Missouri Medicine

The Journal of the Missouri State Medical Association www.msma.org/missouri-medicine May/June 2017



Washington University in St. Louis
School of Medicine

Women's Reproductive Health

Department of Obstetrics & Gynecology

Opioid Misuse & Abuse

Diabetes Management

159th Annual Convention Wrap

Give them focus.

Give to the Missouri State Medical Foundation.



Helping students focus on their medical education for over 50 years, the Missouri State Medical Foundation has benefitted thousands of medical students statewide. We thank the many donors who have committed their energy and resources to fulfilling the Foundation's mission, and we are grateful for their generosity.

For over 15 years, MSMA Scholarships have been funded by the Foundation for students at each of Missouri's medical schools.

The Foundation has also facilitated the creation of scholarship funds through a matching grant program. Our scholarship partners include:

- Boone County Medical Society
- Cole County Medical Society
- Kansas City Medical Society
- Northeast Missouri Medical Society
- Quad Counties Medical Society
- Saint Charles-Lincoln County Medical Society
- MSMA Alliance

Donations may be sent to:
Missouri State Medical Foundation | P.O. Box 1028 | Jefferson City, MO 65102
Contact Pat Mills at 800-869-6762 | Email pmills@msma.org

The Missouri State Medical Foundation is a 501(c)3 organization.

Missouri Medicine

The Journal of the Missouri State Medical Association - Since 1904

Volume 114 | Number 3 | May/June 2017 www.msma.org/missouri-medicine

GUEST EDITORIAL

Son's Death to Opioid Abuse Was "Completely Unnecessary"
by Jim Braibish & Kelly O'Leary 136



PERSPECTIVE

The ER Doctor's Role in Combating the Opioid Epidemic
by **Matthew Gratton, MD** 138

MEDICAL | LEGAL

Call Coverage Rates: What's Driving That Number?
by Wakaba Tessier, Kate Bechen & Wendy Keegan 140

PRESIDENT'S FORUM

Thankful to be a Missourian
by **Warren C. Lovinger, Jr., MD** 144

MSMA Introduces: Medical Student Mentor Program
by **Warren C. Lovinger, Jr., MD** 146



SCIENCE OF MEDICINE
WOMEN'S REPRODUCTIVE HEALTH
WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

A National Leader in Women's Reproductive Health
by **George A. Macones, MD** 155

A History of Developments to Improve *in vitro* Fertilization
by Ashley M. Eskew, MD & Emily S. Jungheim, MD 156

Identifying the Best Way to Manage Labor
by **Alison G. Cahill, MD** 160

Meeting the Contraceptive Needs of a Community: Increasing Access to Long-Acting Reversible Contraception
by Colleen McNicholas, DO & Tessa Madden, MD 163

Zika Virus Takes a Transplacental Route to Infect Fetuses: Insights from an Animal Model
by Indira U. Mysorekar, PhD 168

Apical Vaginal Support: The Often Forgotten Piece of the Puzzle
by Jerry L. Lowder, MD 171

Uterine Morcellation: Fact and Fiction Surrounding the Recent Controversy
by Brooke Winner, MD & Scott Biest, MD 176

ADDITIONAL SCIENTIFIC

Opioid Use Disorder and Pregnancy
by Frederick T. O'Donnell, MD & Daniel L. Jackson, MD 181

Comparison of Family Medicine and General Internal Medicine on Diabetes Management
by Kimberly A. Zoberi, MD, Joanne Salas, MPH, Cassie N. Morgan, MSW & Jeffrey F. Scherrer, PhD 187

Chronic Lymphocytic Leukemia and the Side Effects of Therapy: 2017 Review
by Asim Ahmad, MD & **Clint Daniel Kingsley, MD** 195

FROM YOUR ASSOCIATION

Book Review 148
Correspondence 150
Missouri Medicine In the News 153

159TH ANNUAL CONVENTION REPORTS & HIGHLIGHTS

Meet MSMA's President 200
Meet the MSMA Alliance President 201
State of MSMA - Presidential Address 202
Presidential Inaugural Address 204
50-Year Physician Pin 206
Resolutions & Actions 207
Awards 209
Sponsors & Exhibit Sponsors 210
Credentials & Appointments 210
Elections 211
Council Minutes Summary 212
Reports of the Delegate Handbook 215
Policies 222
Financial Statements: Missouri State Medical Association 222
Financial Statement: Missouri State Medical Foundation 223
Financial Statement: Missouri Physicians Health Program 223
Attendance 224

MSMA Missouri State Medical Association

113 Madison Street ◆ P.O. Box 1028 ◆ Jefferson City, MO 65102
800-869-6762 ◆ Fax: 573-636-8552 ◆ www.msma.org/MissouriMedicine
Editor: John C. Hagan, III, MD ◆ jhagan@bizkc.rr.com
Managing Editor: Lizabeth R. S. Fleenor ◆ lfleenor@msma.org

About *Missouri Medicine*

Missouri Medicine is peer-reviewed, indexed, and content is linked with PUBMED and included in MEDLINE, and EBSCO host data bases. *Missouri Medicine* is owned by the Missouri State Medical Association (MSMA), has been in publication since 1904, and has won numerous awards as best in state publication (Ranley Awards). *Missouri Medicine* provides exclusive content to MedHelp.org, a top world internet health forum with over 12 million unique visitors per month, and the MedHelp.org e-newsletter which has 300,000 subscribers. In recent years *Missouri Medicine* articles have been featured internationally: *Wall Street Journal, Outside Magazine, Runner's World, NBC news, General Surgery News, Anesthesia News*, and many more. Besides having a national presence, *Missouri Medicine* is the largest circulation health care publication in Missouri, and its catchment area includes nine medical schools. Previous issues are archived and available at www.msma.org/missouri-medicine-library.

HOW TO CONTRIBUTE TO MISSOURI MEDICINE

The Editors want to hear from you. For "Instructions for Authors/Style Sheet," download from www.msma.org/missouri-medicine.

LETTERS TO THE EDITOR OR GENERAL COMMENTS

Send an email to jhagan@bizkc.rr.com and copy lfleenor@msma.org. Letters to the editor for publication should be 300 words in length or shorter and should include your full name, specialty and association. Letters are edited for length and clarity.

IN THE NEWS

To submit yourself or a colleague for a mention, send an email to lfleenor@msma.org. Include information on the significant event, promotion or award. Note that we only include MSMA members in this column.

PERSPECTIVES & AS I SEE IT

Missouri Medicine publishes Perspectives on a variety of medical trends, topics and policy matters including legal, legislation, advocacy, insurance, practice management, and public health issues. As I See It is a forum for opinion pieces, whimsy, humor, irony, and reflection on the practice of medicine. All pieces should be referenced and not exceed 1,500 words.

SCIENTIFIC SUBMISSIONS

Scientific articles are peer-reviewed and original articles are accepted for publication on the condition that they have not been published or submitted to other medical journals. MSMA members are given publishing preference and priority. Material appearing in Missouri Medicine is protected by copyright. Authors should e-mail copies of the complete article, contact information, references, tables, illustrations, photos to both jhagan@bizkc.rr.com and lfleenor@msma.org. Notification of receipt of your manuscript is within 10 days. Peer review is completed within 30-45 days of receipt. Refer to the American Medical Association Manual of Style, 9th Ed., AMA, Chicago, 1998, for style or visit www.msma.org/missouri-medicine.

REPRINTS

Reprints of the article may be purchased. Single, entire issues may be purchased, if available. Email lfleenor@msma.org.

ADVERTISING

For reader and demographic profiles, statistics, and advertising rate sheet and contract, download from www.msma.org/missouri-medicine or email lfleenor@msma.org.

DISCLAIMER

All articles, editorials, and letters published represent the opinions of the authors and do not reflect the official policy of the MSMA or the institution with which the author is affiliated unless clearly specified.

COPYRIGHT & POSTAL ENTRY

Owned and published since 1904 by the Missouri State Medical Association. Missouri Medicine, the Journal of the Missouri State Medical Association [ISSN 0026-6620], is published bi-monthly at 113 Madison Street, Jefferson City, Missouri 65102. Periodicals postage paid at Jefferson City, Missouri and at additional mailing offices. Postmaster: Send address changes to Missouri State Medical Association, c/o Membership Dept., P.O. Box 1028, Jefferson City, MO 65102. Copyright 2017 by the Missouri State Medical Association. Printed by the Ovid Bell Press, Inc., Fulton, Missouri. The subscription price per year for non-members is $75.00. Annual subscription for members is included in the annual membership dues. Single copies are $12.00, if available.

Missouri Medicine Editorial Board

OWNER & PUBLISHER

Missouri State Medical Association

MISSOURI MEDICINE EDITOR*

John C. Hagan, III, MD
9401 North Oak Trafficway, Ste. 200
Kansas City, MO 64155
Tel: 816-478-1230 / Fax: 816-454-8478
jhagan@bizkc.rr.com

MANAGING EDITOR

Lizabeth R. S. Fleenor
Missouri State Medical Association
113 Madison Street / P.O. Box 1028
Jefferson City, MO 65102
800-869-6762 / Fax: 573-636-8552
lfleenor@msma.org / www.msma.org

CONTRIBUTING EDITORS*

Justin M. Albani, MD
Jeffrey G. Copeland, MD
Betty M. Drees, MD
David A. Fleming, MD
Arthur H. Gale, MD
William R. Reynolds, DDS, MD
Charles W. Van Way, III, MD

EDITORIAL BOARD

Susan S. Berdy, MD, Allergy/Immunology
Mitchell D. Botney MD, Pulmonary Medicine
Nancy J. Bunge, MD, Pediatrics
Edmond B. Cabbabe, MD, Plastic Surgery
Octavio R. Chirino, MD, OB/Gyn
Joseph A. Corrado, MD, General Surgery
David H. Cort, MD, Gastroenterology
Juan C. Corvalan, MD, Psychiatry
John S. Daniels, MD, Internal Medicine
Louis P. Dehner, MD, Pathology
Jose M. Dominguez, MD, Colon/Rectal Surgery
Jon A. Dyer, MD, Dermatology
John F. Eisenbeis, MD, Otolaryngology
Eden M. Esguerra, MD, Infectious Disease
Gregory R. Galakatos, MD, Orthopaedics
Lancer G. Gates, DO, Hospital Medicine
James J. Gibbons, MD, Anesthesiology
Gary S. Gottesman, MD, Medical Genetics
Jerry D. Kennett, MD, Cardiology
C. Daniel Kingsley, MD, Hematology/Oncology
Charles M. Lederer, MD, Ophthalmology
Katherine R. Lichtenberg, DO, Public Health
Brian L. Mahaffey, MD, Sports Medicine
Michael C. Murphy, MD, Cardiac Surgery
W. Kirt Nichols, MD, Vascular Surgery
John H. Niemeyer, MD, Radiology
Michael L. O'Dell, MD, Family Practice
James H. O'Keefe, MD, Preventive Medicine
John A. Pardalos, MD, Neonatology
Elizabeth A. Piontek, MD, Urology
Keith M. Rich, MD, Neurosurgery
Howard M. Rosen, MD, Endocrinology
Pradeep Sahota, MD, Neurology
Gary G. Singer, MD, Nephrology
Mark T. Steele, MD, Emergency Medicine
Anne E. Winkler, MD, Rheumatology
Gregory M. Worsowicz, MD, Physical Med/Rehab

EDITORS EMERITUS

Donald G. Sessions, MD, 1988-1992
J. Regan Thomas, MD, 1992-2000

*Publications Committee

MSMA Office / Staff Contact Information

113 Madison Street / P.O. Box 1028 / Jefferson City, MO 65102
573-636-5151 / 800-869-6762 / Fax 573-636-8552 / www.msma.org

Executive Vice President: Tom Holloway	Tel Ext - 123	tholloway@msma.org
Govt Relations/Legal: Jeff Howell	Tel Ext - 128	jhowell@msma.org
Legislative Affairs: Kenny Jackson	Tel Ext - 122	kjackson@msma.org
Communications: Lizabeth Fleenor	Tel Ext - 134	lfleenor@msma.org
Health Care Finance: Patrick Mills	Tel Ext - 126	pmills@msma.org
Scientific Affairs: Benita Stennis	Tel Ext - 138	bstennis@msma.org
Membership: Haley Wansing	Tel Ext - 135	hwansing@msma.org
Field Services: Sarah Luebbert	Tel Ext - 122	sarah@msma.org
Office: Cheri Martin	Tel Ext - 121	cmartin@msma.org
Membership Database: Cassie Williams	Tel Ext - 127	cwilliams@msma.org
Reception: Fran Draper	Tel Ext - 120	fran@msma.org
Finance: Lisa Cassmeyer	Tel Ext - 133	lisa@msma.org
Administrative: Carol Meyer	Tel Ext - 132	cmeyer@msma.org

Member Services Information

Go to www.msma.org/membership-perks or call 800-869-6762.

MSMA INSURANCE AGENCY, INC.
www.msma.biz
866-676-2467

MSMA PHYSICIANS HEALTH PROGRAM
www.themphp.org
800-274-0933

CENTER FOR PATIENT SAFETY
www.cps.org
573-636-1014

PRIMARIS
www.primaris.org
800-735-6776

MO ASSOCIATION OF OSTEOPATHIC PHYSICIANS & SURGEONS
www.maops.org
573-634-3415

AMERICAN MEDICAL ASSOCIATION
www.ama-assn.org
312-464-5000

CENTERS FOR MEDICARE & MEDICAID
www.cms.hhs.gov
816-426-5033

MO DEPT OF HEALTH & SENIOR SERVICES
www.dhss.mo.gov
573-751-6400

MO DEPT OF SOCIAL SERVICES
www.dss.mo.gov
573-751-2086

MO DEPT OF INSURANCE
www.insurance.mo.gov
573-751-4126

MO BOARD OF REGISTRATION
www.pr.mo.gov/healingarts.asp
573-751-0098

MO BUREAU OF NARCOTICS & DANGEROUS DRUGS
www.dhss.mo.gov/bndd
573-751-6321

MO HEALTHNET
www.dhss.mo.gov/mhd
573-751-3425

MEDICARE PART B/MO MEDICARE
www.momedicare.com
866-736-0799

NATIONAL MEDICARE HELPLINE
800-633-4227

CLAIM HELPLINE
800-390-3330

PROVIDER HOTLINE
800-735-6776

MO HOSPITAL ASSOCIATION
web.mhanet.com
573-893-3700

CCPA PURCHASING PARTNERS, LP
www.ccpapp.org
312-227-7436

DOCBOOKMD
www.docbookmd.com
888-930-2048

GONEXT - TRAVEL
www.gonext.com
800-842-9023

I.C. SYSTEM, INC.
Collection Service
www.icsystem.com
800-279-3511

LIFELOCK
www.lifelock.com
800-lifelock

MEDICAL WASTE SERVICES
www.medicalwasteservices.org
866-355-7094

MEDJET ASSIST
www.medjet.com
800-527-7478

MISSOURI DRUG CARD
www.missouridrugcard.com
800-869-6762

MONETA FINANCIAL & RETIREMENT PLANNING
www.monetagroup.com
800-833-1301

OFFICITE
www.officite.com/msma
866-638-6519

PART B NEWS GROUP
Publication Subscriptions
877-397-1496

RESOLVE PHYSICIAN AGENCY
www.resolvephysicianagency.com
877-758-3318

TSYS MERCHANT SOLUTIONS
www.tsysmerchantinsights.com
888-749-7860



Son's Death to Opioid Abuse Was "Completely Unnecessary"

by Jim Braibish & Kelly O'Leary

Physician spouse speaks out against dangers of prescription opioids.

The impact of the opioid crisis struck home within the Missouri physician community on Dec. 15, 2014. That's the day when, just two months shy of his 30th birthday, Derek succumbed to an opioid overdose.

The news was devastating for his mother, Kelly O'Leary, a longtime volunteer with the St. Louis Metropolitan Medical Society Alliance, and her husband Timothy O'Leary, MD, a radiation oncologist at Mercy Jefferson Hospital near St. Louis. Since then, Kelly has become an outspoken advocate against the prescribing of opioid painkillers. She has shared her story with Alliance audiences, various community groups and most recently to the Missouri Psychiatric Association.

"He was a good kid. He was very smart, and didn't want this to happen," Kelly said. "His death was completely unnecessary."

By normal standards, Derek was well-accomplished for his age. He had graduated from college, earned an MBA, and served for five years in the U.S. Navy. He was engaged to be married. But, over the last 12 years, he had also struggled off and on with opioid addiction.

First Painkiller Prescription

Derek's involvement with opioids began innocently. In 2002, after breaking his arm playing high school football at age 17, he was prescribed Oxycontin as a normal course of pain relief. Then, playing football a year later, he broke his arm in the same place. He was prescribed Oxycontin again.

At the time, Kelly and her family—and most people—didn't know the risks. "Purdue Pharma marketed Oxycontin to physicians as safe. Actually, it is nothing but legalized heroin," Kelly said. "If you give an opiate to anyone under the age of 25, the risk of addiction is much higher. The brain is still developing."

Derek had described to his mom how, beyond pain relief, the Oxycontin made him feel different.

After high school, Derek attended the University of Florida where he earned a bachelor's degree. But Kelly could see things were not right. Following college, the family urged him to enter outpatient treatment. Kelly recalled: "He had been drinking a lot and abusing prescriptions. They found Vicadin in his system. He had liver failure at age 22 from Vicadin."

Fortunately, the outpatient treatment was successful. Derek worked for a year and then joined the Navy where he handled radar and sonar. In the Navy, sailors are drug tested regularly, Kelly noted.

"He loved the Navy. My son was himself again," she said. Derek took courses and earned his MBA while in the Navy.

But in his fifth year in the Navy, he ran into bad luck and injured his knee. Navy surgeons performed an experimental surgery. Unaware of Derek's history or in spite of it, they prescribed Oxycontin. The addiction returned. Derek continued to get prescriptions from the nurse practitioner.

"He was still receiving Oxycontin four months after surgery. They gave him anything and everything he wanted," Kelly said.

Eventually the Navy did realize he had a problem, and got him into treatment which he continued after his enlistment ended. "Unfortunately, the Veterans



Jim Braibish is managing editor of *St. Louis Metropolitan Medicine* and principal of Braibish Communications. Kelly O'Leary is a volunteer with the St. Louis Metropolitan Medical Society Alliance.

Reprinted from St. Louis Metropolitan Medicine, December 2016

Administration did not handle the situation well. He was released too soon and relapsed," according to Kelly.

Eleven months after leaving the Navy, Derek was living in Toronto with his girlfriend. They planned to marry and move to St. Louis.

But the addiction took over. Derek was found dead in his apartment that December. The toxicology report showed his system had fentanyl, the high-potency synthetic form of heroin. They also found five prescription medications he was obtaining through the VA as a disabled veteran.



With Derek on his Navy ship in 2010, from left, Kelly, Dr. Tim O'Leary, Meghan, and Katy.

Living With Loss

"After my son died, it was the absolute lowest point in my life," Kelly said. "You don't imagine seeing your child in a casket." The entire family worked through the grief process together. Kelly and Dr. O'Leary also have two daughters, ages 17 and 19.

She joined a grief support group specifically for survivors of loved ones lost to substance abuse. She continues to attend the group every Sunday.

Now, she warns others about the dangers. "After my son died, I needed help. Many people were there for me. Now, I am trying to give back to others."

Besides telling her story to Alliance and physician groups, she has spoken to patients at the Harris House Treatment and Recovery Center in south St. Louis. She also volunteers for the St. Louis office of the National Council on Alcoholism and Drug Abuse (NCADA). She appears in a video produced by Mercy and the Greene County Medical Society Alliance (available on YouTube).

Kelly is passionate about preventing others from falling to addiction. Physicians should avoid prescribing these highly addictive drugs and patients should refuse the prescriptions if offered.

For physicians, she says, "Think about the consequences of these drugs before writing prescriptions. Opioids are a tragedy that causes lifelong pain. Physicians have the power to prevent exposure to these drugs with their prescription pads."

Physicians should screen patients for family histories of addiction before writing prescriptions for opioid painkillers, she added. The Navy had failed to check Derek's prior addiction history when prescribing the painkiller.

For patients, she says, "The best way not to become addicted is not to take opioids. When my daughters were given prescriptions for Vicadin by a pediatrician and an oral surgeon, we did not fill them. The girls got by on Advil instead."

She also reminds people that if they have unused prescription medicines, to safely dispose of them at a site such as NCADA or various pharmacies and police stations.

To help those who are addicted, she would like to see more long-term, residential treatment programs. "It takes five years to fully recover from addiction. In Germany and the Netherlands, they have five-year programs where the patient stays at the facility while working in the community."

