between 2007 and 2011, resulted in the identification of common risk variants in six genomic regions. MEIS1 locus is by far the strongest risk factor for RLS with an odds ratio around 2.7[8-10]. In cases of Periodic limb movements in RLS, variants in BTBD9 and MEIS1 are associated with a higher risk. The currently known risk variants still account for only a small proportion of the genetic component of RLS. Most of the genetic risk is contributed by rare variants, which need to be clearly characterized.

Neuropathology of RLS

Autopsy studies show that RLS is not associated with neurodegeneration, gliosis, or formation of pathological entities like plaques and inclusions in the brain or spinal cord. RLS brains show a decreased staining for iron with a robust immunostaining of dopaminergic neurons for tyrosine hydroxylase. Quantitative analysis actually reveals a higher concentration of tyrosine hydroxylase in the substantia nigra[11]. While iron deficient cells elsewhere typically show increased expression of transferrin receptors, the neuromelanin cells in RLS are deficient in transferrin receptors. There is also decreased staining for ferritin in the neuromelanin cells and an increase in transferrin immunostaining[12]. A T-cell protein called Thy-1 that is expressed on neuronal cell membranes is also deficient in RLS brains. This protein is thought to be associated with adherence of the pre- and postsynaptic membranes and promotion of the attachment of vesicles to the presynaptic membrane[13].

Pediatric RLS

RLS is first described in the pediatric literature in 1994. It has been estimated that more than 1 million children in the US are affected by RLS with a prevalence of 2-4%. The symptoms of RLS in children can be nonspecific that include insomnia, sleepiness during the day, restless sleep, growing pains etc. Family history of RLS is very commonly seen in pediatric RLS and is commonly associated with pediatric limb movements in sleep. However, due to the non-specific nature of the symptoms and due to the kids' difficulty in describing the symptoms, the disease is often overlooked, and the diagnosis is delayed. A study found that the time between onset of clinical sleep disturbances and the diagnosis of definite RLS is around 11.6 years[14].

RLS in Pregnancy

The overall prevalence of RLS in pregnant women is as high as 21%. This is 10-fold higher than in general population. The prevalence of RLS increases with each trimester. RLS in pregnancy is associated with a lower quality of life and can increase the risk of complications including hypertension, cardiovascular disease and preeclampsia. Some studies suggest that RLS can negatively affect the neonatal outcomes. Women with RLS often report depressive symptoms, increased daytime sleepiness and insomnia[15].Multiple factors including iron deficiency, hormonal changes and ethnic differences probably contribute to RLS in pregnancy.

RLS and Other Disease Associations

RLS is a complex, heterogeneous disorder with genetic and environmental contribute to its phenotype. Systematic reviews of the association between RLS and other disorders suggest that RLS is highly prevalent in iron deficiency and in renal disorders while there is also some association between RLS and other disorders. Other conditions most consistently associated with RLS in epidemiological studies are major depressive disorder, generalized anxiety disorder, panic disorder, attention-deficit hyperactivity disorder. Below, we briefly discuss the association of RLS with a few select disorders.

RLS and Attention Deficit Hyperactivity Disorder

Evidence from the clinical studies demonstrates an association between RLS and Attention Deficit Hyperactivity Disorder (ADHD). The degree of association between these two conditions differ from one study to the other[16]. The RLS symptoms are usually underdiagnosed in children[17] and both these conditions might share a common dopamine dysfunction.

RLS and Renal disease

RLS is one of the most troublesome conditions experienced by end-stage renal disease patients treated with hemodialysis. The recorded prevalence of RLS in renal disease ranges from 15% to 68%[18]. Nearly all the studies investigating RLS in renal disease patients employed an observational, cross-sectional design, evaluating dialysis patients for symptoms of RLS. Factors

Table 1. Differential diagnoses of RLS. The diagnosis of Idiopathic RLS should be when the symptoms are not explained by other etiologies.

- Nocturnal Sleep related Leg Cramps
- Peripheral Neuropathy
- Habitual/ Anxious foot tapping
- Myalgias
- Painful leg/ feet and moving toes
- Neuroleptic induced akathisia

	Initial Dose	Maximum recommended dose	Half-lives
Pramipexole	**0.125mg/day**	**0.75mg/day**	**8-12 h**
Ropinirole	**0.25mg/day**	**4mg/day**	**6h**
Rotigotine	**1mg/day**	**3mg/day**	**24hr transdermal system**

Table 2. Dopamine agonists used in the treatment of RLS.