She warns, "We were so naïve. People think this will never happen to them." **MM**



The ER Doctor's Role in Combating the Opioid Epidemic

by Matthew Gratton, MD

Emergency medicine physicians seem to get a significant amount of blame for "causing" the opioid epidemic so I was happy to see the following headline "Myth Busted: ED Docs Not a Prime Source of Opioid Prescriptions" in an on-line publication.[1]

The article referred to an abstract presented at the recent American College of Emergency Physicians (ACEP) Research Forum that used a sample from a national database to demonstrate that "the share of opioids obtained from the ED is inversely proportional to the patients' annual opioid consumption with the heaviest opioid users (>95 percentile) receiving a very small percentage of their opioids from EDs (2%.)"[2]

Unfortunately for ER docs, this study was followed by significant national press coverage of a New England Journal of Medicine study documenting "wide variation in the rates of opioid prescribing" among emergency physicians and the "rates of long-term use were increased among patients" who "received treatment from high-intensity opioid prescribers." (High intensity was defined as the top quartile of emergency physician opioid prescribers.)[3] If there is a causal relationship between the ED prescription and later opioid abuse, this would translate to a number needed to harm (NNH) of 48.

However, a commentator pointed out that the reported risk of long term use was 1.51% if the opioids were prescribed by a high intensity prescriber versus 1.16% if prescribed by a low intensity provider yielding a NNH of 286.[4] So, even the same data are subject to different interpretations.

One thing that everyone agrees on is that there is an opioid epidemic. Some statistics from the Department of Health and Human Services demonstrate this. On an average day in the United States, 3,900 people initiate the nonmedical use of prescription opioids; 580 initiate heroin use; and 78 people die from an opioid-related overdose.[5] There seems to be little agreement as to exactly who or what caused the epidemic. Grounder, variously places blame on articles in the medical literature from the 1980s stating that opioids for non-cancer pain were unlikely to produce "maladaptive behaviors;" pharmaceutical manufacturers aggressively marketing opioids for non-cancer pain; the American Pain Society publishing guidelines encouraging use of opioids for non-cancer pain; and The Joint Commission mandating measurement of pain.[6] Patient satisfaction surveys in general and HCAHPS (Hospital Consumer Assessment of Healthcare Providers and Systems) in particular, with multiple questions about pain management, are often mentioned as contributing factors. The recently described increase in the death rate of middle-aged white Americans, so called "deaths of despair" due to suicide, drug and alcohol abuse, may be a part of the cause, rather than just an effect of opioid abuse. [7]

It is almost certain that there is no "one" cause of the epidemic, and likewise, there is not likely to be any "one" solution, but rather a number of actions that can be taken. A comprehensive review by Hawk et al. divides some of these solutions into three groups: primary prevention; increasing access to effective treatment; and harm reduction. [8] Primary prevention includes education for patients and physicians, use of pain contracts and urine drug testing prior to prescribing opioids, the use of prescription drug monitoring programs (PDMPs,) and the closing of so-called "pill mills." Increasing access to effective treatment includes expanding and enhancing medication assisted treatment (MAT) using methadone or buprenorphine/naloxone, and expanding "screening, brief intervention and referral to treatment" (SBIRT.) Harm reduction strategies include taking a public health approach to opioid use, not to endorse drug use, but to understand that it occurs and take steps to reduce harmful consequences. This includes education of users and families and the widespread distribution of naloxone to users, families, and first responders and encouragement of providers



Matthew Gratton, MD, MSMA member since 2001, is Professor and Chair, Emergency Medicine, Truman Medical Center and University of Missouri - Kansas City School of Medicine.
Contact: Matthew.Gratton@tmcmed.org

to prescribe naloxone to patients at high risk of overdose.

The effectiveness of PDMPs remains "inconclusive" even though every state has adopted one form or another except Missouri.[9] Dowell et al. investigated the effect of mandatory PDMP review and pain clinic laws on opioid prescriptions and death rates from 2006 – 2013.[10] Opioid prescriptions declined by 8% and prescription opioid overdose death rates declined by 12%. However, mandatory PDMP review was only initiated in states that also adopted pain clinic laws and so it was not possible to "clearly define" which change drove the decrease.

It is possible that the use of PDMPs may decrease opioid diversion, and fraud, but there are still data privacy and security concerns as well as possible unintended consequences to patients needing opioid medication and problems with mandatory consultation requirements.[11] Of course some physicians are opposed to mandatory consultation as a "burdensome intrusion into clinical practice" but there are other problems.[9]

Operational issues such as registration, multiple logins, delays in information being entered into the system and consultation "not being integrated into clinical workflow" will impact information usefulness and increase the time that the physician spends at the computer and not interacting with the patient.[9] In some cases it may be difficult to interpret information obtained from the PDMP.

Some have suggested "positive" approaches to encouraging physicians to use the PDMP (rather than the "negative" approach of mandates.) Specifically, "pay for performance, malpractice discounts, or immunity from liability for prescribers who diligently use the system."[9] If PDMP information could be "automatically" accessed (i.e. no separate login, no specific request, information just being presented, analogous to a drug interaction warning) anytime a physician was ordering an opioid medication via an electronic ordering system, some of these issues would be mitigated.

So, what is an ER doc supposed to do? A number of action items have been proposed by ACEP.[12] Common sense opioid prescribing guidelines have been proposed and adopted by multiple organizations, including the Missouri State Medical Association, the Missouri Hospital Association, and others.[13] These guidelines include prescribing the shortest possible course of short-acting opioids, not refilling lost prescriptions, using evidence-based guidelines when possible, not using opioids for dental pain unless necessary and others.

Much has been written in the non-peer reviewed literature about the "opioid-lite" emergency room.[14] The idea is to use non-opioid medications for common problems like back pain, ureteral colic, strains and sprains and the like. More reliance on acetaminophen, IV lidocaine (for ureteral colic,) steroids, lidocaine patches, and gabapentin and other medications are emphasized. However, there is relatively little science behind some of these recommendations in the ED setting and more research is necessary to ensure safety and efficacy Ultrasound guided nerve blocks are also advocated by some.

Evidence-based, rapid assessment tools should be used to determine which patients are at higher risk for substance abuse.[12] Use of a PDMP when available. Multiple counties in Missouri have joined the St. Louis County PDMP and it is available in some parts of the state. While there are issues as mentioned above, it is clear that some look at the PDMP as a valuable resource. While not ready for widespread implementation at this time, the use of SBIRT and the initiation of MAT in the ED using buprenorphine/naloxone has been recommended and studied.[15]

Together, the house of medicine can work with the public and legislators to successfully stem the tide of opioid abuse in the United States.

References

1. Busko, M. "Myth Busted: ED Docs Not a Prime Source of Opioid Prescriptions." Medscape. 27 October 2016. www.medscape.com/viewarticle/871026. Accessed 15 February 2017
2. Menchine M, Aseen S, Seabury S. The Office or Emergency Department: Where Do Heavy Opioid Users Get Their Medications? Ann Emerg Med; (68) 4S: S79
3. Barnett M, Olenski A, Jena A. Opioid-Prescribing Patters of Emergency Physicians and Risk of Long-Term Use. NEJM; (376) 7: 663 – 673
4. Hochman M, Cohen P. "Slow Medicine: Opioids and High Prescribers." Medpage Today. 24 March 2017. www.medpagetoday.com/blogs/slowmedicine/64105. Accessed 13 April 2017
5. "The Opioid Epidemic: By the Numbers." The Department of Health and Human Services. www.hhs.gov/sites/default/files/Factsheet-opioids-061516.pdf. Accessed 14 April 2017
6. Grounder C. "Who Is Responsible for the Pain-Pill Epidemic?" The New Yorker. 8 November 2013. www.newyouker.com/business/currency/who-is-responsible-for-the-pain-pill-epidemic. Accessed 3 March 2017
7. Broddy J. "The Forces Driving Middle-Aged White People's 'Deaths of Despair.'" National Public Radio. 13 March 2017. http://www.npr.org/sections/health-shots/2017/03/23/521083335/the-forces-driving-middle-aged-white-peoples-deaths-of-despair. Accessed 13 April 2017
8. Hawk K, Vaca F, D'Onofrio G. Reducing Fatal Opioid Overdose: Prevention, Treatment and Harm Reduction Strategies. Yale J of Bio and Med 2015; (88): 235 – 245
9. Haffagee R, Jena A, Weiner S. "Mandatory Use of Prescripion Drug Monitoring Programs. JAMA 2015; (313) 9: 891 – 892
10. Dowell D, Zhang K, NoonanR, Hockenberry J. Mandatory Provider Review and Pain Clinic Laws Reduce the Amounts of Opioids Prescribed and Overdose Death Rates. Health Affairs 2016; (35) 10: 1876 – 1883
11. Islam M, McRae I. An Inevitable Wave of Prescription Drug Monitoring Programs in the Contex of Prescription Opioids: Pros, Cons and Tensions. BMC Pharm and Tox 2014; (15) 46
12. "Opioid Resources." American College of Emergency Physicians. www.acep.org/opioids/. Accessed 31 March 2017
13. "Opioid Initiative." Missouri Hospital Association. http://web.mhanet.com/opioid-initiative.aspx. Accessed 13 April 2017
14. Walker G. The Opioid-Lite Emergency Department. Emergency Medicine News 2016; (38) 12: 1, 31
15. D'Onofrio G, O'Connor P, Pantalon M, et al. Emergency Department-Initiated Buprenorphine/Naloxone Treatment for Opioid Dependence, A Randomized Trial. JAMA 2015; (313) 16: 1636 – 1644.

MM

Call Coverage Rates: What's Driving That Number?

by Wakaba Tessier, Kate Bechen & Wendy Keegan

Market factors fluctuate significantly in the health care industry necessitating a regular review of call coverage arrangements.

Pressures on Hospital Emergency Departments

The Emergency Medical Treatment and Active Labor Act (EMTALA), state hospital licensing requirements and the ever looming threat of medical malpractice claims require hospitals to have adequate physician on-call emergency coverage. EMTALA in particular requires hospitals with emergency departments to provide emergency services to patients regardless of their ability to pay and requires hospitals to maintain a list of on-call physicians.[1] EMTALA does not, however, similarly require physicians to provide emergency services. Consequently, hospitals at times are hard pressed to ensure adequate coverage. This challenge is compounded by high rates of uninsured patients, physician shortages, changing physician expectations, and rapid evolution and uncertainty in the health care arena.





This article was written by Wakaba Tessier, (left), Kate Bechen, (center), and Wendy Keegan, (right). Kate is a partner in the Milwaukee Office, Wakaba is an associate in the Kansas City Office, and Wendy is a senior counsel in the Austin Office of Husch Blackwell LLP. The information contained in this article should not be construed as legal advice or a legal opinion on any specific facts or circumstances. The contents are intended for general information purposes only, and readers are urged to consult their own attorney concerning their own specific situation and any specific legal questions.
Contact: Harvey.Tettlebaum@huschblackwell.com

Hospitals rely on a variety of tools, alone and in combination, to meet their physician on-call emergency coverage obligations: increasing the number of employed physicians, entering into transfer agreements with neighboring hospitals, establishing minimum levels of call coverage for medical staff membership in the medical staff bylaws, and paying physicians to provide emergency department coverage through call coverage agreements.

A 2010 survey by the American Hospital Association found that at least half of responding hospitals paid for emergency department call coverage, with general surgery, orthopedics and OB/GYN the leading specialty areas.[2] As reported in the survey, expenditures for call coverage are substantial - of the responding hospitals, 29% reported spending under $100,000 annually, 30% reported spending between $100,000 and $499,000, 20% reported spending between $500,000 to $999,999, and 21% reported spending $1,000,000 or more on emergency department call coverage.[3] Half of the hospitals reported increased expenditures for call coverage the previous twelve months ranging from 1% to 50%.[4]

This article will discuss the legal requirements and potential pitfalls of call coverage agreements and then turn to real world considerations.

What Are They?

Call coverage agreements are generally made between a hospital and a physician group or an individual physician. Physicians typically agree to respond to calls from the emergency department within a certain period of time, either in person or by phone as necessary, and in exchange the hospital agrees to make some type of payment.

Call coverage agreements may require either restricted or unrestricted call. Restricted call requires the physician to remain at the hospital and unencumbered by other obligations, whereas unrestricted call allows the physician to carry a pager and have more freedom to take call from home or their regular practice. In addition to being on call for the emergency department, call coverage agreements routinely require physicians to be on-call for

in-patient consults and to provide continued care for any patients they admit through the emergency department.

The most common form of payment for call coverage services is a per diem fee, which varies based on the specialty, whether call is restricted or unrestricted, acuity of care, frequency of calls and other variables – many of which are discussed in more detail below. Other alternatives are payment for uncompensated care, and delivery of a pool of funds administered on a department basis by the hospital, medical staff or a combination of the two. As discussed in more detail below, the amount and form of compensation will necessarily correlate with scope of call coverage services the physician provides.

Legal Considerations

Arrangements between hospitals and physicians involving compensation of any type are subject to rigorous federal and state regulation, and call coverage agreements are no exception.

The federal anti-referral law, also referred to as the Stark law (Stark), prohibits referrals between physicians and hospitals if there is any financial relationship between them, unless an exception applies.[5] Stark is a strict liability prohibition, meaning the parties' intent is irrelevant, and that an arrangement is unlawful unless it squarely meets an exception. Call coverage agreements are usually structured to meet either the exception for personal services or the fair market value exception.[6] Violation of Stark will result in repayment of all amounts received for unlawful referrals, and possible civil penalties and exclusion from federal health care programs.

The federal anti-kickback law (AKS) prohibits the knowing and willful payment or receipt of any remuneration for referrals.[7] The AKS is an intent based prohibition. Arrangements that meet one of a number of AKS safe harbors are deemed to pose little risk of fraud and abuse. Arrangements that do not meet all of the elements of a safe harbor are not per se unlawful, but should be scrutinized closely and will be deemed unlawful if even one purpose of the arrangement is to encourage referrals.

The Office of the Inspector General (OIG) enforces the AKS and has issued several advisory opinions over the last ten years regarding call coverage agreements.[8] The specifics of the reviewed arrangements varied, but in each case the OIG cited the following guidance from its Supplemental Compliance Program Guidance for Hospitals:

The general rule of thumb is that any remuneration flowing between hospitals and physicians should be at fair market value for actual and necessary items furnished or services rendered based upon an arm's-length transaction and should not take into account, directly or indirectly, the value or volume of any past or future referrals or other business generated between the parties.[9]

In each of the call coverage advisory opinions, the OIG relied upon the requestors' certification, based on an independent evaluation, that the compensation was fair market value for actual and necessary services, and without regard to the volume or value of referrals between the parties. Other factors the OIG favorably cited included: determination of the per diem amount annually and in advance, the opportunity to participate in call coverage was offered to physicians uniformly, and that the associated costs of the arrangement were absorbed by the hospital and not passed on to federal health care programs.

Most states, including Missouri, have their own version of the federal anti-referral [10] and anti-kickback laws. The Missouri AKS is limited to the Missouri Medicaid program (MO HealthNet) and other programs which are financed by the state or federal government (Government Payor).[11] The provisions of the Missouri AKS are substantially similar to the federal AKS as they prohibit anyone from knowingly offering or paying any remuneration for referrals for services payable by a Government Payor.[12]

Although on its face, the Missouri False Claims Act (FCA) may not be directly applicable, it may be implicated if on-call coverage amounts exceed fair market value or the amount to which the physician is entitled. The Missouri FCA generally prohibits a health care provider from knowingly making, or causing to be made, a false statement or false representation of a material fact in order to receive payment from the Missouri Medicaid program or other Government Payor program. The prohibition includes concealing or failing to disclose information with the intent to obtain payment to which the health care provider is not entitled or to obtain an amount greater than that which the health care provider is entitled.[13] The receipt of on-call coverage fees in excess of fair market value, or failure to comply with provisions in the on-call coverage agreement may create liability under the Missouri FCA if such non-compliance is viewed as forfeiture of the physician's entitlement to certain payments from Government Payors.

Adding to this regulatory minefield, depending on the specific circumstances, a call coverage agreement could implicate federal and state tax-exempt, anti-supplementation, corporate practice of medicine and antitrust regulations. The Missouri Hospital Association (MHA) has warned that "[n]o issue is more thorny than call coverage."[14]

MHA has recommended that either the physician's employment agreement, or a separate on-call coverage agreement, "should address how the physician is paid (if at all) when the physician is actually called. Further, any call pay should be taken into account when considering the total fair market value of the physician's compensation."[15] This is an assessment that can sometimes be forgotten but is very important in situations where, for example, one physician has several agreements with a hospital (a professional services agreement, a call coverage agreement, and a medical director agreement). The aggregate compensation needs to be reviewed and double counting (two agreements essentially covering the same service) must be avoided. MHA also recommends that hospitals assess and identify the minimum number of physicians in a practice area necessary to provide call coverage.[16]

Additional Factors Affecting Call Coverage Compensation

Hospital management teams consider other factors in addition to the legal issues outline above. Ultimately, call coverage compensation should be fair market value but determining fair market value is easier said than done. Certainly executives consider the market data available through valuation firms, but in reality hospital executives can struggle with determining fair market value because of a wide and varying range of factors present in their hospital's particular market. The following list addresses some of the factors taken into consideration when determining the call coverage rate for a particular specialty at a particular hospital.

Size of the Coverage Pool: In certain geographic areas there can be either an over- or under abundance of physicians trained in a certain specialty. This may lead to higher or lower call coverage rates based on the market. If a hospital simply can't attract qualified physicians to provide call coverage in a certain specialty, the hospital will likely raise its call coverage rates to attract the scarce resource.

Call Frequency: If on-call physicians can expect a large number of call-ins (larger than say another hospital in town), the call coverage rate will likely be higher to compensate for that higher volume.

Size/Status of Hospital: Tertiary care facilities, for example, routinely pay higher call coverage rates than rural counterparts due to the expected volume and complexity of the cases likely to be seen at the tertiary care facility.

Importance of Program/Department: If, for example, a hospital has focused on certain departments or programs (perhaps as a center of excellence), there may be a greater likelihood of higher call coverage rates to attract highly skilled specialists.

Case Acuity: Average case acuity can dictate coverage rates. Rates at a preeminent academic medical center will be based, in part, on the expected complexity of the case load, length of surgeries/consults, and emergent nature of the cases in question.

Undesirable Payor Mix: Hospitals with a high volume of indigent patients or under-insured patients sometimes find it difficult to retain physicians for call coverage since the likelihood of the physicians' securing new patients is low and, sometimes, the location of the hospitals is undesirable.

Type of Call Coverage: The more restrictive the requirements of call coverage, the higher one can expect the compensation to be. For example, restricted call coverage usually necessitates that the physician stay on site. And even with unrestricted call coverage arrangements the response time requirements can impact compensation rates.

Conclusion

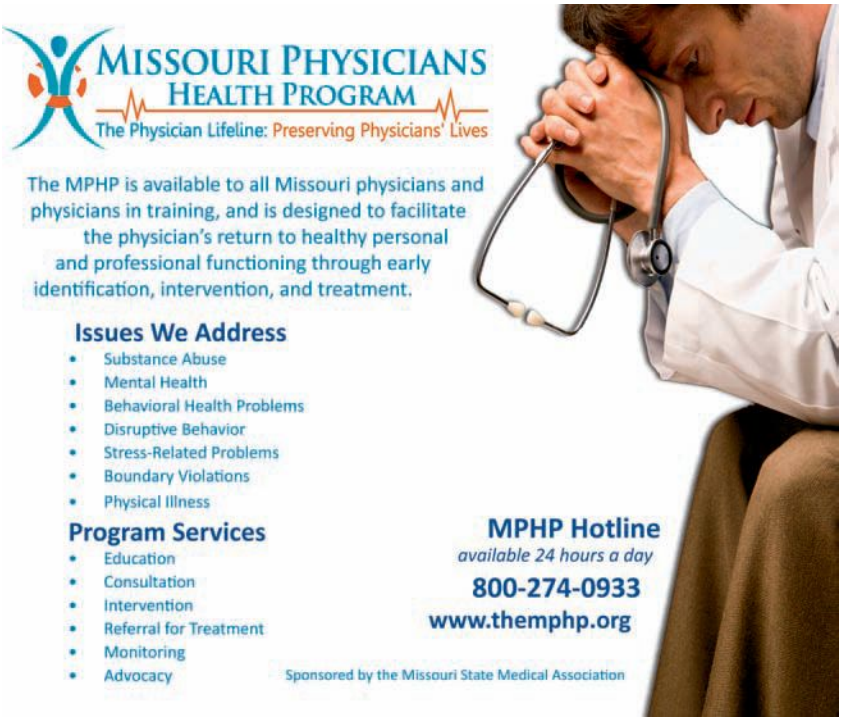
Determining the call coverage rate for a particular specialty, at a given hospital, in a certain geographic area is usually not a simple process, nor is it a one-time determination. Market factors fluctuate significantly in the health care industry necessitating a regular review of call coverage arrangements. While higher levels of hospital-employed physicians somewhat alleviates this issue, it is unlikely to go away anytime soon. Because of the host of legal compliance concerns and the complex market drivers, it is often difficult for an individual physician to truly assess whether the offered rate is competitive. But that doesn't mean that a physician should not try to negotiate a higher rate or other more preferential terms – in the vast majority of situations the worst response would be no and then the physician could decide whether or not to accept the original offered rate. Focusing on what makes the physician unique is usually

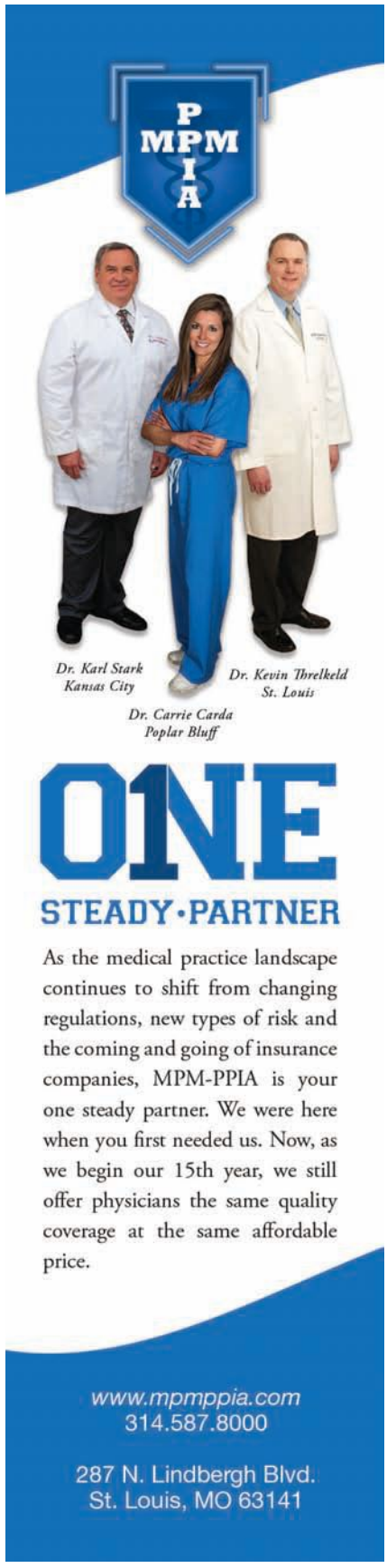
a better approach than pointing out how much a colleague makes, since such an argument is almost always not based on full information, nor will the hospital be able or willing to discuss particulars of another physician's arrangement. Demonstrated commitment to the area, affiliation with a larger physician group, willingness to take weekend/holiday call coverage and just a few examples of ways a physician can enhance her bargaining power.

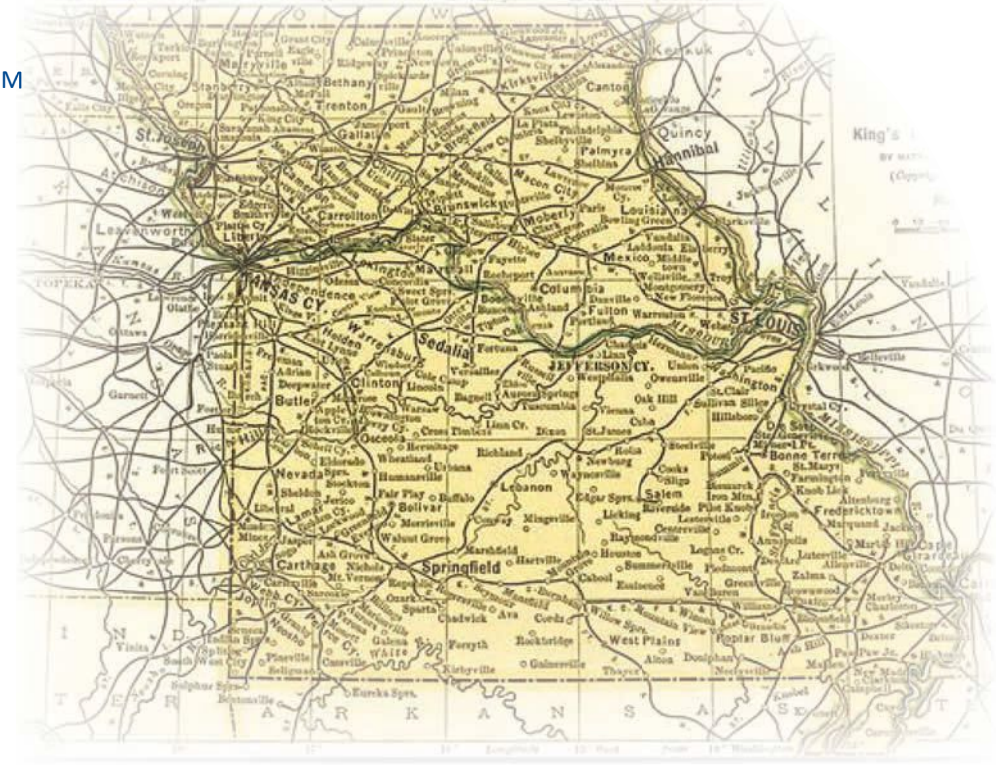
References

1. 42 U.S.C. § 1395dd; 42 C.F.R. § 489.24.
2. American Hospital Association website, available at http://www.aha.org/content/00-10/100524-thschartpk.pdf
3. Id.
4. Id.
5. 42 U.S.C. § 1395nn; 42 C.F.R. § 350 *et seq*.
6. Id.
7. 42 U.S.C. § 1320a-7b.
8. OIG Advisory Opinion No. 07-10 (September 20, 2007); OIG Advisory Opinion No. 09-05 (May 14, 2009); OIG Advisory Opinion No. 12-15 (October 23, 2012, Corrected March 8, 2013).
9. 70 Fed. Reg. 4858, 4866 (January 31, 2005).
10. Missouri's Stark Law is restricted to the referral of physical therapy services. Section 334.253 of the Missouri Revised Statute prohibits a physician from making a referral to an entity for the furnishing of any physical therapy services with which the physician, physician's employer, or immediate family member, of such referring physician has a financial relationship. A financial relationship exists if the referring physician, the referring physician's employer, or immediate family member (i) has a direct or indirect ownership or investment interest in the entity whether through equity or debt, or other means; or (ii) receives remuneration from a compensation arrangement from the entity for the referral.
11. Mo. Rev. Stat. § 191.905.2.
12. Mo. Rev. Stat. § 191.905.3.
13. Mo. Rev. Stat. § 191.905.1(3).
14. See Physician Bona Fide Employment Contracting Guide, Missouri Hospital Association, 2013, available at http://web.mhanet.com/MHA_Physician_Employ_Contract_Guide_1.pdf (last accessed February 5, 2017).
15. Id.
16. Id.

MM







Thankful to be a Missourian

by Warren C. Lovinger, Jr., MD

I am truly excited to be starting my year as your President of the Missouri State Medical Association. We had a great annual meeting in Kansas City, where in timeless tradition, your 2016-2017 MSMA President, Ravi Johar, MD, of St. Louis, passed the gavel to me.

I have "hit the ground running" during these first six weeks of my tenure. I have been our representative to the annual medical society meetings of three neighboring states: Oklahoma, Iowa, and Arkansas. My main impression from these trips is that *I am very thankful to be a Missourian*.

The state of Oklahoma is grappling with a $1 billion budget shortfall, which will likely lead to a 30% decrease in funding for many programs, including health care. While Iowa physicians were celebrating passage of a state Tort Reform bill by their legislature, they were also confronting a shortfall of funding for the Iowa Medical Society. The Arkansas Medical Society was still reeling from passage of a constitutional amendment that legalized medical marijuana for 20 diagnoses (ranging from PTSD to osteoarthritis) that could include more than half of their population. They are just confronting the physician's role as gatekeeper to this poorly studied "treatment."

Another highlight of the past few weeks has been my trips to 28 of the 114 counties in Missouri. These have been mostly in the northwest and southwest corners of our state. During these outings, I have had the privilege of meeting two young family practice physicians, both members of MSMA, who are serving their rural communities with skill and enthusiasm. I would like to feature them here as "Unsung Heroes of the Hinterland."

On April 28, I met Kenneth Lambert, DO, who is one of four physicians in Bethany, Missouri, a town of 3,300 that is 20 miles south of Iowa. He and his peers all work for the Harrison County Community Hospital.



Warren C. Lovinger, Jr., MD, MACP, MSMA member since 1979, and President for 2017-2018, is an Internal Medicine physician, Nevada, Missouri.
Contact: wclovinger@gmail.com





Unsung Heroes of the Hinterland

Above, Kenneth Lambert, DO, (right), MSMA member since 2015, and Dr. Lovinger, (left) in Bethany, Missouri.

Inset, Connie Butler, MD, (right), MSMA member since 2008, and Dr. Lovinger, (left), in Cassville, Missouri.

He is a native of nearby Worth County. After receiving a PhD in immunology at MU-Columbia, he became a Doctor of Osteopathy at KC-UMB, and then did a family practice residency at Jefferson City's Capitol Regional Medical Center. He and his wife Becky (also a Northwest Missourian) are expecting their first child in May, and are looking forward to a bright future in the vibrant community of Bethany.

Two hundred and fifty miles directly south is the town of Cassville, Missouri, in Barry County. It has a population of 3,300, and is 15 miles north of the Arkansas border. On May 5, I had the pleasure of meeting Connie Butler, MD, who has practiced there for 12 years, as an employee of the Mercy System. She is one of six physicians in Cassville, with her office next to Mercy-Cassville Hospital. Her diversified practice includes prenatal care and endoscopic procedures. Dr. Butler is a Nebraska native, graduated from University of Nebraska School of Medicine, and did a family practice residency at Via Christi Hospital in Wichita, Kansas, before moving to southwest Missouri. She and her husband, Chadd, have ten-year-old twins, and have developed strong connections to their rural community.

As I continue my travels around our great state, usually accompanied by my wife, Marilyn, I will strive to visit and congratulate many more of our Missouri physicians. I will report in future issues of *Missouri Medicine* about these "unsung heroes of the hinterland." **MM**

MSMA Introduces:
Medical Student Mentor Program

by Warren C. Lovinger, Jr., MD

Sign Up!
www.msma.org/student-mentorship

Membership recruitment and retention is a critically important task for any organization. At the Missouri State Medical Association, it is especially important that we reach out to medical students—our youngest colleagues. Yet, any invitation must also provide benefits that make membership and participation rewarding.

Ravi Johar, MD, (then MSMA President) and I had the opportunity to discuss ideas with three University of Missouri - Columbia (UMC) medical students—Ariel Carpenter, Matt Faubion, and Jared Lammert during an American Medical Association meeting. From our brainstorming arose the idea of a "Medical Student Mentor Program." The program pairs a medical student with a graduate physician (MSMA member) in our state. Some physicians might have as many as five students. Geographic and specialty interests of the student is also accommodated. This relationship may be as simple as an occasional phone call or email from the student to his/her mentor to ask basic questions or advice. Such issues as career direction, clerkship priorities, or residency choices might benefit greatly from the input of a graduate physician, who would have experienced this themselves. The student and Missouri physician might also choose to meet in Columbia or the mentor's community. Obviously, a valuable relationship could develop. This would hopefully also promote the student's connection to the MSMA and all that it has to offer.

A "Pilot Program" of this mentoring concept – initially at one institution – is necessary before expanding it to all seven Missouri medical and osteopathic schools. UMC was chosen for this effort, due to its central location. Patrice Delafontaine, MD, UMC School of Medicine Dean, and Michael Hosokawa, EdD, Interim Senior Associate Dean for Education, warmly received the Student Mentor Program. MSMA is thus introducing the program and initial enrollment of UMC medical students at the start of the 2017-2018 academic year. Recruitment of graduate physician mentors started at MSMA's Annual Convention. It was gratifying that some 60 MSMA members promptly volunteered! Dr. Johar is the coordinator, in collaboration with MSMA staff and Executive Committee.

If all goes as planned, the Medical Student Mentor Program could, over a few years, expand to involve students at the other six medical and osteopathic institutions. It might also be possible to involve residents at those training sites, as they would also benefit from graduate physician mentors. Over time, we hope the program grows into a large network of physicians, medical students, and residents. It would certainly be a great model for participation and membership recruitment/retention.

As this program develops, we need the help of more graduate physicians around Missouri. This would require a minimum of time commitment, but would likely provide benefits for years to come. Contact MSMA's Haley Wansing at 800-869-6762, email hwansing@msma.org, or sign up at www.msma.org/student-mentorship.

Reprinted with permission from the Cape County Medical Journal.

MM

Practice in a health model of the future.

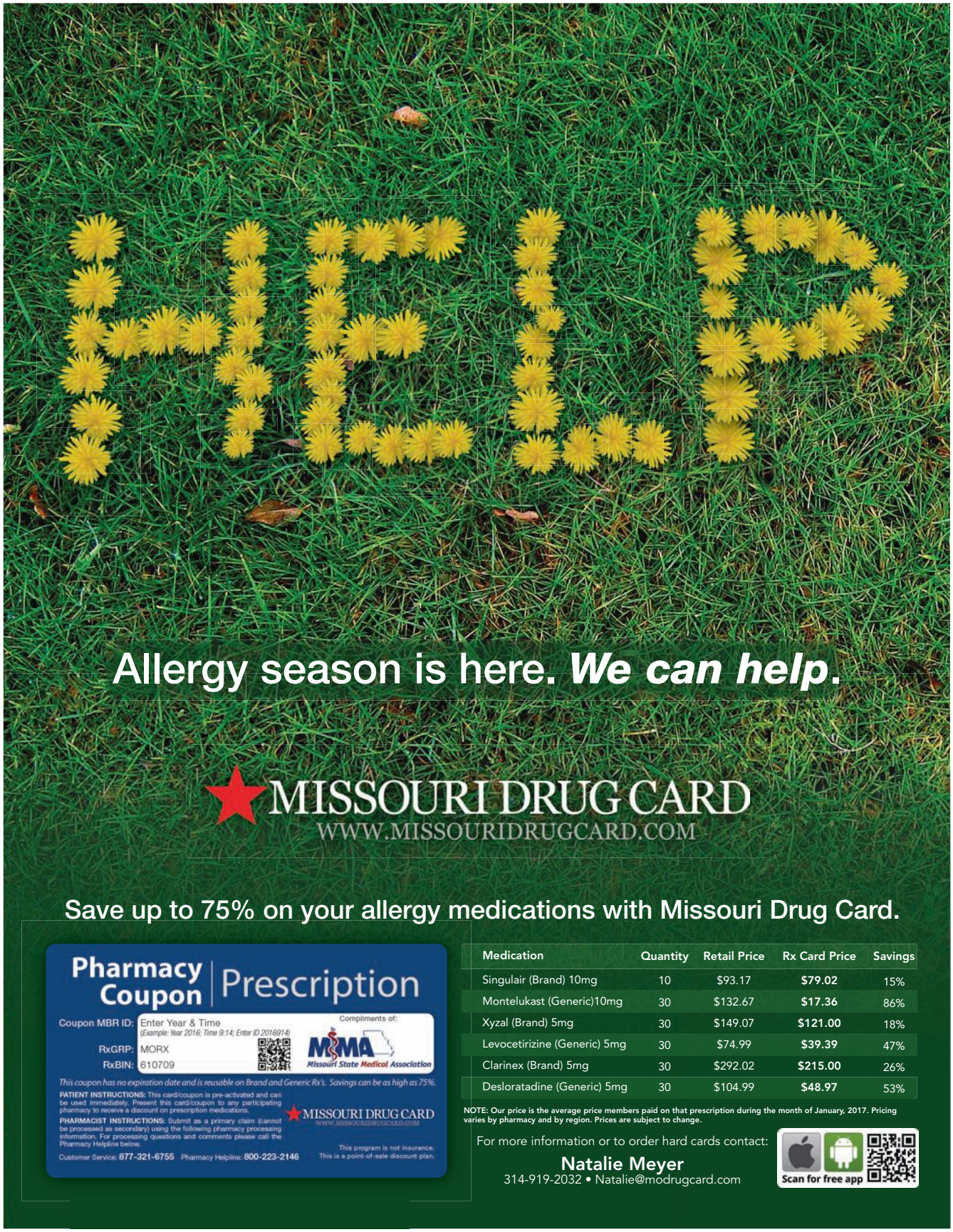
Mercy in Arkansas, Kansas, Missouri and Oklahoma, is seeking BC/BE physicians to join thriving practices. Positions offer an excellent benefits package including health, dental, and vision benefits, life insurance, vacation and CME, retirement plan and more. Available opportunities may include:

- Anesthesia
- Cardiology
- Dermatology
- Critical Care
- CV/CT Surgery
- Emergency Medicine
- Endocrinology
- Family Medicine
- Gastroenterology
- General Surgery
- Gynecologic Oncology
- Head and Neck Surgery
- Hematology/Oncology
- Hospitalist
- Nocturnist
- Infectious Disease
- Internal Medicine
- Maternal Fetal Medicine
- Neonatology
- Neurology
- Neurosurgery
- OB/GYN – Traditional
- OB/GYN Hospitalist
- Occupational Medicine
- Ophthalmology
- Optometry
- Oral & Maxillofacial Surgery
- Orthopedic Surgery
- Otolaryngology
- Pain Management
- Pathology
- Plastic Surgery
- Podiatry
- Psychiatry
- Pediatrics
- Pediatric Emergency Medicine
- Pediatric Endocrinology
- Pediatric GI
- Pediatric Hem/Onc
- Pediatric Internal Medicine
- Pediatric Neurology
- Pediatric Surgery
- Pediatric Urgent Care
- Physical Medicine and Rehabilitation
- Pulmonology/Critical Care/Sleep Medicine
- Radiation Oncology
- Radiology-Interventional
- Rheumatology
- Robotics
- Trauma Surgery
- Urology
- Vascular Surgery

For more information, please contact: Angie Abraham, MBA
Executive Director of Physician Recruitment • Mercy Clinic
Phone: 877-880-6650 | Fax: 888-290-8300
Email: angie.abraham@mercy.net

AA/EOE

Mercy


Allergy season is here. We can help.
MISSOURI DRUG CARD
WWW.MISSOURIDRUGCARD.COM
Save up to 75% on your allergy medications with Missouri Drug Card.
Pharmacy Coupon | Prescription
Coupon MBR ID: Enter Year & Time
(Example: Year 2016; Time 9:14; Enter ID 2016914)
RxGRP: MORX
RxBIN: 610709
Compliments of:
MSMA
Missouri State Medical Association
This coupon has no expiration date and is reusable on Brand and Generic Rx's. Savings can be as high as 75%.
PATIENT INSTRUCTIONS: This card/coupon is pre-activated and can be used immediately. Present this card/coupon to any participating pharmacy to receive a discount on prescription medications.
PHARMACIST INSTRUCTIONS: Submit as a primary claim (cannot be processed as secondary) using the following pharmacy processing information. For processing questions and comments please call the Pharmacy Helpline below.
MISSOURI DRUG CARD
WWW.MISSOURIDRUGCARD.COM
Customer Service: 877-321-6755 Pharmacy Helpline: 800-223-2146
This program is not insurance. This is a point-of-sale discount plan.
Medication | Quantity | Retail Price | Rx Card Price | Savings
Singulair (Brand) 10mg | 10 | $93.17 | $79.02 | 15%
Montelukast (Generic)10mg | 30 | $132.67 | $17.36 | 86%
Xyzal (Brand) 5mg | 30 | $149.07 | $121.00 | 18%
Levocetirizine (Generic) 5mg | 30 | $74.99 | $39.39 | 47%
Clarinex (Brand) 5mg | 30 | $292.02 | $215.00 | 26%
Desloratadine (Generic) 5mg | 30 | $104.99 | $48.97 | 53%
NOTE: Our price is the average price members paid on that prescription during the month of January, 2017. Pricing varies by pharmacy and by region. Prices are subject to change.
For more information or to order hard cards contact:
Natalie Meyer
314-919-2032 • Natalie@modrugcard.com
Scan for free app

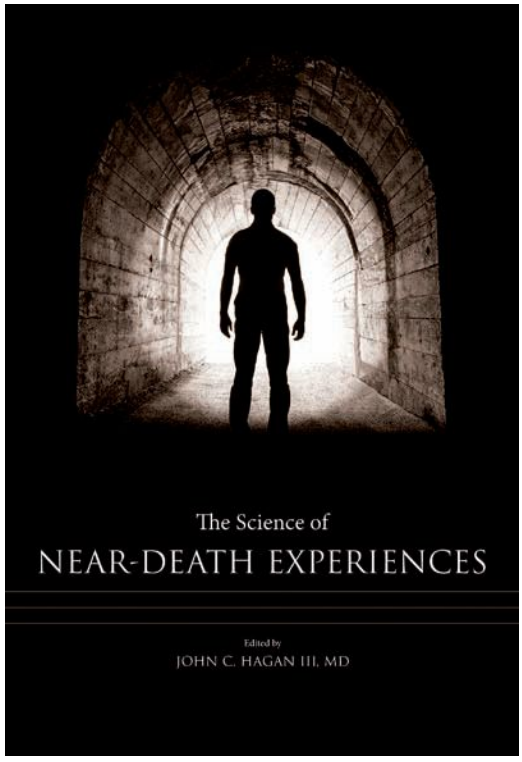
The Science of Near-Death Experiences

by John C Hagan III, MD, Editor

University of Missouri Press
Hardcover. 169 pp. ISBN 978-0-8262-2103-2

Submitted by Joel Eissenberg, PhD

Interest in near-death experiences (NDEs) stems primarily from the hope that there is a welcoming afterlife. The possibility that science can be rallied in support of that hope is an appealing one. The "Science" in the title of this book refers to the taxonomy of NDE perceptions and the attempts to compare NDE reports to our current understanding of neurophysiology



John C. Hagan, III, MD, has recruited the modern founder of NDE investigation, Raymond A. Moody, MD, PhD, to make his case in Chapter 1. Dr. Moody lays out the dominant themes for the rest of the book: reports of NDEs have a long pedigree; reported experiences shared by people of diverse backgrounds and ages bear remarkable similarities; and people who report NDEs believe it changed their lives for the better and no longer fear death.