	Starting dose <65 yrs	Starting dose >65 yrs	Usual effective dose
Gabapentin	**300 mg**	**100mg**	**900-2400mg**
Pregabalin	**75mg**	**50mg**	**150-450mg**
Gabapentin Enacarbil	**600mg**	**300mg**	**600mg**

Table 3: α2δ ligands used in the treatment of RLS symptoms.

associated with an increased risk for RLS included increase intake of calcium antagonists, lower baseline levels of intact parathyroid hormone, duration of dialysis, lower serum transferrin saturation, type II Diabetes Mellitus, the number of associated co-morbidities, lower education levels and Caucasian ethnicity[18]. Successful renal transplant in end-stage renal failure patients can substantially improve the course of RLS[19].

RLS and Cardiac Disease

Two cross-sectional studies detected higher numbers of patients with RLS among individuals with lower coronary flow (27%) compared with those with normal coronary flow (17%). In women with duration of physician diagnosed RLS > 3 years, the Odds Ratio of non-fatal myocardial infarction and fatal cardiovascular disease (CVD) were 1.80 and 1.49 respectively[18]. However, large epidemiological cohorts assessing RLS using three well-known questionnaires could not detect any increased risk of CVD in patients with RLS. Using interviews for diagnosis of RLS, the Wisconsin Sleep cohort found an association between RLS and CVD[20]. Similarly, a significantly increased risk of cardiovascular disease (22.7%) was reported in Taiwanese patients assessed by validated phone interviews[18].

RLS and Other Neurological Diseases

In migraine patients, the prevalence of RLS as a comorbid disorder ranges from 8.7% to 39%[21]. Studies investigating the risk of stroke in RLS patients did not find any higher incidence of stroke in RLS patients. However, poststroke patients may develop an

	Augmentation	End of the dose Rebound	Tolerance	Natural Progression of the disease	Exacerbating factors
Worse before Rx	Yes	Yes	No	Yes	Yes
Spread to arms	Yes	No	No	Yes	Yes
Earlier Onset	Yes	Yes	No	Yes	Yes
Breakthrough at night	Yes	Yes	No	Yes	Yes
Worsening with dose escalation	Yes	No	No	No	No
Improvement with dose reduction	Yes	No	No	No	No

Table 4. Comparison between Augmentation, end of the dose rebound of RLS symptoms, Tolerance to treatments, Natural progression of the disease and symptom profile in the setting of exacerbating factors.

increased prevalence of RLS, which might be related to cardiovascular risk factors. Patients with *de novo*, untreated Parkinson disease (PD) did not differ from controls in terms of RLS prevalence. However, RLS prevalence in PD patients who are treated is higher than expected. Majority of the studies report an increased prevalence of RLS in patients with polyneuropathy[22]. Several studies reported a higher frequency of RLS in patients with MS with the reported frequencies varying from 13.3% to 65.1%[23].

Diagnosis and Differential Diagnosis of RLS

The diagnosis of RLS is clinical. There is no conclusive diagnostic test. It is important for the clinician to identify any secondary cause for the symptoms of RLS. A polysomnogram is not required in the diagnosis though the presence of periodic limb movements during the sleep study would strongly suggest the existence of RLS. A positive family history of RLS supports the diagnosis (Table 1).

Laboratory testing should screen for iron deficiency and renal/ hepatic dysfunction. Routine imaging studies in idiopathic RLS are normal and are not indicated. However, most of the MRI studies using iron-sensitive sequences suggest a state of reduced brain iron content in RLS patients. PET and SPECT studies consistently support dysfunction of dopaminergic pathways involving both nigrostriatal and mesolimbic pathways[24].

Treatment of Restless Legs Syndrome

Dopaminergic medications have been the mainstay treatment of Willis-Ekbom disease. Prior to the advent of L-dopa and dopamine agonists, benzodiazepines were the treatment of RLS symptoms for a long time. Some cases were tried on baclofen and antiepileptic drugs (gabapentin, carbamazepine, valproic acid) with some success[1]. In the United States, three dopamine receptor agonists (DAs) have been approved based on numerous large placebo controlled studies that showed therapeutic efficacy with relatively minor side effects[25]. Table 2 shows the various DAs used in the treatment of RLS symptoms along with the initial starting doses and the maximum recommended doses. Levodopa should be avoided due to its high incidence of Augmentation.