In Chapter 2, Bruce Greyson, MD, summarizes some explanatory models for NDEs and his counterarguments, the reported effects—positive and negative—of NDEs on those who experience them, and the challenges that NDEs pose to our current understanding of neurophysiology and psychology.

Chapter 3, by Dean Radin, PhD, is a digression. Its topic is telepathy, for which Dr. Radin is a champion. The point appears to be that telepathic phenomena, like NDEs, provide evidence that our minds are more than the sum of our brain parts. The Ganzfield Experiments, which Radin regards as a gold standard of telepathy research, have been challenged by several authors whose work Radin fails to cite (e.g., Hyman 1985; Milton and Wiseman, 1999; Blackmore 2001). The evidence for telepathy remains in doubt, and this chapter doesn't advance the scientific case for NSEs. One observation used as grounds to question the localization of consciousness in the brain is cited by Pim von Lommel, MD, in chapter 4 (p. 45): " . . . even blind people have described veridical [verifiable information which they could not have obtained by any normal means] perceptions during out-of-body experiences at the time of their NDEs." This claim is cited to the 1999 book "Mindsight: near-Death and Out-of-Body Experiences in the Blind" in which they discuss 21 NDE experiences in the blind who reported accurately things that could only have been perceived through vision, and whose reports were supported by witnesses. This is hard to reconcile with the known difficulty of those who gain sight for the first time or after a long period of blindness to comprehend visual images. In her book "Dying to Live: Near-Death Experiences," Susan Blackmore summarizes her investigation of the evidence: " . . . these claims present no real challenge to a scientific account of the NDE."

Chapters 5 and 6 provide luminous first-hand accounts of NDEs with out-of-body experiences from physicians. Both authors found their lives after their experiences transformed in a positive and lasting way, and write movingly.

Chapter 7, by Jeffrey Long, MD, presents the argument that accounts of NDEs and their consequences are physical phenomena and not illusions of a dying brain. He adduces nine lines of evidence in support of his argument, only the last of which—after-effects of NDEs—can be independently verified by a neutral observer.

In chapter 8, Janice Miner Holden, EdD, takes a deep dive into the topic of veridical (verified or truthful) perception reports associated with NDEs. Importantly, she considers controlled experiment to scientifically test claims of paranormal verdicality. The paradigm involves the placement of remote visual targets "in the corners of hospital rooms in which near-death episodes were most

likely to occur . . . in such a way as to be visible only from a vantage point of looking down from the ceiling. No living person was to know the exact content of the stimuli, thus rendering the design double-blind. Once the patient was resuscitated from a near-death episode in one of the "marked" rooms, knowledge of the content of the visual stimulus would be assessed." Dr. Holden describes several intermittent and small-scale tests, with no evidence for NDEs yet emerging from these studies. Dr. Holden explains this failure as a consequence an inadequate sample size and/or the tendency of the NDErs to focus on observations that have personal salience.

The special case of childhood NDEs is discussed by Penny Sartori, PhD, in Chapter 9. Dr. Sartori recounts several moving anecdotes to document that such reports can come from developing minds, and she underscores the importance of a compassionate hearing for such children to support healthy development to adulthood.

Dr. Greyson returns with Nancy Evans Bush, MA, in chapter 10, to address the dark side of NDEs. While most NDE accounts range from neutral to ecstatic, some NDErs report sadness, emptiness or horror. Reactions to such experiences range from religious conversion to haunting to dismissal. What distinguishes euphoric from traumatic NDEs is unknown, although the authors offer some tentative speculation. The guidance for the physician here, as with all patients reporting NDEs, is non-judgmental listening.

Chapter 11 begins with the autobiographical NDE of the author, Eban Alexander III, MD, replete with the sort of clinical detail that an academic neurosurgeon can supply. He brings similar detail to his kaleidoscopic NDE associated with a seven-day coma brought on by bacterial meningioencephalitis. His NDE had a strong religious coloration and featured the vision of a mysterious young woman, later discovered to be a sister he had never met. Dr. Alexander grapples here with the limits of our current understanding of physiological consciousness and concludes that the brain does not create consciousness.

In contrast, Kevin Nelson, MD, reaches the opposite conclusion in chapter 12. Here, he attempts to answer the claims of the other authors that our current understanding of brain physiology cannot explain NDEs. Indeed, he points out that patients have reported many of the same phenomena under conditions that are nowhere near death. He bluntly challenges the assertions that NDEs occur at a time when all brain activity ceases and concludes that " . . . the narratives of NDEs fit securely within the framework of conventional neuroscience."

In Chapter 13, Dr. Alexander is given the opportunity to rebut the arguments made by Dr. Nelson. The tone of his approach is set in the first paragraph: "Any evaluation of reports of near-death experiences must involve a mind-set that is suitable to the task . . . and if the mindset is too limited, we compromise our ability to approach the grander truth underlying our observations and attempts to understand them." He goes on to refer to "the simplistic falsehoods of physicalism." The chapter continues with similar unfortunate ad hominems and arguments from authority that are outside of scientific discourse.

All but two of the chapters are reprinted from articles published in *Missouri Medicine*. As with many books comprised of chapters by different authors, there is significant redundancy between the chapters in describing NDE episodes. I didn't find the redundancy distracting.

For the health care provider, the clear message to be able to recognize a NDE; know how to "treat" NDEs, which is essentially with validation, sympathetic listening and referrals to reading and groups that support NDErs. To do that, they need to know what a 'typical" and 'atypical" NDE is and the differential diagnosis to rule out organic disease (e.g., delirium tremens, psychosis, drug reaction, metabolic abnormalities, Charles-Bonnet Syndrome in poorly sighted people).

For a reductionist reader who has never had a NDE of the sort described in this book, the burden of proof for an extra-organic basis for NDE rests with those who argue for that assertion. Three aphorisms apply in evaluating the case made for a science of NDEs:

1. The plural of anecdote is not data. The fact that many people report a similar experience is not grounds to reach for paranormal explanations. As a species, our neurological wiring is similar, so it would be unsurprising to find that our brains react similarly to NDEs and that they would experience near-death in a common archetypal language. What passes for data in NDE research is the acceptance of anecdotes as absolute and literal truth. Science demands independent verification and reproducibility.

2. Extraordinary claims require extraordinary evidence. In this case, the extraordinary claim is that the physiological laws that operate in the human brain cannot be sufficient to account for reports of NDEs. While many remarkable stories are told in these pages, detailed investigation of NDE claims by Keith Augustine and others tell a less compelling tale (https://infidels.org/library/modern/keith_augustine/HNDEs.html). As noted by Augustine (2007), NDE reports are often taken years after the event, and the interviewer

Science of Near-Death Experiences

The book,*The Science of Near-Death Experiences*, brings together a group of papers written by physicians, PhDs, and nurses who have either experienced such events or about others who have done so. The ability for cardio-respiratory resuscitation covers the spectrum of life to near death back to life. These events, even though they cannot be adequately scientifically explained, are very real to those having had such experiences. The events leave indelible effects on their lives, both positively and negatively. The book explores the various scientific and religious thoughts involved and discussions of controversy. I think all physicians and other health care personnel should have an understanding of the issues and be able to council accordingly. I would also recommend its reading not only to medical personnel but to all who administer counseling, both religiously and socially.

Lenard L. Politte, MD, FACP
MSMA member since 1977
Clinical Professor of Medicine
University of Missouri School of Medicine
Columbia, Missouri

Pay for Genomics

I read "Direct-to-Consumer Genomics: Harmful or Empowering?" by Joel Eissenberg (Jan/Feb 2017) with interest. This is a timely and informative article. As the professional medical community and patients adjust to a shift from treating episodes of acute illness to a more preventative approach to health care, genomics will play a very important role. Genomics can lead to collaboration between patients and professionals to optimize pharmaceuticals based on individual variations in metabolism, target increased cancer screening to those at genetic risk and focus preventive health and nutrition strategies for those most likely to develop certain diseases. This article gives a thoughtful overview of the current state of personal genomics and some of the concerns related to making genomic information directly available to the lay community.

John W. Wallis, PhD
Washington University Genome Institute
St. Louis, Missouri

may ask leading questions that result in patterns reflecting the interview questions.

3. Absence of evidence is not evidence of absence. Many or most authors conclude that modern medicine simply hasn't yet delivered a convincing mechanistic explanation to account for NDEs. While this is true, it doesn't *ipso facto* place NDEs outside of natural laws. Many natural phenomena—floods, weather, earthquakes, comets, solar and lunar eclipses—at one time lacked mechanistic explanations and were ascribed to supernatural forces. It is premature to assume that our present state of knowledge of the brain stands for all time.

It is clear that NDErs experience something remarkable and in many cases transformative. However, the burden of proof for an extra-organic mechanism underlying NDEs is not met in this book. How, as scientists, can we account for NDE reports, and how should we study them in a rigorous, objective way is left as an exercise for the reader. That said, Dr. Hagan has showcased the current state of NDE studies, written and edited for the curious, the NDEers and the friends of NDEers. The writing is generally of high quality. It is a work of advocacy, and the editor has done an earnest job of advocating for an extra-physiological mechanism for NDE and for listening sympathetically to those who report NDEs. NDEs are certainly provocative medical curiosities. For those who find in NDE reports intimations of life after death, there is much to fuel that optimism in these pages.

References

- Augustine, K. 2008. Hallucinatory near-death experiences. https://infidels.org/library/modern/keith_augustine/HNDEs.html
- Blackmore, S. Dying to Live: Near-Death Experiences. Buffalo, NY: Prometheus Books, 1993.
- Blackmore, S. 2001. "What can the paranormal teach us about consciousness?" Skeptical Inquirer, March/April
- Hyman, R. "The Ganzfeld Psi Experiment: A Critical Appraisal." *J. Parapsychology.* 1 Sep. 1985, Volume 49: 3-49.
- Milton, J., Wiseman, R. "Does Psi Exist? Lack of Replication of an Anomalous Process at Information Transfer." *Psychological Bulletin.* 1 Jan. 1999, Volume 125, Number 4: 387-391.

Genomic Database Grows

On April 30, 2017, the *Wall Street Journal* published a short article by Peter Huber and Paul Howard announcing "Personalized Medicine is Here."[1] Indeed, personalized medicine has been "here" for over a century, at least since ABO blood types were discovered in 1901 by Karl Landsteiner, who won the Nobel Prize in Physiology or Medicine in 1930 for this landmark in personalized medicine.[2] What the *Wall Street Journal* article referred to was the FDA approval of 23andMe to provide genetic risk reports for ten diseases, including hereditary thrombopenia, celiac disease, and Parkinson's disease. Until now, 23andMe was providing only ancestry information and genetic data without interpretation.

Earlier this year, I wrote in *Missouri Medicine* about 23andMe and the direct-to-consumer marketing of genomics information.[3] The confluence of massive price drops for DNA sequencing technology and high-speed computing has put personal genomics within reach of an American middle class consumer. Companies like 23andMe are providing personalized genomics information without the intermediation of a physician, raising important ethical concerns that I discussed in my article. In particular, the ability to identify risk markers for untreatable and fatal diseases places a major emotional burden on the consumers who are found to carry those risks. Consulting a trained health care professional before testing to prepare for adverse news, as well as after testing to interpret the results, would be highly advisable.

The authors of the *Wall Street Journal* piece consider the FDA approval to be a good thing, going so far as to prophesize: "In fact, the right to know the risks contained in your genetic code will likely become the most fundamental medical right of the 21st century." I was similarly supportive, if somewhat less exuberant, in my *Missouri Medicine* piece. I concluded that the current published literature suggests no lasting harm comes from giving people access to their genomics data and that there is no justification for requiring medical intermediation for access to personal genomic data. I also noted that the current state of medical knowledge has not kept up with the detail with which we can examine genomes. This reality is implicitly acknowledged by the FDA in their highly circumscribed roster of diseases and their admonition that the tests "are intended to provide genetic risk information to consumers," but they "cannot determine a person's overall risk of developing a disease or condition."

It is safe to predict that the list of diseases for which 23andMe and other commercial testing companies will be permitted to provide risk reports will increase rapidly in the coming years. Linking genomics data to clinical outcomes is a central mission of the Veterans Administration "Million Veterans Program," currently the largest genomic database in the world. As the data improve in predictive quality, physicians can anticipate increasingly frequent and detailed requests for help in guiding their patients through the labyrinths of personalized medicine. Keeping pace with the increasing tempo of genetic risk discovery is beyond the capacity of most practitioners. Perhaps the answer to this imminent crisis is 'impersonalized medicine' in the form of IBM's Watson, which is already exploiting natural language processing, question-and-answer technology, and the ability to rapidly sift through mountains of clinical literature to come up with recommendations to guide the physician-patient encounter. With direct-to-consumer genomics data, personalized medicine is a collaboration of patient, physician, and technology.

1. https://www.wsj.com/articles/personalized-medicine-is-here-1493584199
2. http://www.nobelprize.org/nobel_prizes/medicine/laureates/1930/landsteiner-bio.html
3. Eissenberg JC; Direct-to-consumer genomics: harmful or empowering? Missouri Med 2017; 114: 26-32.

Joel C. Eissenberg, PhD
Professor and Associate Dean for Research
Edward A. Doisy Department of Biochemistry and Molecular Biology
Saint Louis University School of Medicine
St. Louis, Missouri

Join Missouri Medicine's Index of Authors



Instructions for Authors
www.msma.org/missouri-medicine

Scientific & Clinical Manuscripts
Departments, Perspectives & Opinions

- Medical-Legal - Legal topics that range from professional liability to ethics.
- Socio-Economic - Articles on legislation, policy, insurance, management, etc.
- Public Health - Reports that cover topical and important public health issues.
- Perspectives - Topics presented by health care professionals with different areas of expertise.
- As I See It - A forum of general interest.
- In the News - Summaries of MSMA business and highlights of members.
- Opinions - Praise, criticism and comments about particular articles, events or issues

Editor John C. Hagan, III, MD | jhagan@bizkc.rr.com
Managing Editor Lizabeth Fleenor | lfleenor@msma.org



There are opportunities for physicians to gain extraordinary experience serving part-time in America's Navy Reserve. And all while maintaining a civilian practice. You can work in any of more than 30 specialty/subspecialty areas – from General Practice to Neurosurgery. Enjoy excellent pay and benefits – including the potential for additional specialty pay of up to $75,000.* And be part of a network that's both patient-focused and world-class.

WANT TO LEARN MORE? CONTACT YOUR NAVY RESERVE MEDICAL RECRUITER TODAY.

800-777-6289 | jobs_stlouis@navy.mil

*Contact a Navy Reserve Medical Recruiter for details. ©2015. Paid for by the U.S. Navy. All rights reserved.

1003DADRM011

AMERICA'S NAVY RESERVE

MSMA Members in the News

Read more about what our members are doing at www.facebook.com/momedical



MSMA member since 2008, Sudhir Batchu, MD, is now seeing patients in Jefferson City.



MSMA is proud to have the new Dean of Saint Louis University School of Medicine, Kevin Behrns, MD, as a member of MSMA.



Alan Buchele, MD, MSMA member since 1997, has opened a new clinic in Pittsburg, KS, in addition to his practice in Joplin.



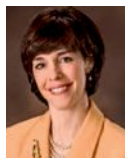
A big congrats goes out to Kevin Byrne, DO, who has been an MSMA member since 2014, for being named Lake Regional Physician of the Year. He is pictured here (right) with John Patton, DO, who presented the award to him and happens to be a new member to MSMA this year.



Raghav Govindarajan, MD, MSMA member since 2013, Columbia, was selected as a 2017 recipient of the Exceptional Mentor Award by the American Medical Women's Association and also the Clerkship Director Teaching Award by the American Academy of Neurology.







Congratulations to Drs. Max Heeb, Debra Koivunen, and Bridget McCandless. These three members were recipients of the Distinguished Service Awards presented by the University of Missouri School of Medicine Alumni Organization. Combined, they represent more than 75 years of membership in MSMA.



We are pleased to announce that Richard Hellman, MD, of North Kansas City, was recently selected to receive his third "Distinguished Reviewer" Award from the American Diabetes Association and the Editorial Board of Diabetes Care. He's been a valued member of MSMA since 1976.



Congratulations, Ramiro Icaza, MD, on practicing at EBO MD in Jackson. His membership support in MSMA since 1984 is greatly appreciated.



Jerry Kennett, MD, of Columbia, MSMA Past President and member since 1980, was chosen by Westminster College officials as this year's Lifetime Achievement Award winner.



Cory Offutt, MD, MSMA member since 2009 during medical school, is now seeing patients in Licking. MSMA thanks him for his service to organized medicine from the start.



The Springfield-Greene County Health Department couldn't have chosen a better person than James Rogers, MD, MSMA member since 1985, as winner of the inaugural Harold K. Bengsch Award for Public Health Collaboration.



Melody Stone, MD, is now seeing patients in Maryville, in addition to St. Joseph. Her membership in MSMA since 2011 is greatly appreciated.

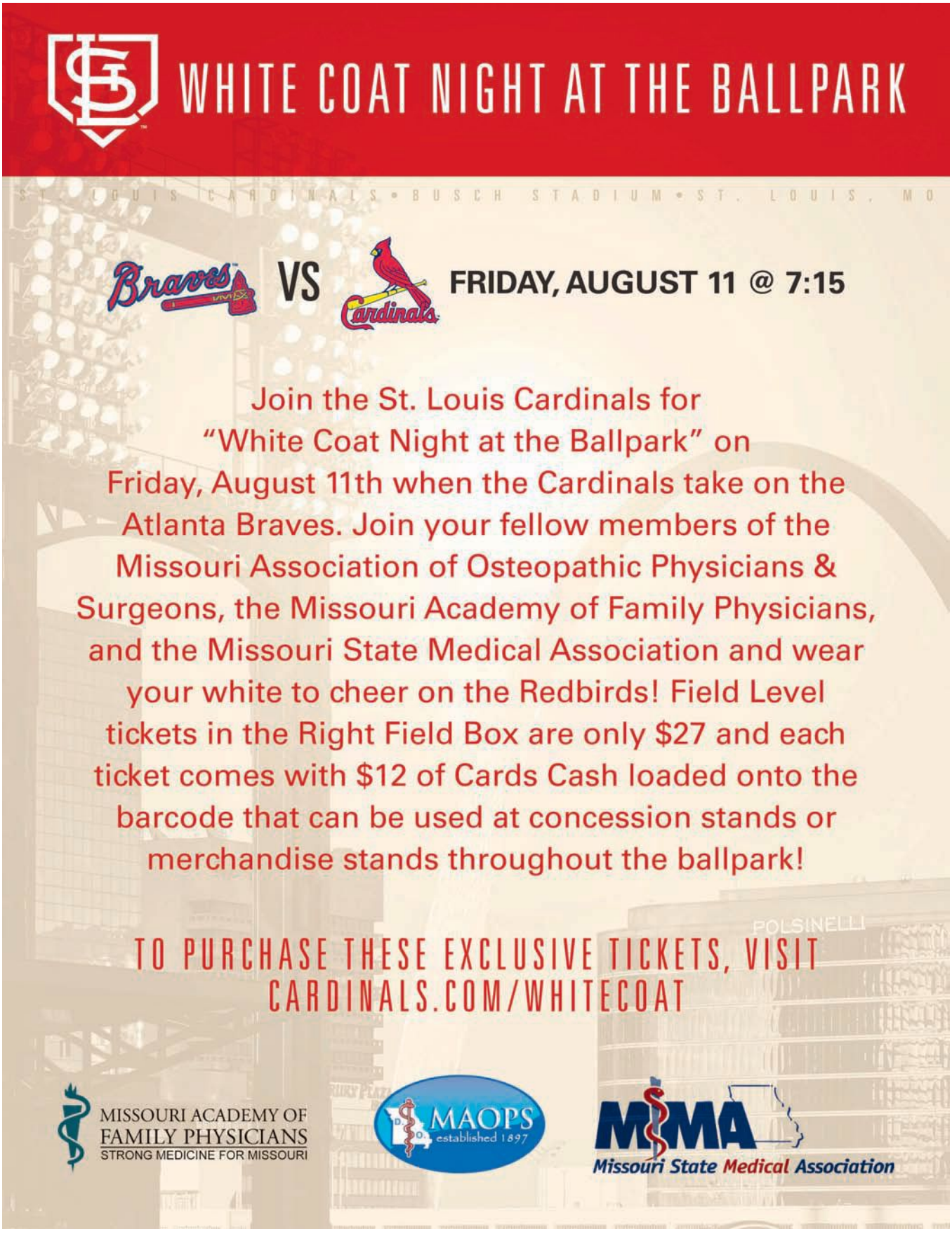


Randall Williams, MD, is the new DHSS Director, and MSMA is pleased to have him as a new member, too. Here he is pictured with Missouri Governor Eric Greitens (left).

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

Errata

In the March/April 2017 issue, Arthur Gale's essay on Adam Hammer, MD: The St. Louis Physician Who Made the First Ever Diagnosis of Coronary Thrombosis and Acute Myocardial Infarction in a Living Patient, was reprinted with permission from *St. Louis Metropolitan Magazine*.


WHITE COAT NIGHT AT THE BALLPARK
ST. LOUIS CARDINALS • BUSCH STADIUM • ST. LOUIS, MO
Braves
VS
Cardinals
FRIDAY, AUGUST 11 @ 7:15
Join the St. Louis Cardinals for "White Coat Night at the Ballpark" on Friday, August 11th when the Cardinals take on the Atlanta Braves. Join your fellow members of the Missouri Association of Osteopathic Physicians & Surgeons, the Missouri Academy of Family Physicians, and the Missouri State Medical Association and wear your white to cheer on the Redbirds! Field Level tickets in the Right Field Box are only $27 and each ticket comes with $12 of Cards Cash loaded onto the barcode that can be used at concession stands or merchandise stands throughout the ballpark!
TO PURCHASE THESE EXCLUSIVE TICKETS, VISIT CARDINALS.COM/WHITECOAT
MISSOURI ACADEMY OF FAMILY PHYSICIANS
STRONG MEDICINE FOR MISSOURI
MAOPS established 1897
MSMA
Missouri State Medical Association

A National Leader in Women's Reproductive Health

by George A. Macones, MD

I am pleased to introduce the Department of Obstetrics and Gynecology at Washington University in St. Louis to the readership of *Missouri Medicine*. Our Department has a rich tradition of providing outstanding clinical care, research, and education.





George A. Macones, MD, MSCE, MSMA member since 2007, is the Mitchell and Elaine Yanow Professor, and Head, Obstetrics and Gynecology Chairman, Department of Obstetrics and Gynecology, Washington University School of Medicine, St. Louis.
Contact: maconesg@wudosis.wustl.edu

The Department is comprised for 46 full-time faculty, representing all specialties and subspecialties of OB/GYN, as well as Divisions of Clinical and Basic Research. Our residency program is accredited for nine residents per year, and is currently ranked eighth nationally by Doximity. We have fellowship training programs in Maternal-Fetal Medicine, Reproductive Endocrinology and Infertility, Gynecologic Oncology, Female Pelvic Medicine, and Reconstructive Surgery, and Pediatric and Adolescent Gynecology.

Our research programs are robust in clinical, basic, and translational research, and our Department ranks sixth nationally for funding for the NIH to OB/GYN departments. Additionally, we are proud to be one of five Prematurity Research Centers funded by the March of Dimes. Our clinical programs are all thriving, and we are looking forward to moving into a new Women and Infants Center on the campus in August 2017. This Center will be transformative in our community, and will serve as a hub for women's health care both locally and regionally.

In the following pages, readers will learn about some of the important activities of our Department:

- Ashley Eskew and Emily Jungheim from our Division of Reproductive Endocrinology and Infertility describe recent improvements in IVF.
- Alison Cahill from our Division of Maternal Fetal Medicine has worked nationally to improve labor management, and she has a beautiful piece that describes recent developments in this area.
- Colleen McNicholas and Tessa Madden from our Division of Family Planning discuss an important women's health issue: access to long-acting reversible contraception.
- Indira Mysorekar for our Division of Basic Research talks about fundamental work, performed in our Department, about mechanisms of Zika transmission in pregnancy.

Again, I am delighted to briefly introduce our Department to readers of *Missouri Medicine*. **MM**

A History of Developments to Improve *in vitro* Fertilization

by Ashley M. Eskew, MD & Emily S. Jungheim, MD

The central goal of infertility treatment has not changed over time—to help build healthy families.





Ashley Eskew, MD, (left), is Fellow, and Emily S. Jungheim, MD, MSCI, (right), is Associate Professor, Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Washington University School of Medicine.
Contact: eskewa@wudosis.wustl.edu

Abstract

Methods of *in vitro* fertilization (IVF) have advanced dramatically since the first IVF baby was born in 1978. Originally yielding single-digit success rates, IVF is now successful in nearly 50% of cases in which the woman is younger than 35 years. Here, we describe the improvements in laboratory techniques and advances in our abilities to manipulate reproductive physiology that have facilitated this improvement. Additionally, we describe efforts to ensure safety standards in this competitive field.

A Brief History of *in vitro* Fertilization

Human reproduction research has always been fraught with both scientific and ethical challenges that initially hindered development of treatments for infertility. However, in the 1960s and 1970s, our understanding of the events in human oocyte fertilization grew to the point that *in vitro* fertilization (IVF) of human oocytes became possible. Ultimately, this knowledge led to the widely acclaimed first live birth of a "test tube baby," Louise Brown, in England in 1978.[1] In this sentinel IVF birth, the mother had a natural menstrual cycle, physicians laparoscopically retrieved a single pre-ovulatory oocyte from her ovary, fertilized it *in vitro*, and then transferred the resulting eight-cell embryo into her uterus.

Three years later, the first IVF baby in the U.S., and the 15th worldwide, was born. In this case, rather than rely on the one oocyte that would be produced naturally, the mother was injected for several days with human menopausal gonadotropin to induce several follicles in the ovary to produce oocytes. After this process, termed controlled ovarian stimulation (COS), physicians laparoscopically retrieved the pre-ovulatory oocytes, fertilized them *in vitro*, and then transferred day 3 or day 5 embryos into the mother's uterus. In 1985, the first IVF baby in Missouri was born to a couple who underwent IVF at Washington University, and delivered at what is now Barnes-Jewish Hospital[2]. Since that time, the practice of IVF has continued to evolve at an astounding pace.

Today, IVF accounts for millions of births worldwide and 1-3% of all births every year in the U.S. and Europe.[3] The increasing demand for fertility treatment drives research and development of technologies to optimize IVF regimens and success. In the vast majority of IVF cases, infertile couples undergo treatment to conceive a genetically-related child. However, couples are also undergoing IVF so that their embryos can be genetically tested to decrease transmission of single-gene mutations associated with morbidity.[4,5] Additionally, use of donor sperm and oocytes is becoming increasingly common, and women who are unable to carry a pregnancy are now able to use gestational carriers.

Below, we highlight several of the major milestones that have made IVF an extremely effective tool to care for these patients.

Controlled Ovarian Stimulation

The initial studies of IVF conducted in women undergoing natural menstrual cycles yielded on average 0.7 oocytes per retrieval and a 6% per cycle pregnancy rate.[6] In the 1980s, researchers at the Jones Institute in Norfolk, Virginia, began injecting women with gonadotropins to stimulate multiple ovarian follicles to produce oocytes. These oocytes were then fertilized *in vitro,* and the healthiest appearing embryos were implanted in the woman's uterus. This advent of controlled ovarian stimulation (COS) improved average oocyte yields to 2.1–2.6 and average pregnancy rates to 23.5% per cycle in 1982 and 30% in 1983.[4,6] Initially, human chorionic gonadotropin (hCG) was used to trigger ovulation because it is physiologically homologous to luteinizing hormone, which increases rapidly in a natural cycle to trigger ovulation. In early IVF procedures, an important concern was premature ovulation, which would make retrieving oocytes impossible despite careful and labor-intensive COS. However, two innovations to IVF practice, including the use of gonadotropin releasing hormone (GnRH) agonists in the 1980s and of GnRH antagonists in 2001, made it possible to prevent premature ovulation and reliably control oocyte retrieval. Several different medication regimens exist, but all follow the same concept: injectable medications upregulate endogenous hormones to recruit multiple ovarian follicles to yield multiple oocytes at retrieval.[7]

Ovarian Hyperstimulation Syndrome

Two problems occurred as a result of injections of supraphysiologic doses of gonadotropins. First, to improve the chances that a woman would become pregnant with one fetus that would survive to term, physicians began fertilizing multiple oocytes and implanting multiple embryos. This practice sometimes results in women carrying twins and even higher order multiples of fetuses, putting the fetuses at risk of low birth weight and preterm birth. Second, the most common and severe iatrogenic complication of ovarian stimulation is ovarian hyperstimulation syndrome (OHSS). OHSS occurs when the ovaries are excessively stimulated and then either triggered with injected hCG to stimulate ovulation or by the endogenous increase in hCG that occurs when a woman gets pregnant. OHSS is characterized by hemoconcentration from leaky vessels and third spacing of fluid that leads to ascites and electrolyte abnormalities. Symptoms range from mild abdominal distention to renal failure and death as a result of thromboembolic phenomena or end-organ damage. Despite extensive research, the exact pathogenesis of this syndrome remains unclear but is noted to have increasing incidence with an increasing number of developing follicles and elevated levels of estradiol, which is made by the ovarian follicles. To address this concern, in 1979, physicians began monitoring COS by serially measuring the serum estradiol levels and transvaginally assessing ovarian follicles to better monitor for risk factors. Identifying patients at risk allowed physicians to take preventative measures such as adjusting medications appropriately and more frequently monitoring symptoms.[8-10]

The current limitation to COS is that it requires time and labor-intensive monitoring. Additionally, gonadotropin is rapidly degraded in the body, so women have to undergo daily injections for 10 days. However, scientists such as Washington University professor Irving Boime are developing long-acting forms of gonadotropins that may one day reduce the number of required injections and the amount of monitoring.[11]

Embryo Culture

Since the early days of *in vitro* embryo culture, efforts have been directed toward improving the culture system to optimize embryo development and increase the number of high-quality embryos available for transfer. Initially, embryo culture media was fashioned from media intended for culture of somatic cells and supplemented with serum.[12,13] Numerous researchers have optimized media for embryo metabolism and development by supplementing it with various macromolecules, altering the energy substrate composition and amino acid balance, and adding growth factors. For many years, laboratories made their own culture media, but now it is commercially produced, resulting in improved consistency and quality control between different laboratories and practices.[14] Much attention will undoubtedly continue to be directed toward refining culture media to further optimize embryo development and clinical outcomes.

Improvements in embryo culture over the years have allowed us to extend *in vitro* culture of embryos to the blastocyst stage, permitting detailed morphologic assessment of embryos and better selection of embryos for transfer. This has been key to our ability to maximize pregnancy rates in IVF while minimizing the number of embryos transferred and thus minimizing the risk of multiple gestations. Extended culture has also allowed us to perform preimplantation genetic testing of embryos, a process that is best applied when the embryos are far enough developed in culture to sustain removal of several cells for genetic testing.

Improved embryo culture, in combination with improved COS, allow us to generate more embryos than are initially transferred. Today, approximately 50% of IVF cycles performed via COS in our center result in the creation of excess embryos of good quality that can be frozen for the patient's future use. Thus, the woman can often

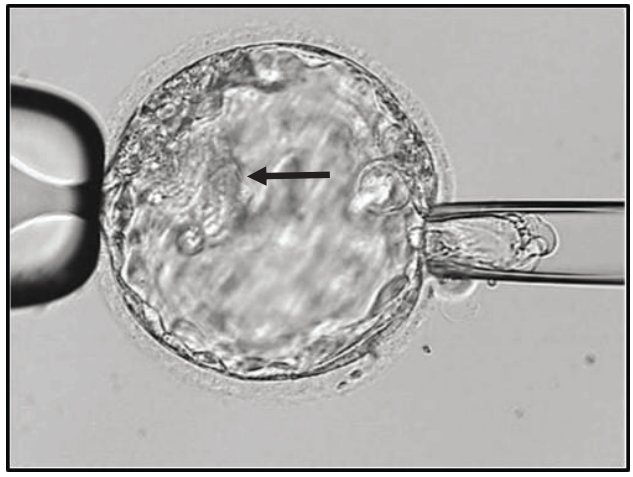
avoid further COS injections and invasive oocyte retrieval. This process is now efficient enough that women facing gonadotoxic treatments such as chemotherapy can preserve future fertility by undergoing COS and having their oocytes retrieved and frozen.

Preimplantation Genetic Testing

Before 1990, options to prevent transmission of genetic defects were limited to invasive techniques such as chorionic villus sampling and amniocentesis, after which termination could be offered if the fetus was found to be affected. Throughout the 1990s, as surplus embryos became available, techniques were developed to utilize the time between days three and five after oocyte fertilization as an opportunity to identify which embryos were affected by chromosomal imbalance or a specific gene disorder before transfer to the uterus.[15] The initial technique was to screen cleavage-stage embryos by fluorescence in situ hybridization, but that was later found to lower birth rates and cause more harm than good.[16,17] Now, we biopsy cells from the trophectoderm of blastocyst-stage embryos, (see Figure 1), and perform one of two types of preimplantation genetic testing. The first, preimplantation genetic diagnosis (PGD) applies when one or both genetic parents carry a mutation, such as those linked to Huntington's disease or cystic fibrosis, and testing is performed to ensure the single-gene trait has not been passed to the embryo. PGD is commonly done by polymerase chain reaction as this method is more accurate than fluorescence in situ hybridization and allows us to obtain sufficient genetic material for evaluation from only a few cells, thus decreasing harm. Although this process requires vitrification of the embryo to allow sufficient time for analysis, recent studies suggest that cycles using frozen and fresh embryos are nearly equally successful, making this a feasible option for couples.[18,19] Importantly, PGD does not appear to increase the risk of obstetric complications, including fetal malformation related to the biopsy procedure.[20]

The other type of testing is preimplantation genetic screening (PGS), which is used to look for embryonic aneuploidy. Although not routinely recommended as a standard of care in IVF as it has not been shown to improve outcomes in low-risk patients, PGS can be beneficial in a select patient population. PGS offers prognostic value for patients who are deemed high risk for embryo aneuploidy (abnormal number of chromosomes), including those of advanced maternal age (≥35 years old) and those diagnosed with recurrent pregnancy loss. Patients should receive genetic counseling before electing PGS or PGD to ensure they fully understand the risks and limitations of these techniques. Genetics will certainly continue to play a large role in shaping the future of practice in reproductive medicine, and although innumerable advances have been made, there is still work to be done to discern how PGS and PGD are best applied in IVF.

Figure 1: A pipette (left) holding a blastocyst near the inner cell mass (arrow) while a needle (right) biopsies trophectoderm cells.



Reducing the Risk of Multiple Gestations Associated with IVF

In the early years of IVF, several embryos were implanted with the hope that at least one would survive, often leading to multiple births. For example, in 2004, 36.6% of women younger than 35 years of age undergoing IVF had a live birth after being implanted with, on average, 2.5 embryos per cycle. As a result, 32.7% of the women delivered twins and 4.9% delivered triplets. Improvements in embryo culture and cryopreservation techniques, in addition to guidelines regarding the number of embryos to be transferred, (see Table 1), have reduced the quantity but increased the quality of embryos transferred, thus reducing the risk of multiples. Thus, in 2014, 48.7% of women younger than 35 undergoing

Table 1
Recommended limits on the numbers of embryos to transfer

Age (years)	< 35	35-37	38-40	41-42
Prognosis				
Cleavage Stage Embryos				
- Favorable	1	1	≤ 3	≤ 4
- All others	≤ 2	≤ 3	≤ 4	≤ 5
Blastocysts				
- Euploid	1	1	1	1
- Favorable	1	1	≤ 2	≤ 3
- All others	≤ 2	≤ 2	≤ 3	≤ 3

Adapted from ASRM Committee Opinion: Limits on number of embryos to transfer. Fertil Steril 2017.

IVF had a live birth—11.8% of those births were twin deliveries, and 0.4% were triplet deliveries. This reduction in multiples is largely the result of minimizing the number of embryos transferred to just one.

IVF Outcomes Reporting

Efforts to track IVF activity and outcomes started in 1985 and were initially voluntary. However, since Congress passed the Fertility Clinic Success Rate and Certification Act in 1992, clinics have been required to report IVF outcomes data to the Centers for Disease Control (CDC) to provide transparency and protect patients from false claims of IVF success.[21,22] Public reporting of outcomes has become increasingly viewed as a promising strategy to improve health care outcomes.[23] IVF success rates for all reputable clinics are now available on the web from both the CDC and the Society for Assisted Reproductive Technology (SART), an affiliate of the American Society for Reproductive Medicine.[22,24] SART is an excellent resource for both patients and physicians that provides ample information including detailed guides of various ART protocols and procedures, as well as success rates of individual technologies at practices across the country. Their first annual publication was in 1988 and has been increasingly used to help guide continued improvement and evaluation of ART programs. SART reporting differs from that of the CDC in that it includes cycle start information, whereas CDC data only offers outcome statistics for completed cycles.[22,24] More than 90% of clinics are SART members, and the SART registry reports data on more than 95% of ART treatment cycles in the U.S. Between the two reporting systems, a large amount of information is available allowing for detailed analysis of data for transparency and continued opportunities for improvement of patient outcomes. SART also makes it easy for patients to understand the quality of the IVF lab they are entrusting their care to—one of the greatest predictors in their chances of achieving a live birth through IVF.

Conclusion

The field of reproductive endocrinology and infertility has progressed at an astounding pace over the past three decades as we have developed new techniques, medications, testing, and strategies to treat infertile couples. Now, many previously sterile couples are able to conceive, carry, and deliver healthy children of their own. Despite the major advances described here, much attention will remain devoted to assessing the long-term outcomes of the children born as a result of IVF; the oldest child of IVF is merely 38 years old. The central goal of infertility treatment has not changed over time—to help build healthy families.

References

1. Steptoe, PC. Edwards RG. Birth after reimplantation of a human embryo. The Lancet. 1978;312:366.
2. http://www.upi.com/Archives/1985/01/25/First-test-tube-babies-born-in Missouri/8289475477200/
3. Chandra A, Copen CE and Stephen EH (2014) Infertility Service Use in the United States: Data from the National Survey of Family Growth, 1982-2010. National Health Statistics Reports; no 73. Hyattsville, MD: National Center for Health Statistics.
4. Beall SA, DeCherney A. History and challenges surrounding ovarian stimulation in the treatment of infertility. Fertil Steril. 2012;97:795-801.
5. Wang J, Sauer MV. In vitro fertilization (IVF): a review of 3 decades of clinical innovation and technological advancement. Therapeutics and clinical risk management 2006;2:355-64.
6. Edwards RG, Steptoe PC, Purdy JM. Establishing full-term human pregnancies using cleaving embryos grown in vitro. Br J Obstet Gynaecol, 1980;87:737-56.
7. Fritz MA, Speroff L. Clinical Gynecology Endocrinology and Infertility. 8th ed. 2011.
8. Edwards RG, Steptoe PC. Current status of in-vitro fertilisation and implantation of human embryos. Lancet, 1983;2:1265-9.
9. Ylostalo P, Ronnberg L, Jouppila P. Measurement of the ovarian follicle by ultrasound in ovulation induction. Fertil Steril 1979;31:651–5.
10. Smith DH, Picker RH, Sinosich M, Saunders DM. Assessment of ovulation by ultrasound and estradiol levels during spontaneous and induced cycles. Fertil Steril 1980;33:387–90.
11. Fauser BC, Mannaerts BM, Devroey P, Leader A, Boime I, Baird DT. Advances in recombinant DNA techology: corifollitropin alfa, a hybrid molecule with sustained follicle-stimulating activity and reduced injection frequency. Hum Reprod Update. 2009 15(3):309-21.
12. Quinn P, Kerin J, Warnes G. Improved pregnancy rate in human in vitro fertilization with the use of a medium based on the composition of human tubal fluid. Fertil Steril 1985;44:493–8.
13. Menezo Y, Testart J, Perrone D. Serum is not necessary in human in vitro fertilization, early embryo culture, and transfer. Fertil Steril 1984;42:750–5.
14. Swain JE, Carrell D, Cobo A, Meseguer M, Rubio C, Smith GD. Optimizing the culture environment and embryo manipulation to help maintain embryo developmental potential. Fertil Steril 2016;105:571-87.
15. Handyside AH, Kontogianni EH, Hardy K, et al. 1990. Pregnancies from biopsied human preimplantation embryos sexed by Y-specific DNA amplification. Nature, 344:768-70.
16. Fritz MA. Perspectives on the efficacy and indications for preimplantation genetic screening: where are we now? Hum Reprod 2008;23:2617–21.
17. Mastenbroek S, Twisk M, van der Veen F, Repping S. Preimplantation genetic screening: a systematic review and meta-analysis of RCTs. Hum Reprod Update 2011;17:454–66.
18. Preimplantation genetic testing: a Practice Committee opinion. Fertil Steril. 2008:90:S136-S143
19. Schoolcraft WB, Treff NR, Stevens JM, Ferry K, Katz-Jaffe M, Scott RT Jr. Live birth outcome with trophectoderm biopsy, blastocyst vitrification, and single-nucleotide polymorphism microarray-based comprehensive chromosome screening in infertile patients. Fertil Steril 2011;96:638–40.
20. Beukers F, van der Heide M, Middelburg KJ et al. Morphologic abnormalities in 2-year-old children born after in vitro fertilization/intracytoplasmic sperm injection with preimplantation genetic screening: follow- up of a randomized controlled trial. Fertil Steril 2013; 99(2):408-413.
21. The Fertility Clinic Success Rate And Certification Act (FCSRCA) of 1992 (Wyden Law) Requirements. Federal Register 2000;65:53310–6.
22. Centers for Disease Control and Prevention. Assisted reproductive technology (ART). Available at: http://www.cdc.gov/art/artdata/index.html, Accessed: 8/15/2016
23. U.S. Department of Health and Human Services Strategic Plan. Available at: http://www.hhs.gov/secretary/about/priorities/strategicplan2014-2018.pdf, Accessed: 8/15/2016
24. www.sart.org

Disclosure

None reported. **MM**

Identifying the Best Way to Manage Labor

by Alison G. Cahill, MD

By identifying the optimal management strategy for the second stage of labor, we hope to make a small contribution to reducing the rates of iatrogenic operational vaginal and cesarean deliveries.