Along with DAs, $\alpha 2\delta$ ligands also are used in the treatment of RLS. They can be used along with DAs or alone. They can be especially helpful in patients with RLS who also have peripheral neuropathy as Gabapentin

and Pregabalin help with the positive symptoms of symptomatic neuropathy. Table 3 shows the α2δ ligands used in the treatment of RLS along with the recommended starting doses.

In pregnant women, non-pharmacological options like exercise, yoga, pneumatic compression devices are the first line of therapy. Co-existing sleep disorder and other aggravating factors should also be addressed. Pharmacological options in pregnancy include iron therapy, clonazepam, gabapentin and Levodopa. DAs are to be avoided in pregnant women.

Perampanel acts as a non-competitive selective antagonist at the postsynaptic ionotropic AMPA glutamate receptor and was found to be effective in a two-month open-label trial in patients with idiopathic RLS[26]. Future controlled studies might open the possibility of Perampanel becoming a promising alternative to dopaminergic therapies.

Dipyridamole is a non-selective inhibitor of equilibrative nucleoside transporters ENT1 and ENT2 causing an increase in extracellular adenosine and was found to be effective in a small open label clinical trial to improve both sensory and motor symptoms of RLS along with sleep[27]. This study suggests that adenosine can also be a target for therapeutic intervention in RLS. Direct targeting of A1 receptors, however, does not seem to be a therapeutic option due to significant peripheral effects of bradycardia and hypotension.

High frequency deep brain stimulation (DBS) is frequently used to treat a variety of movement disorders including PD, essential tremor, and dystonia. The most commonly used targets for DBS are Globus Pallidus Interna (GPi), Subthalamic Nucleus and Ventro-Intermediate Nucleus of Thalamus. Improvement in the symptoms of RLS was reported in a cases of PD and dystonia[28,29] treated with DBS with GPi as the target. Few cases of refractory RLS treated with DBS, with GPi as target, showed improvement in the symptoms of RLS[30].

Non-Pharmacological Treatments for RLS

Multiple nonpharmacological treatment options exist to help with the symptoms of RLS. They include exercise, counter stimulation therapy devices (hot/cold baths, warm blankets, limb massagers, compression stockings, counter pulsation devices), near infrared light therapy and acupuncture. Each has varying levels of evidence of therapeutic benefit and can be used in conjunction with the standard treatment.

Augmentation

Augmentation is a feature of RLS patients on treatment with dopaminergic medications where the severity of the symptoms is worse than before the initiation of medication. Discontinuation of the medication results in amelioration of the symptoms. This phenomenon was first described by Allen and Earley[31] in 1996 in patients receiving levodopa/carbidopa for the treatment of RLS. In their study, about 3/4th of the patients with RLS who are on levodopa/carbidopa developed worsening of symptoms. Current evidence suggests that the prevalence of augmentation is close to 50% in patients using DA receptor agonists for approximately 10 years[32]. (Table 4).

The following strategies can help minimize the risk of augmentation in patients with RLS:

- Use dopaminergic medications intermittently if the symptoms are not present all the time.
- Start with the smallest recommended dose and avoid going beyond the recommended daily maximum dosing.
- Iron deficiency increases the risk of augmentation. Thus, as a standard of care, iron deficiency should always be examined before pharmacological treatment.
- If augmentation develops with symptoms happening earlier, the same dose of dopaminergic medication can be split.
- Consider longer acting dopamine agonist like Rotigotine.
- Consider α2δ ligand and lower the dose or discontinue DAs. Similarly, a low dose opioid medication can be used instead of DAs. Between discontinuing the DAs and initiating alternative treatment, a 10-day washout of DAs may be considered.

Conclusion

Restless legs syndrome is one of the most common movement disorders characterized by an irresistible, often uncomfortable, urge to move the legs. The symptoms have a circadian rhythmicity occurring mainly in the evening and night times. The diagnosis of this condition is purely clinical and secondary causes of restless legs syndrome should be recognized. Brain iron dysregulation underlies the pathophysiology of this condition. Although dopaminergic treatments have been the mainstay therapy of RLS, they are complicated with the occurrence of augmentation. RLS is associated with many other systemic illnesses and untreated RLS can have significant morbidity.

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Disclosure

None reported.

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