Alison G. Cahill, MD, MSCI, MSMA member since 2016, is Director, Division of Maternal Fetal Medicine, Associate Professor, Department of Obstetrics and Gynecology, Washington University School of Medicine.
Contact: cahilla@wudosis.wustl.edu

Abstract

The second stage of labor, defined as the interval from complete cervical dilation through delivery of the fetus, is the most physiologically demanding period of labor for both the mother and the fetus. Additionally, prolongation of this stage can lead to operative deliveries, which are associated with increased risks of adverse neonatal and maternal outcomes. However, the optimal technique for managing maternal pushing during this stage, immediate or delayed pushing, is unknown. Washington University School of Medicine is addressing this question by conducting a large, multi-site, randomized controlled trial that will assess both maternal and neonatal outcomes. Completion is expected by 2018.

The Need for Modern Information to Manage Labor

Over three million women labor and deliver annually in the United States.[1] Not surprisingly, the most frequent care that obstetricians provide is managing labor. Unfortunately, despite the frequency of labor and need for labor management, many aspects of the best practices to optimize outcomes for women and their infants are unknown. The most physiologically demanding period of labor for both the mother and the fetus, and thus the period most in need of management, is the second stage, defined as the interval from complete cervical dilation through delivery of the fetus. For the mother and baby, a prolonged second stage of labor can lead to numerous negative outcomes as described below. Additionally, a prolonged second stage of labor is a common indication for either operative vaginal delivery or a cesarean delivery, both of which have negative consequences for the mother and infant, as described below. Despite the huge impact labor management can have on mode of delivery and outcomes, the optimal technique for managing maternal pushing during the second stage of labor remains unknown.

Historically, when the second stage of labor began (at 10 centimeters cervical dilation), women involuntarily pushed to deliver their infants. However, today, regional anesthesia (which is used by more than 85% of women delivering in a hospital setting) successfully blunts both maternal labor pain and the reflexive urge to push. Thus, management of the second stage of labor has become care-giver driven. The two most common approaches to second stage management are delayed pushing or immediate pushing. In delayed pushing, the baby is allowed to descend spontaneously and the mother does not begin pushing until the baby's head is visible or she feels an irresistible urge to push. In practice, this delay is approximately one hour.[2] In immediate pushing, the mother is instructed to initiate pushing with uterine contractions once complete cervical dilation occurs.

Although limited research has been done in this area, the largest randomized trial, of 1,862 nulliparous women, was reported in 2000, and showed that delayed pushing was associated with reduced composite birth morbidity.[3] Given these findings, the Association of Women's Health, Obstetrics, and Neonatal Nurses published guidelines in 2008 recommending delayed pushing until the second stage of labor unless contraindicated by maternal or fetal condition. Since then, delayed pushing has gained widespread use; nationwide, an estimated 50% of practitioners practice delayed pushing with their patients.

Unfortunately, more up-to-date data do not fully support use of delayed pushing. For example, several small studies have compared delayed and immediate pushing, and reported results that are contradictory with regard to benefit and harm to the neonate and mother.[2] Additionally, the study published in 2000 included delivery methods that are no longer used in modern obstetric practice in the United States, such as use of mid-pelvic rotational forceps.[3] We recently conducted a meta-analysis of available studies and found that, among high-quality trials, delayed pushing did not improve the spontaneous vaginal delivery rate but did prolong duration of the second stage.[2] Additionally, a large observational study conducted by our group at the Washington University School of Medicine indicated that delayed pushing is associated with worse labor outcomes than immediate pushing.[4] Given these conflicting reports, and the importance of the second stage of labor, we need high-quality data about which management strategy results in the best outcomes for mothers and babies.

Maternal and Neonatal Morbidities Associated with the Second Stage of Labor

Physiological Alterations and Maternal Morbidity Risk

Although most women of child-bearing age are healthy, they are at significant risk of maternal morbidity and even mortality during the labor and delivery process. Pregnancy is characterized by a 50% increase in cardiac output and effective circulating blood volume. At the onset of labor, and then progressively during the first stage of labor as uterine contraction frequency and intensity increase, the cardiovascular system is further challenged. In the second stage, these cardiovascular demands are further challenged by maternal expulsive efforts, generating significant intra-abdominal and thoracic pressures and limiting blood delivery to the uterus and placenta. Further, as demonstrated by several large cohort studies, the risks of maternal infection, hemorrhage, and laceration increase with each hour of second stage duration.[5-7]

Pelvic Floor Injuries

Up to 25% of women who deliver suffer from pelvic floor injuries, specifically injury to the levator ani muscle (LAM).[8] LAM injury is strongly associated with fecal incontinence and pelvic organ prolapse years after delivery,[9,10] which can negatively affect quality of life.[11] Because LAM injuries go undetected, the labor management strategies, and specifically those for the second stage, that are associated with an increased risk of LAM injuries are unknown. Thus, to improve long-term outcomes, it is important to understand the association between labor management strategies and LAM injury, risk of fecal and urinary incontinence, risk of prolapse, and quality of life.

Neonatal Morbidities

Fetal gas exchange is completely reliant on maternal blood flow and delivery of oxygenated blood to the placenta. It is not surprising then, that otherwise healthy term infants born from the second stage of labor have a lower blood pH than those delivered by cesarean during the first stage of labor.[12] Thus, the risks of neonatal acidemia (low pH and elevated base excess), neonatal depression, and significant morbidities requiring intensive care all increase with increasing duration of the second stage of labor.[6,13,14]

Neonatal and Maternal Morbidities from Operative Deliveries

A prolonged second stage of labor can lead to operative delivery, defined as cesarean or operative vaginal delivery. Operative deliveries now occur in 37% of births[15] and are associated with increased risk of most labor and delivery-related complications for the mother, including maternal hemorrhage, infection, severe perineal lacerations, thromboembolism, and even death. Additionally, when a woman has a cesarean delivery, her risk of delivery by cesarean in future pregnancies is dramatically elevated.[16] For the baby, operative deliveries are associated with neonatal respiratory depression, low Apgar scores, acidemia, birth trauma, and neonatal intensive care admissions.[17]

Improving Practice through Research

Given the importance of the second stage of labor, the Washington University School of Medicine Maternal-Fetal Medicine division is conducting a clinical trial to identify the best strategies for labor management.[18] Specifically, Drs. Alison Cahill and Methodius Tuuli are leading the largest trial, to date, among laboring women in the United States. This randomized clinical trial seeks to define which technique for maternal pushing in the second stage of labor optimizes outcomes for women and

their infants. This trial is accruing 3,200 patients at four sites, Washington University in St. Louis, University of Alabama in Birmingham, University of Pennsylvania, and Oregon Health and Science University. Women are being randomized to either push immediately upon reaching 10 cm dilation or to wait 60 minutes before pushing.

Our delivery outcomes will include length of the second stage of labor, length of time spent pushing, and operative delivery rates. Our neonatal outcomes will include umbilical cord arterial acidosis, suspected neonatal sepsis, respiratory distress, transient tachypnea, meconium aspiration with pulmonary hypertension, hypoxic-ischemic encephalopathy, hypoglycemia, and need for hypothermia treatment. Our maternal outcomes will include the following: the rate of spontaneous vaginal delivery in nulliparous women, objective measures (such as ultrasound imaging) of damage to the puborectalis component of the LAM and the anal sphincter complex, and vaginal anatomic measures and patient-reported outcomes related to pelvic floor injury including urinary and fecal incontinence and pelvic organ prolapse symptoms. This study, which we will complete by 2018, will provide level 1 evidence about the optimal management strategy for the second stage of labor.

Conclusions and Broader Perspective

The 100% increase in the cesarean delivery rate in the last 30 years (from 16.5% in 1980 to 32.8% in 2010)[19] has had a significant population and public health impact, as operative deliveries are linked directly and indirectly to increases in virtually all child-birth related morbidities. However, because the reasons for this increase have been multifactorial, reducing the national rate of cesarean deliveries will require a series of discoveries, each contributing evidence for improved labor and delivery care. By identifying the optimal management strategy for the second stage of labor, we hope to make a small contribution to reducing the rates of iatrogenic operational vaginal and cesarean deliveries in the U.S. If our trial hypothesis, that immediate pushing leads to better outcomes than delayed pushing, proves correct, then we anticipate that widespread adoption of immediate pushing would reduce the rate of iatrogenic cesarean and operative vaginal deliveries by 5%, resulting in approximately 12,000 fewer second-stage cesareans and 48,000 fewer operative vaginal deliveries performed, with an estimated cost savings of approximately $200 million each year.[1,20] We are excited that the Washington University Maternal-Fetal Medicine group will help define the optimal strategy to manage the second stage of labor and further improve the way we care for mothers and their infants.

References

1. Hamilton BE, Martin JA, Ventura SJ. Births: preliminary data for 2009. Natl Vital Stat Rep. 2010;59(3):1-19.
2. Tuuli MG, Frey HA, Odibo AO, Macones GA, Cahill AG. Immediate compared with delayed pushing in the second stage of labor: a systematic review and meta-analysis. Obstetrics and gynecology. 2012;120(3):660-668.
3. Fraser WD, Marcoux S, Krauss I, Douglas J, Goulet C, Boulvain M. Multicenter, randomized, controlled trial of delayed pushing for nulliparous women in the second stage of labor with continuous epidural analgesia. The PEOPLE (Pushing Early or Pushing Late with Epidural) Study Group. American journal of obstetrics and gynecology. 2000;182(5):1165-1172.
4. Frey HA, Tuuli MG, Cortez S, et al. Does delayed pushing in the second stage of labor impact perinatal outcomes? American journal of perinatology. 2012;29(10):807-814.
5. Le Ray C, Audibert F, Goffinet F, Fraser W. When to stop pushing: effects of duration of second-stage expulsion efforts on maternal and neonatal outcomes in nulliparous women with epidural analgesia. American journal of obstetrics and gynecology. 2009;201(4):361.e361-367.
6. Rouse DJ, Weiner SJ, Bloom SL, et al. Second-stage labor duration in nulliparous women: relationship to maternal and perinatal outcomes. American journal of obstetrics and gynecology. 2009;201(4):357.e351-357.
7. Allen VM, Baskett TF, O'Connell CM, McKeen D, Allen AC. Maternal and perinatal outcomes with increasing duration of the second stage of labor. Obstetrics and gynecology. 2009;113(6):1248-1258.
8. Albrich SB, Laterza RM, Skala C, Salvatore S, Koelbl H, Naumann G. Impact of mode of delivery on levator morphology: a prospective observational study with three-dimensional ultrasound early in the postpartum period. Bjog. 2012;119(1):51-60.
9. Heilbrun ME, Nygaard IE, Lockhart ME, et al. Correlation between levator ani muscle injuries on magnetic resonance imaging and fecal incontinence, pelvic organ prolapse, and urinary incontinence in primiparous women. American journal of obstetrics and gynecology. 2010;202(5):488.e481-486.
10. Lewicky-Gaupp C, Brincat C, Yousuf A, Patel DA, Delancey JO, Fenner DE. Fecal incontinence in older women: are levator ani defects a factor? American journal of obstetrics and gynecology. 2010;202(5):491.e491-496.
11. Handa VL, Zyczynski HM, Burgio KL, et al. The impact of fecal and urinary incontinence on quality of life 6 months after childbirth. American Journal of Obstetrics & Gynecology.197(6):636.e631-636.e636.
12. Gilstrap LC, 3rd, Hauth JC, Hankins GD, Beck AW. Second-stage fetal heart rate abnormalities and type of neonatal acidemia. Obstetrics and gynecology. 1987;70(2):191-195.
13. Altman MR, Lydon-Rochelle MT. Prolonged second stage of labor and risk of adverse maternal and perinatal outcomes: a systematic review. Birth (Berkeley, Calif). 2006;33(4):315-322.
14. Saunders NS, Paterson CM, Wadsworth J. Neonatal and maternal morbidity in relation to the length of the second stage of labour. Br J Obstet Gynaecol. 1992;99(5):381-385.
15. Ali UA, Norwitz ER. Vacuum-assisted vaginal delivery. Reviews in obstetrics & gynecology. 2009;2(1):5-17.
16. Barber EL, Lundsberg LS, Belanger K, Pettker CM, Funai EF, Illuzzi JL. Indications contributing to the increasing cesarean delivery rate. Obstetrics and gynecology. 2011;118(1):29-38.
17. Miller JM, Jr. Maternal and neonatal morbidity and mortality in cesarean section. Obstet Gynecol Clin North Am. 1988;15(4):629-638.
18. Cahill AG, Tuuli MG. Labor in 2013: the new frontier. American journal of obstetrics and gynecology. 2013;209(6):531-534.
19. Duttaroy AK. Transport of fatty acids across the human placenta: a review. Progress in lipid research. 2009;48(1):52-61.
20. Allen VM, O'Connell CM, Farrell SA, Baskett TF. Economic implications of method of delivery. American journal of obstetrics and gynecology. 2005;193(1):192-197.

Disclosure

None reported. **MM**

Meeting the Contraceptive Needs of a Community: Increasing Access to Long-Acting Reversible Contraception

by Colleen McNicholas, DO & Tessa Madden, MD

The contraceptive and family planning needs of our patients are diverse, but with attention to reducing barriers to the most highly effective contraceptive methods, we can better help women plan and space their pregnancies.





Colleen McNicholas, DO, MSCI, (left), Assistant Professor, Division of Family Planning, and Tessa Madden, MD, MPH, (right), Associate Professor, Director, Division of Family Planning; both in the Department of Obstetrics and Gynecology, Washington University School of Medicine.
Contact: mcnicholasc@wudosis.wustl.edu

Abstract

To control their reproductive lives, women must have access to all contraceptive methods including the most effective reversible methods, intrauterine devices, and implants. The Contraceptive CHOICE Project, a study of 9,256 women in St. Louis, showed that when barriers to contraception are removed, many women choose intrauterine devices and implants, substantially reducing rates of unintended pregnancy and abortion. This article discusses strategies we learned from the CHOICE Project to improve uptake of the most effective contraceptive methods.

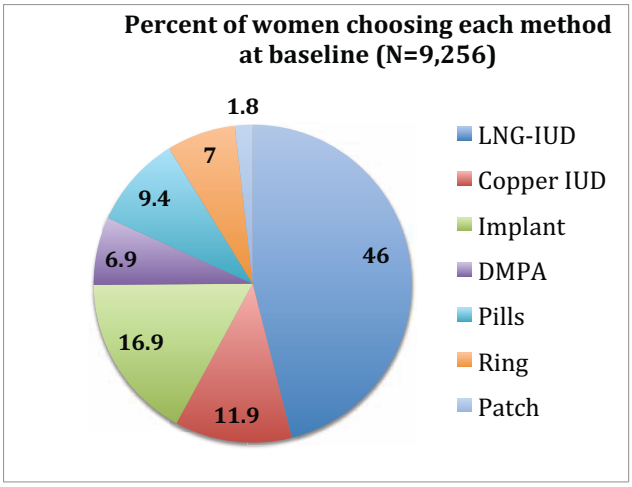
The Public Health Challenge of Unintended Pregnancy

The United States has the highest unintended pregnancy rates among developed nations: more than 45% of pregnancies are unintended nationally.[1] In Missouri in 2010, 51% of all pregnancies were unintended with a public cost of $518 million. [1] Approximately one in three women will undergo an abortion during their lifetimes.[2] Unintended and teen pregnancy can result in reduced educational or employment attainment as well as increased risk of poverty and poor health outcomes. Although the U.S. has made significant strides in reducing teen pregnancy, it still leads developed nations with a teen pregnancy rate of 52.4 pregnancies per 1,000 15-19 year-olds.[3] In surveys, U.S. women report that their ideal family includes just two children,[4] meaning that women spend nearly three decades of their reproductive lives trying to avoid or prevent pregnancy. Additionally, regardless of desired family size, most women and families report that timing and spacing of their pregnancies is important, citing a variety of medical, social, and economic reasons.[5-7] The inconsistency between the actual rates of unintended pregnancy and women's ideal reproductive life plans suggests that women are not receiving the contraceptive care they want and need.

Delivery of Contraceptive Care

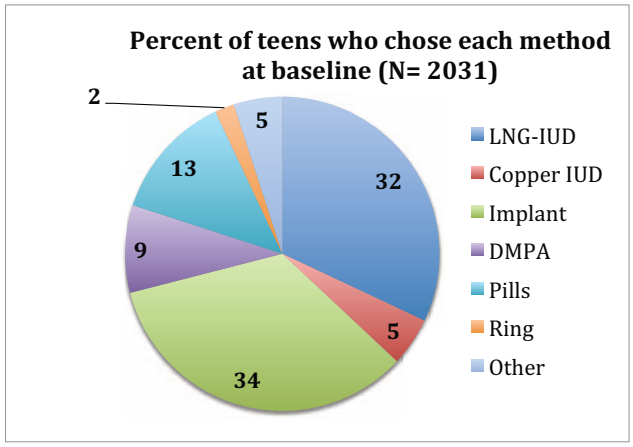
The provision of contraceptive care has long been the role of the obstetrician-gynecologist and the family medicine practitioner. However, assessing family planning needs is the responsibility of all medical professionals, especially those treating reproductive-age

Figure 1: Distribution of Contraceptive Method Choice at Baseline in the Contraceptive CHOICE Project.



DMPA, depot medroxyprogesterone acetate injection; IUD, intrauterine device; implant, levonorgestrel implant; pills, oral contraceptive pills; ring, vaginal ring

Figure 2: Distribution of Contraceptive Method Choice at Baseline for Teen in the Contraceptive CHOICE Project.



women with chronic medical conditions. Historically, both women and clinicians have chosen oral contraceptive pills (OCPs), with little discussion about the appropriateness of the methods or discussion of other options. Because OCPs require daily compliance, the failure rate can be as high as 9% with typical use. In contrast, the most effective reversible methods, long-acting reversible contraceptives (LARCs), including intrauterine devices (IUDs) and the contraceptive implant, are "forgettable" and have typical use failure rates of less than 1%. Although use of LARCs has increased from 2.6% to 11.7% over the last few years, OCPs, female sterilization, and male condoms remain the most frequently used methods in the U.S. at 25.9%, 25.1%, and 15.3% respectively.[8] Increased awareness about and access to LARCs can increase the use of these methods.

The Contraceptive CHOICE Project

The Contraceptive CHOICE Project, a prospective cohort study of 9,256 reproductive-age women in the St. Louis area, illustrated a model of contraceptive care that can help women achieve their reproductive life goals. The project was designed to evaluate the impact of eliminating common barriers such as education, access, and cost on the uptake of LARCs. The CHOICE Project enrolled a racially and economically diverse group of women aged 14–45. Participants underwent a standardized contraceptive counseling session with a trained non-clinician in which all available reversible methods were discussed in decreasing order of effectiveness (e.g., IUD and implants first and condoms last). Participants chose and received their desired method on the day of enrollment at no out-of-pocket cost. We followed participants for two to three years depending on the time of enrollment. Participants were allowed to switch methods if they were dissatisfied with their initial chosen method. Study outcomes included method choice, continuation, satisfaction, and rates of unintended pregnancy and abortion.

Among the 9,256 women enrolled, 75% chose a LARC method at enrollment; 46% of women chose the levonorgestrel IUD, 12% chose the copper IUD, and 17% chose the etonogestrel implant (see Figure 1).[9] Women chose LARC methods at over 10 times the rate of the general U.S. population, and LARC users reported higher rates of continuation and satisfaction than non-LARC users.[10] Additionally, similar to adult women in our cohort, more than 70% of adolescent girls chose a LARC method (see Figure 2), and their rates of continuation and satisfaction were similar to older women. [11,12] This finding should reassure clinicians that when young women choose a long-acting method, they are likely to be satisfied with and continue use of the method.

The CHOICE Project validated the superior effectiveness of LARC; users of shorter-acting methods such as OCPs, the contraceptive patch, and the vaginal ring were 22 times more likely to experience an unintended pregnancy than IUD and implant users.[13]

Although we found no difference in unintended pregnancy by age among LARC users, we found that OCP, contraceptive patch, and vaginal ring users under the age of 21 were twice as likely as adult women to experience an unintended pregnancy.[13]

The potential population impacts of our intervention are profound. We found that rates of abortion amongst CHOICE participants were less than half of the regional and national rates.[9] These findings were consistent across age demographics. Most notably, compared to teens nationwide, CHOICE teens had 75% lower rates of pregnancy, birth, and abortion.[11]

Strategies to Improve Contraceptive Care

The CHOICE Project was designed to address multiple barriers to reversible contraception. We argue that many of the strategies from the CHOICE Project can be implemented or adapted to improve contraceptive care in everyday practice. We highlight three key barriers to contraceptive care that CHOICE addressed: cost, education, and access.

Cost

The CHOICE Project eliminated the cost of the contraceptive method by providing all methods free of charge to participants. The public health community, including the Institute of Medicine, the Centers for Disease Control and Prevention (CDC), and the American College of Obstetricians and Gynecologists, have identified contraception as an essential part of preventive care. As such, these institutions have advocated for contraception to be a covered benefit of all health insurance without cost sharing. Although the Affordable Care Act included this provision, implementation has become entangled in political discourse. As a result, many women still struggle to secure affordable access to their desired contraceptive method. The CHOICE Project team continues to advocate on the local, regional, and national levels for equitable and affordable access to contraceptive care for all women.

Education

Early in the CHOICE Project, we found that most women had limited knowledge about available methods; participants generally underestimated the effectiveness of LARC and overestimated the effectiveness of OCPs, the patch, and the ring.[14] To address this knowledge gap effectively, we delivered education on all reversible methods in a standardized fashion beginning with the most effective methods.[15] This structured approach to counseling may allow women to more accurately consider the risk of method failure while deciding which method is best for them. In addition, the CHOICE model used trained non-clinician educators. This helped remove the time constraints of a clinician's schedule and allowed the patient adequate time for counseling. Other practice setting have adapted this model and trained medical assistants or nurses for this role.

Education barriers are not limited to patients, and many myths surrounding LARC still exist amongst practicing clinicians. To best serve our patients and their contraceptive needs, we must be vigilant in providing evidence-based care.

Access – Same-day Initiation

One of the most important ways that the CHOICE Project reduced barriers to contraception, particularly LARC methods, was by providing same-day initiation when medically appropriate. Data from other studies clearly demonstrate that any delay in delivery of a desired method increases the patient burden, increases the risk that the woman will become pregnant before returning for care, and decreases the likelihood that the patient will actually receive a contraceptive method.[16,17] LARC methods are often not inserted on the same day they are chosen for a multitude of reasons. One of the most common reasons cited is concern about the possibility of a luteal-phase pregnancy. To reasonably rule out a pregnancy, clinicians can make use of the simple checklist provided by the CDC Selected Practice Recommendations[18] (see Table 1). In the CHOICE Project, only 0.5% of women were diagnosed with a luteal-phase pregnancy following enrollment, suggesting that the overall risk is very low.[19] Another reason some providers are unwilling to place a same-day LARC method is concern about infection. The CDC's Medical Eligibility Criteria for Contraceptive Use provides evidence-based indications

Table 1: How to be reasonably certain a woman is not pregnant

How to be reasonably certain a woman is not pregnant
If a patient has no symptoms or signs of pregnancy and meets <u>any one</u> of the following criteria:
• is ≤7 days after the start of normal menses
• has not had sexual intercourse since the start of last normal menses
• has been correctly and consistently using a reliable method of contraception
• is ≤7 days after spontaneous or induced abortion
• is within 4 weeks postpartum
• is fully or nearly fully breastfeeding (exclusively or the vast majority [≥85%] of feeds are breastfeeds), amenorrheic, and <6 months postpartum

Adapted from CDC Select Practice Recommendations.
http://www.cdc.gov/reproductivehealth/contraception/usspr.htm

for contraceptive use.[20] The most recent publication supports following CDC recommendations for *Chlamydia trachomatis* and *Neisseria gonorrhea* screening and placing the LARC method, including IUDs, at the time of screening. Women with positive tests should be treated as soon as possible but do not need to have their IUDs removed. Although other sexually transmitted infections are not a contraindication to LARC placement, a history of pelvic inflammatory disease and post-partum or post-abortion endometritis within the past three months is a contraindication to IUD insertion.

A final potential barrier to same-day LARC insertion is the concern that an unscheduled insertion will delay clinic flow. Health centers can use several strategies to help maximize the efficiency of visits, keeping in mind that every visit should be viewed as an opportunity to address a woman's reproductive life plan and thus an opportunity to reassess contraceptive use. First, if all members of the health care team are knowledgeable about contraception, including LARC methods, they can counsel patients, thereby freeing up clinician time. Second, use of decision aids or informational videos in the waiting room can help patients identify factors that are important to them in choosing a contraceptive method. Finally, creating instrument packs containing all required supplies for LARC insertion can help streamline procedures.

Access – Immediate Postpartum LARC Placement

Another strategy to increase access to LARC methods is to provide IUDs and implants in the immediate postpartum setting, as recommended by the American College of Obstetricians and Gynecologists.[21] This is important because up to 45% of women report having unprotected intercourse before the routine six-week postpartum visit, putting them at risk for rapid repeat pregnancy.[22] Provision of LARC methods in the immediate postpartum period can reduce this risk, and there are few contraindications to providing these methods in this setting. Twenty-one state Medicaid programs, including Missouri's, reimburse for IUDs and implants in the postpartum hospital setting. Although rates of IUD expulsion are higher after immediate postpartum insertion than at other times (10–27% vs. 2-10%),[23] this risk is likely offset by the low rates of postpartum follow-up among women at highest risk for rapid repeat pregnancy.

Access – Special Populations

We highlight four populations in which LARC methods are often not used but in which use could increase. First, women receiving emergency contraception most commonly receive oral levonorgestrel or ulipristal acetate. However, the copper IUD has been shown to be the most effective form of emergency contraception, greater than 99% effective within 120 hours of unprotected sexual intercourse. The copper IUD has the added benefit of providing "forgettable" contraception, thus nearly eliminating the chance that a woman will need emergency contraception again. Second, LARC methods are appropriate for and acceptable to adolescents. Although some providers have been reluctant to provide LARC methods to teens, this practice is supported by both the American

Academy of Pediatrics and the American College of Obstetricians and Gynecologists.[24, 25] Third, with the increasing epidemic of obesity, consideration of effectiveness of methods in women of varying body mass index is relevant. Importantly, data from CHOICE demonstrated that LARC methods are equally effective regardless of body mass index.[26] Finally, women who have been using the 52 mg letonorgestrel-IUD or the etonogestrel implant for their FDA-approved durations can continue to use these methods for at least one more year without fearing any loss of effectiveness.[27-28]

Thoughts and Conclusion

The contraceptive and family planning needs of our patients are diverse, but with attention to reducing barriers to the most highly effective contraceptive methods, we can better help women plan and space their pregnancies. Preventing unintended pregnancy is an important way to reduce maternal and neonatal morbidity and mortality and help our patients reach their education, career, and life goals.

References

1. Finer LB and Zolna MR, Declines in unintended pregnancy in the United States, 2008–2011, New England Journal of Medicine, 2016, 374(9):843–852, http://nejm.org/doi/full/10.1056/NEJMsa1506575.
2. Jones RK., Kavanaugh M. Changes in Abortion Rates Between 2000 and 2008 and Lifetime Incidence of Abortion. Obstet Gynecol: 2011; 117 (6): 1358-1366.
3. Kost K and Maddow-Zimet I. U.S. Teenage Pregnancies, Births and Abortions, 2011: State Trends by Age, Race and Ethnicity,2016, New York: Guttmacher Institute, http://www.guttmacher.org/report/us-teen-pregnancy-state-trends-2011
4. Institute TG. Fulfilling the Promise: Public Policy and U.S. Family Planning Clinics. New York: Guttmacher Institute;2000.
5. Mayer JP. Unintended childbearing, maternal beliefs, and delay of prenatal care. Birth. 1997;24(4):247-252.
6. Barber JS, Axinn WG, Thornton A. Unwanted childbearing, health, and mother-child relationships. J Health Soc Behav. 1999;40(3):231-257.
7. Orr ST, Miller CA, James SA, Babones S. Unintended pregnancy and preterm birth. Paediatr Perinat Epidemiol. 2000;14(4):309-313.
8. Kavanaugh M, Jerman J, Finer L. Changes in the use of long-acting reversible contraceptive methods among US women, 2009-2012. Obstet Gynecol. 2015; 126 (5): 917-25.
9. Peipert JF, Madden T, Allsworth JE, Secura GM. Preventing unintended pregnancies by providing no-cost contraception. Obstet Gynecol. 2012;120(6):1291-1297.
10. Peipert JF, Zhao Q, Allsworth JE, et al. Continuation and satisfaction of reversible contraception. Obstet Gynecol. 2011;117(5):1105-1113.
11. Secura GM, Madden T, McNicholas C, et al. Provision of no-cost, long-acting contraception and teenage pregnancy. N Engl J Med. 2014;371(14):1316-1323.
12. Rosenstock JR, Peipert JF, Madden T, Zhao Q, Secura GM. Continuation of reversible contraception in teenagers and young women. Obstet Gynecol. 2012;120(6):1298-1305.
13. Winner B, Peipert JF, Zhao Q, et al. Effectiveness of long-acting reversible contraception. N Engl J Med. 2012;366(21):1998-2007.
14. Eisenberg DL, Secura GM, Madden TE, Allsworth JE, Zhao Q, Peipert JF. Knowledge of contraceptive effectiveness. Am J Obstet Gynecol. 2012;206(6):479 e471-479.
15. Madden T, Mullersman JL, Omvig KJ, Secura GM, Peipert JF. Structured contraceptive counseling provided by the Contraceptive CHOICE Project. Contraception. 2013;88(2):243-249.
16. Tocce K, Sheeder J, Python J, Teal SB. Long acting reversible contraception in postpartum adolescents: early initiation of etonogestrel implant is superior to IUDs in the outpatient setting. J Pediatr Adolesc Gynecol. 2012;25(1):59-63.
17. Bergin A, Tristan S, Terplan M, Gilliam ML, Whitaker AK. A missed opportunity for care: two-visit IUD insertion protocols inhibit placement. Contraception. 2012;86(6):694-697.
18. Division of Reproductive Health NCfCDP, Health Promotion CfDC, Prevention. U.S. Selected Practice Recommendations for Contraceptive Use, 2013: adapted from the World Health Organization selected practice recommendations for contraceptive use, 2nd edition. MMWR Recomm Rep. 2013;62(RR-05):1-60.
19. Min J, Buckel C, Secura GM, Peipert JF, Madden T. Performance of a checklist to exclude pregnancy at the time of contraceptive initiation among women with a negative urine pregnancy test. Contraception. 2015;91(1):80-84.
20. Curtis KM, Tepper NK, Jatlaoui TC, et al. U.S. Medical Eligibility Criteria for Contraceptive Use, 2016. MMWR Recomm Rep. 2016;65(3):1-103.
21. Committee Opinion No. 670: Immediate Postpartum Long-Acting Reversible Contraception. Obstet Gynecol. 2016;128(2):e32-37.
22. Brito MB, Ferriani RA, Quintana SM, Yazlle ME, Silva de Sa MF, Vieira CS. Safety of the etonogestrel-releasing implant during the immediate postpartum period: a pilot study. Contraception. 2009;80(6):519-526.
23. Lopez LM, Bernholc A, Hubacher D, Stuart G, Van Vliet HA. Immediate postpartum insertion of intrauterine device for contraception. Cochrane Database Syst Rev. 2015(6):CD003036.
24. Adolescents and long-acting reversible contraception: implants and intrauterine devices. Committee Opinion No. 539. American College of Obstetricians and Gynecologists. Obstet Gynecol 2012;120:983–8.
25. Contracpetion for Adolescents. American Academy of Pediatrics Policy Statement. Pediatrics. 2014; 134 (4).
26. Xu H, Wade JA, Peipert JF, Zhao Q, Madden T, Secura GM. Contraceptive failure rates of etonogestrel subdermal implants in overweight and obese women. Obstet Gynecol. 2012;120(1):21-26.
27. McNicholas C, Maddipati R, Zhao Q, Swor E, Peipert JF. Use of the etonogestrel implant and levonorgestrel intrauterine device beyond the U.S. Food and Drug Administration-approved duration. Obstet Gynecol. 2015;125(3):599-604.
28. Ali M, Akin A, Bahamondes L, et al. Extended use up to 5 years of the etonogestrel-releasing subdermal contraceptive implant: comparison to levonorgestrel-releasing subdermal implant. Hum Reprod. 2016.

Disclosure

None reported.

MM

Zika Virus Takes a Transplacental Route to Infect Fetuses: Insights from an Animal Model

by Indira U. Mysorekar, PhD

We will use our mouse model as a foundation for defining viral pathogenic mechanisms and testing candidate vaccines, anti-ZIKV antibodies, and other therapeutic modalities needed to combat this rapidly expanding epidemic.



Indira U. Mysorekar, PhD, is in the Departments of Obstetrics and Gynecology and Pathology and Immunology, and is Associate Director, Centre for Reproductive Health Sciences, Washington University School of Medicine.
Contact: indira@wustl.edu

Abstract

Zika virus (ZIKV) has been linked to intrauterine growth restriction (IUGR), spontaneous miscarriage, and microcephaly in infants of women infected during pregnancy. To determine how ZIKV affects the fetus, we infected pregnant mice subcutaneously (mimicking a mosquito bite) with ZIKV. Multiple techniques revealed that ZIKV replicated within placental trophoblasts, fetal endothelial cells, and the fetal neocortex. We also noted severe placental defects, IUGR, and fetal death. Thus, our mouse model recapitulated ZIKV infection in human pregnancy and demonstrated that ZIKV can be transmitted from mother to fetus via the placenta.

Introduction to Zika Virus

Zika virus (ZIKV) is an insect-borne virus similar to Dengue, yellow fever, Japanese encephalitis, and West Nile viruses. Like other members of the family flaviviridae and the genus flavivirus, ZIKV is enveloped and icosahedral and has a non-segmented, single-stranded, positive-sense RNA genome. It is transmitted to humans and non-human primates by the Asian tiger mosquito Aedes aegypti.[1]

Origins and Symptoms of ZIKV

ZIKV is named after the place where it was first identified and isolated in 1947: the Ziika Forest in Uganda, Central Africa. The virus was identified as a causal agent in small outbreaks in a narrow equatorial belt from Africa to Asia in the 1950s and 1960s. In 2007, an epidemic was recorded on the island of Yap in the Federated States of Micronesia. This outbreak was initially thought to be Dengue virus, but serological analyses identified the virus as ZIKV. During the first 50 years after it was discovered, ZIKV was not regarded as a significant pathogen, as the majority of infections were asymptomatic. Even symptomatic cases of ZIKV present with mild symptoms that clear within three to five days, including fever, headache, muscle and joint pain, conjunctivitis, and skin rash.[2] However, in 2007, a ZIKV outbreak in French Polynesia received attention from the Centers for Disease Control because a number of infected individuals presented with neurological symptoms including temporary paralysis, which were later diagnosed as Guillain-Barré Syndrome. Between 2007 and 2016, ZIKV spread eastward to the Americas, leading to the current global epidemic. In early 2015, a major ZIKV outbreak was recorded in Bahia, Brazil, and was confirmed as resulting from viral transmission from French Polynesia. The Bahia ZIKV outbreak was followed by similar outbreaks in neighboring regions, leading the Brazilian Ministry of Health to issue a ZIKV alert in April 2015.

Fetal Outcomes Associated with Maternal ZIKV Infection

In the past year, the incidences of Guillain Barré syndrome in all age groups [3] and microcephaly in newborns of infected mothers[4] have both increased. As a result, the World Health Organization declared ZIKV a

public health emergency in February 2016.[5] Although the relationship between ZIKV infection in pregnant women and microcephaly in their infants was at first unclear, data now strongly indicate that ZIKV infection during pregnancy causes microcephaly. For example, a prospective cohort study of symptomatic, ZIKV-infected pregnant women showed that 29% of fetuses exhibited developmental abnormalities including microcephaly, IUGR, fetal demise, and stillbirth.[6] The first trimester of pregnancy is a crucial period for brain development, and ZIKV infection during this time is likely to be more strongly associated with microcephaly than infections later in pregnancy, as demonstrated in French Polynesia. [7, 8]

Scope of the Problem

At present, no specific vaccines or treatment for ZIKV infection are available because, in part, we have limited knowledge of the molecular pathogenesis of the virus. Because of the growing public health concern, we urgently needed to establish animal models of ZIKV infection that define mechanisms of maternal-fetal transmission, satisfy the criteria for proof of teratogenicity[8], and facilitate testing of therapeutic modalities and candidate vaccines (reviewed in[9]).

A Mouse Model of ZIKV Infection in Pregnancy

Recently, we developed a mouse model of ZIKV infection during pregnancy.[10] We used ZIKV strain H/PF/2013 (isolated in French Polynesia in 2013) propagated in kidney epithelial cells (called Vero cells) under biosafety level 2 or 3 containment. Flaviviruses such as ZIKV have evolved to cause disease by overcoming one of the host immune defense pathways in humans and non-human primates, type I interferon–receptor (IFNAR1) signaling. However, ZIKV cannot efficiently overcome murine IFNAR1 signaling and thus normally would not infect a mouse. Therefore, we used mice in which both copies of the Ifnar1 gene were defective ($Ifnar1^{-/-}$). Because we wanted the fetuses to have a largely intact interferon response, we mated $Ifnar1^{-/-}$ females to wild-type males, thereby producing fetuses that had one functioning copy of the Ifnar1 gene. Mice were allowed to breed for a short time so that we could accurately follow fetal development. At embryonic day 6.5 (E6.5; gestation in mice is 19-21 days, thus E6.5 is analogous to the first trimester of pregnancy in women), we injected ZIKV into the mice subcutaneously to mimic the route of infection from a mosquito bite. We sacrificed the mice between E13.5 and E16.5, which would be equivalent to the late second or early third trimester, dissected out the placentas and fetuses, and assessed them in detail.

ZIKV Infection During Pregnancy Causes Murine IUGR and Fetal Death

By E13.5, the majority of fetuses of ZIKV-infected $Ifnar1^{-/-}$ mice had died and been resorbed (resorption in mice is analogous to spontaneous abortion in humans). We measured the crown-rump length and occipito-frontal head diameter of the remaining fetuses and found that they were significantly smaller than fetuses of uninfected mothers, indicating that ZIKV infection causes IUGR in mice as it does in humans[6, 11]. To assess viral load in the pregnant mothers and fetuses, we isolated RNA (ZIKV is an RNA virus) from maternal spleen and blood, placentas, and fetal heads at E13.5. We detected high levels of ZIKV in all tissues examined. Of note, the placentas contained ~1,000-fold higher concentration of ZIKV RNA than the maternal serum, suggesting that ZIKV preferentially replicates within the placenta.

ZIKV Infection Severely Damages the Placenta

Similar to the human placenta, the mouse placenta comprises both maternal and fetal-derived components; in the mouse, these are termed the junctional and labyrinth zones, respectively (see Figure 1). In the labyrinth zone, fetal capillaries lined by fetal blood vessel endothelium are separated from maternal sinusoids by a layer of mononuclear trophoblasts and a syncytiotrophoblast (STB) bilayer.[12, 13] In both human and mouse placentas, STBs separate fetal and maternal blood and mediate exchange of nutrients, waste, and gases. The mouse placenta lacks cells analogous to the human cytotrophoblasts and instead contains spongiotrophoblasts found in the junctional zone. Analogous to the human extravillous trophoblasts are the mouse trophoblast giant cells, which invade the maternal decidua to facilitate implantation of the placenta into the uterine wall (see Figure 1).

To determine at a cellular level how ZIKV reached the fetus, we asked where in the placentas ZIKV was located. We found ZIKV RNA in different trophoblast cells including spongiotrophoblasts (see Figure 2). Transmission electron microscopy of placentas revealed ZIKV virion particles assembling within the endoplasmic reticulum of trophoblasts and fetal endothelial cells that line fetal capillaries. In addition, histopathological analysis of the placentas showed extensive vascular damage with irregularly shaped fetal capillaries, damaged placental microvasculature, and a number of nucleated fetal erythrocytes, key indicators of fetal stress. Finally, we examined fetal brains and found extensive neuronal death (reviewed in[9]). From these findings, we concluded that maternal ZIKV infection compromises the placental barrier by infecting fetal trophoblasts and thereby enters the fetal circulation and impairs development.

Perspectives and Future Directions

Our study was the first to administer ZIKV to mice early in gestation (at E6.5, equivalent to the first trimester

Figure 1
Illustration depicting structure of human versus mouse placenta with analogous cell types indicated.

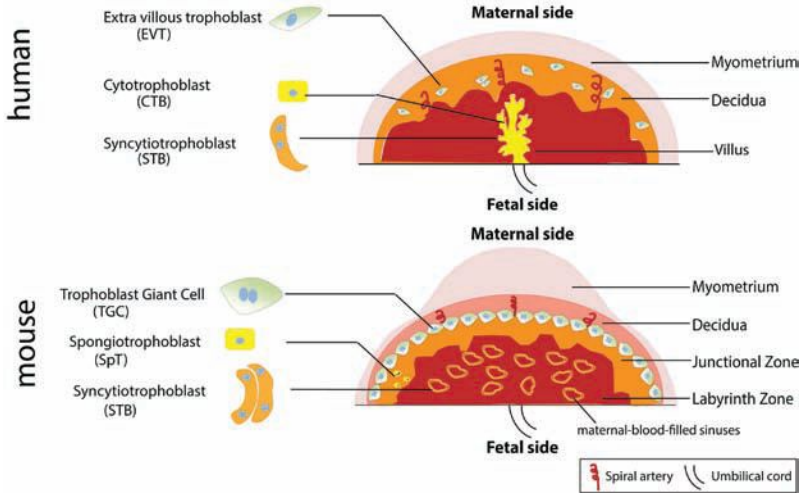
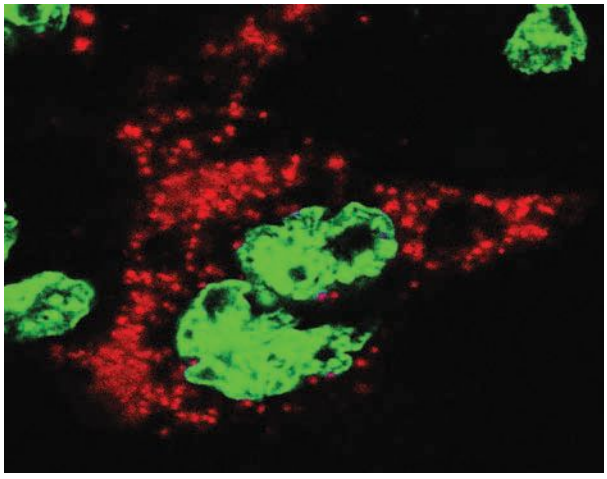


Figure 2
Image depicting the Zika virus particles in red encased inside a spongiotrophoblast with nuclei stained green.



in human gestation); other investigators infected mice at E13.5 (closer to late second-early third trimester in human pregnancy).[14-17] The high rate of fetal death we observed is consistent with the observation in humans that the most severe manifestations of ZIKV-induced fetal abnormalities are associated with infections in the first and second trimesters.[6, 7, 18] Additionally, our study unequivocally demonstrated that ZIKV can take a transplacental route to infect fetuses. Consistent with our findings, recent studies have demonstrated that ZIKV infects human placental trophoblasts, endothelial cells, and placental macrophages.[19-22]

Principal findings from our murine studies support observations in human pregnancy that ZIKV infection during pregnancy causes transplacental infections and fetal demise. Furthermore, we demonstrate that ZIKV spreads to the fetal brain where it leads to neuropathologies that have been observed in human neonates. Our ongoing studies are focused on determining the mechanisms of viral entry into the placenta and fetal endothelium. Further, we will use our mouse model as a foundation for defining viral pathogenic mechanisms and testing candidate vaccines, anti-ZIKV antibodies, and other therapeutic modalities needed to combat this rapidly expanding epidemic.

References

1. Musso, D. & Gubler, D.J. Zika Virus. Clin Microbiol Rev 29, 487-524 (2016).
2. Kindhauser, M.K., Allen, T., Frank, V, Santhana, R.S. & Dye, C. Zika: the origin and spread of a mosquito-borne virus. Bull World Health Organ 94, 675-686C (2016).
3. Cao-Lormeau, V.M. et al. Guillain-Barre Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study. Lancet 387, 1531-9 (2016).
4. Mlakar, J. et al. Zika Virus Associated with Microcephaly. N Engl J Med 374, 951-8 (2016).
5. Calvet, G.A., Santos, F.B. & Sequeira, P.C. Zika virus infection: epidemiology, clinical manifestations and diagnosis. Curr Opin Infect Dis 29, 459-66 (2016).
6. Brasil, P. et al. Zika Virus Infection in Pregnant Women in Rio de Janeiro - Preliminary Report. N Engl J Med (2016).
7. Cauchemez, S. et al. Association between Zika virus and microcephaly in French Polynesia, 2013-15: a retrospective study. Lancet 387, 2125-32 (2016).
8. Rasmussen, S.A., Jamieson, D.J., Honein, M.A. & Petersen, L.R. Zika Virus and Birth Defects--Reviewing the Evidence for Causality. N Engl J Med 374, 1981-7 (2016).
9. Mysorekar, I.U. & Diamond, M.S. Modeling Zika Virus Infection in Pregnancy. N Engl J Med 375, 481-4 (2016).
10. Miner, J.J. et al. Zika Virus Infection during Pregnancy in Mice Causes Placental Damage and Fetal Demise. Cell 165, 1081-91 (2016).
11. Sarno, M. et al. Zika Virus Infection and Stillbirths: A Case of Hydrops Fetalis, Hydranencephaly and Fetal Demise. PLoS Negl Trop Dis 10, e0004517 (2016).
12. Simmons, D.G. & Cross, J.C. Determinants of trophoblast lineage and cell subtype specification in the mouse placenta. Dev Biol 284, 12-24 (2005).
13. Watson, E.D. & Cross, J.C. Development of structures and transport functions in the mouse placenta. Physiology (Bethesda) 20, 180-93 (2005).
14. Cugola, F.R. et al. The Brazilian Zika virus strain causes birth defects in experimental models. Nature 534, 267-71 (2016).
15. Li, C. et al. Zika Virus Disrupts Neural Progenitor Development and Leads to Microcephaly in Mice. Cell Stem Cell 19, 120-6 (2016).
16. Wu, K.Y. et al. Vertical transmission of Zika virus targeting the radial glial cells affects cortex development of offspring mice. Cell Res 26, 645-54 (2016).
17. Yockey, L.J. et al. Vaginal Exposure to Zika Virus during Pregnancy Leads to Fetal Brain Infection. Cell 166, 1247-1256 e4 (2016).
18. Cauchemez, S. et al. Association between Zika virus and microcephaly in French Polynesia, 2013-15: a retrospective study. Lancet (2016).
19. Tabata, T. et al. Zika Virus Targets Different Primary Human Placental Cells, Suggesting Two Routes for Vertical Transmission. Cell Host Microbe 20, 155-66 (2016).
20. Noronha, L., Zanluca, C., Azevedo, M.L., Luz, K.G. & Santos, C.N. Zika virus damages the human placental barrier and presents marked fetal neurotropism. Mem Inst Oswaldo Cruz 111, 287-93 (2016).
21. Jurado, K.A. et al. Zika virus productively infects primary human placenta-specific macrophages. JCI Insight 1 (2016).
22. Quicke, K.M. et al. Zika Virus Infects Human Placental Macrophages. Cell Host Microbe 20, 83-90 (2016).

Disclosure

None reported.

MM

Apical Vaginal Support: The Often Forgotten Piece of the Puzzle

by Jerry L. Lowder, MD

While surgeons await evidence-based guidelines for both what defines significant apical support loss and when an ASP should be performed, they can use a patient's genital hiatus of >3.75 cm as a marker to further screen for significant apical vaginal support loss.



Jerry L. Lowder, MD, MSc, is Associate Professor and Director, Division of Female Pelvic Medicine and Reconstructive Surgery, Department of Obstetrics and Gynecology, Washington University School of Medicine.
Contact: lowderj@wudosis.wustl.edu

Abstract

Pelvic organ prolapse is common among women who have delivered vaginally or had a hysterectomy. In a total hysterectomy, the apical vaginal support is transected. Although evidence supports re-establishment of apical support, our research showed that this rarely occurs in hysterectomies. To address our lack of definitions of "significant" apical support loss and recommendations to guide surgeons as to when they should perform an apical support procedure, we analyzed patient data and found that a simple assessment of the genital hiatus can effectively screen for significant apical support loss. Our work will hopefully highlight the importance of apical support loss and current deficits in research and clinical guidelines.

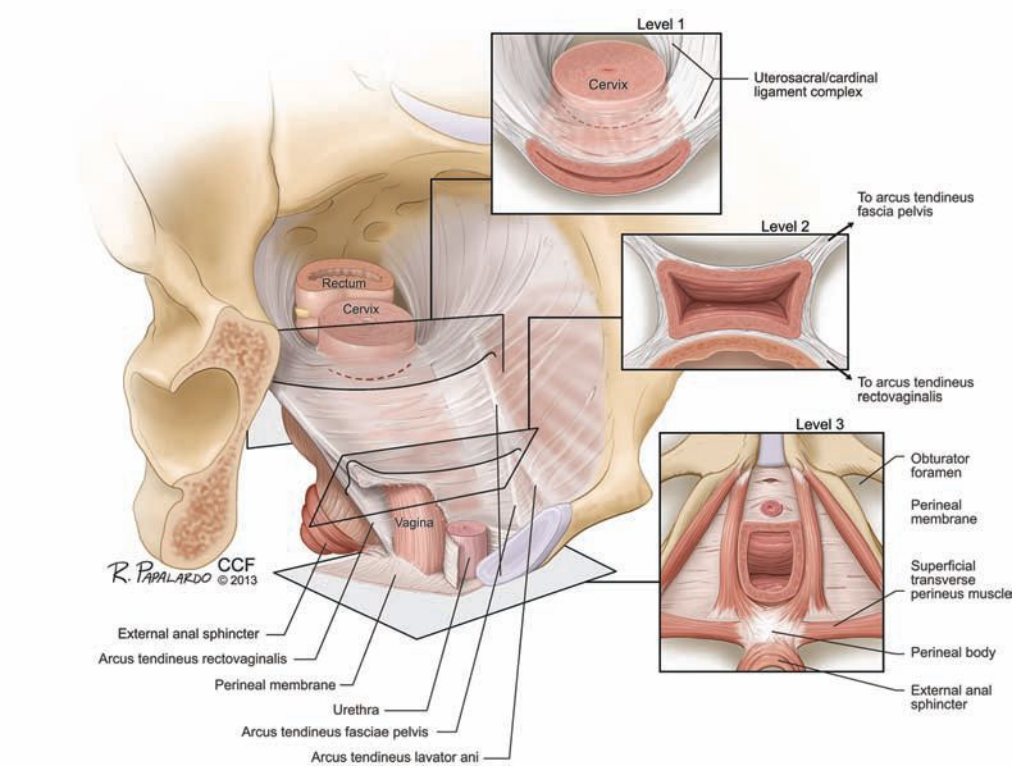
Introduction

Pelvic organ prolapse (POP) is a disorder in which one or more of the vaginal walls (anterior, posterior, or apex/vault) descend into the vagina canal. POP is estimated to affect more than three million women in the U.S.,[1] and between 2.9% and 8% of women experience symptomatic prolapse, defined as seeing or feeling a bulge from the vagina.[2-4] It is estimated that over 300,000 women undergo surgery for POP annually, and the lifetime risk of surgery for POP and/or urinary incontinence is 11%.[5, 6] A Swedish study estimated that POP affects up to 50% of parous women over 50 years of age,[7] and other studies have shown that 40%-75% of parous women have some amount of prolapse on examination.[8-10] However, the degree of symptoms women report vary greatly, and women are often asymptomatic until the leading edge of prolapse is at or beyond the hymen.[11-14] POP can cause alterations in bladder and bowel function and a sensation of pelvic pressure or a palpable vaginal bulge. As vaginal prolapse worsens, these symptoms tend to increase.[4, 14, 15] All of these symptoms can impair a woman's physical, sexual, and emotional health, and her body image. The health care and related personal costs for pelvic floor disorders are significant. For example, the estimated annual cost of ambulatory care for pelvic floor disorders in the U.S. in 2005-2006 was just under $300 million.[16]

Although pregnancy and delivery are the greatest risk factors for development of prolapse (approximately 31% of women have some degree of prolapse after pregnancy and vaginal delivery[17]), hysterectomy also likely plays a significant role in the development of prolapse, and specifically in post-hysterectomy vaginal vault prolapse. It has been estimated that 6-8% of women who undergo a hysterectomy develop post-hysterectomy vaginal vault prolapse requiring surgical repair, and epidemiologic studies have estimated that the risk of surgery for prolapse after hysterectomy is 1.3-3.6 per 1,000 women/years.[20, 21, 24]

This association is concerning for two reasons. First, hysterectomy is the most common major gynecologic surgery performed in the U.S.; over 500,000 were performed in 2005.[18, 19] Second, although historically, hysterectomies were most commonly performed to

Figure 1
Schematic of integrated levels of female pelvic organ support.
Reprinted with permission from Elsevier Saunders Urogynecology and Reconstructive Pelvic Surgery, 4th Edition copyright 2015



correct uterine prolapse, now only 17% of hysterectomies performed for benign indications are performed to correct uterine prolapse.[19] Together, these data suggest that the majority of hysterectomies for benign conditions are performed in women who have overall good pelvic organ support. In such women, hysterectomy may be putting women at risk of future POP if surgical strategies are not used to prevent it.

Hysterectomy may put women at risk of future POP because of the support structures of the vagina and the procedures used to remove the uterus.[20-23] The "keystone" of pelvic organ support is the uterosacral and cardinal ligament (USCL) complex, a strong connective tissue attachment from the sacrum and coccyx and lateral pelvic sidewalls to the cervix and upper one-third of the vagina. DeLancey et al. suggest that the intact vertical fibers of the USCL complex suspend and prevent prolapse of the vaginal apex.[25] However, at the time of complete hysterectomy (removal of both cervix and uterus), the surgeon transects the USCL complex regardless of surgical route (abdominal, vaginal, minimally invasive), thus damaging the "level I" support structure (see Figure 1).

Unless specific procedures are performed at time of hysterectomy to reattach the vaginal cuff to the USCL complex, level I support is lost in women without prolapse and is not re-established in women with prolapse. This loss of vaginal support likely leads to increased intra-abdominal forces on the remaining vaginal support, which may already be damaged in parous women, predisposing women to prolapse or recurrence of prolapse.[26, 27] When a hysterectomy is performed not for uterovaginal prolapse, support of the top of the vagina can be re-established by placing stitches from the vaginal cuff to the USCL by any surgical route. When a hysterectomy is performed for pelvic organ prolapse (existing loss of level I anatomic support), advanced surgical procedures can also be performed by all surgical routes to re-suspend the vaginal apex. In women for whom future sexual activity is not an issue, a vaginal obliteration (closure procedure) can be performed.[28]

Hysterectomy Not for Prolapse

The vast majority of hysterectomies are performed for benign conditions for a diagnosis other than POP.[19] In the only randomized surgical trial for prevention of post-hysterectomy vaginal vault prolapse, Cruikshank et al. showed in 1999 that use of a modified-McCall's procedure (which attaches the top of the vagina directly to the USCL complex via sutures) resulted in a significantly lower rate of apical vaginal prolapse at two years than use of a simple cuff closure or a Moscowitz-type vaginal closure[26] (which closes the lining of the abdominal cavity [peritoneum] in a purse-string stitch but does not incorporate the USCL complex or other supporting structures).

Despite this Level 1 evidence of the value of establishing apical support during hysterectomy, I noted in my reviews of hysterectomy operative reports for women I was treating for post-hysterectomy vaginal prolapse that their surgeries had often not included re-establishment of apical support. This observation led our group at the University of Pittsburgh

to study rates of concomitant apical support procedures at time of hysterectomy not for prolapse. We first used ICD-9 codes to query our institutional database and identified 11,085 hysterectomies that met our study criteria and were performed for conditions other than a diagnosis of prolapse over the 11-year study period (2000-2010). This number included 8,003 (72.2%) total abdominal hysterectomies, 2,145 (19.4%) vaginal hysterectomies, and 939 (8.5%) supracervical hysterectomies (SCH). The majority of hysterectomies were performed for benign gynecologic indications (70.1%), and the remaining (29.1%) were performed for a gynecologic-related cancer diagnosis not requiring radical hysterectomy. Of 8,003 total abdominal hysterectomies performed over 11 years, only 73 (0.9%) included an apical support procedure (ASP). The rates of ASP were low in all types of hysterectomies: 4 of 897 (0.4%) laparoscopic total hysterectomies, 7 of 939 (0.7%) supracervical hysterectomies, 4 of 369 (0.4%) laparoscopic supracervical hysterectomies, 172 of 2,145 (8.0%) vaginal hysterectomies, and 98 of 1,104 (8.9%) laparoscopically assisted vaginal hysterectomies.[30]

To determine whether the low rate of ASPs was solely a regional phenomenon, we repeated this study in a publicly available national database, the Nationwide Inpatient Sample (NIS).[31] From 2004 through 2013, during which 3,257,429 hysterectomies were performed for benign indications other than uterovaginal prolapse, only 91,152 (2.8%) included an ASP. In multivariable analysis, older age, route of hysterectomy, and larger hospital size and hospital type (teaching, urban) were associated with performance of an ASP.

Our findings in both an institutional and a national database revealed that despite level I evidence data published in 1999 recommending re-establishment of apical vaginal support at time of hysterectomy not for prolapse, this is not routinely done. However, recently released guidelines from the American Association of Gynecologic Laparoscopists (AAGL) and the Royal College of Obstetricians & Gynecologists (RCOG) provide some hope that practice patterns will change. In 2014 and 2015, respectively, these two organizations (referencing the 1999 Cruikshank et al. paper) incorporated the use of a McCall's procedure during hysterectomy to treat non-prolapse-related disease into their evidence-based guidelines to decrease the risk of postoperative apical prolapse.[15, 29] I am optimistic that these evidence-based guidelines will result in more surgeons performing ASPs when they perform hysterectomies.

Hysterectomy For Prolapse

Until very recently, there were no guidelines recommending at what level of uterovaginal prolapse an ASP should be performed. To date, surgeons have been guided by expert opinion, as emphasized in a 2007 American College of Obstetricians and Gynecologists (ACOG) practice bulletin, that hysterectomy alone is not acceptable management for uterovaginal prolapse given that removal of the uterus does not treat inadequate apical support.[28, 32] Likewise, the International Consultation on Incontinence (ICI) states that apical vaginal support, regardless of the presence or absence of the uterus, must be assessed, and that the best surgical correction of the anterior and posterior walls may fail unless the apex is adequately supported.[33] The 2015 RCOG practice guideline mentioned above recommend that sacrospinous fixation (attaching the top of the vagina to the sacrospinous ligament) at time of vaginal hysterectomy should be considered when the vault descends to the introitus during closure. In a thorough review of the literature, this was the first recommendation I found that references a level of descent at which an apical support procedure should be performed.[29]

Given the low rates of re-establishment of apical support in hysterectomy not for prolapse, we were interested to know the rates of ASPs in women with uterovaginal prolapse, which we used as a proxy for apical vaginal prolapse. In our institutional database, 13,973 hysterectomies were performed from 2000 through 2010. Of these, 2,465 (17.6 %) were performed for the diagnosis of uterovaginal prolapse and included 1,693 vaginal (68.7%), 530 abdominal (21.5%), and 242 laparoscopic (9.8%) hysterectomies.[34] The subjects were predominantly Caucasian and had a mean age of 56±13.6 years. Surgeons included 107 generalists, 8 urogynecologists, 4 minimally invasive gynecologists, and 11 gynecological oncologists. Uterovaginal prolapse was the first diagnosis code for 80% of the procedures. In only 1,358 cases (55.1 %) were concurrent ASPs performed. Of the 1,107 cases without ASPs, generalists performed 95.7%. Of the 1,358 cases with concurrent ASPs, 68.3% were performed by urogynecologists, 24.7% by generalists, 6.4 % by minimally invasive gynecologists, and 1.2 % by gynecological oncologists.

To determine whether these findings were solely a regional phenomenon, we again used the NIS database.[31] During the study period, 720,098 hysterectomies were performed for the diagnosis of uterovaginal prolapse. The majority (64.4%) of hysterectomies were performed vaginally, whereas 19.7% were laparoscopic, and 13.45 were abdominal. An ASP was performed in only 268,858 (37%) cases. We found only a slight increase in the number of ASPs performed over the study period.

Together, our findings reveal that despite: 1) expert opinion; 2) an ACOG statement that hysterectomy alone is inadequate treatment to address uterovaginal prolapse; and

3) a recent RCOG evidence-based guideline recommending a level at which an apical support procedure should be performed, nationally a little over one-third of women undergoing hysterectomy with a diagnosis of uterovaginal prolapse have an ASP performed.

Lack of Guidelines

Until very recently, surgeons have had no evidence-based recommendations to guide their decision-making about when an ASP should be performed. Although the RCOG guideline is a helpful start, we argue that if "the vault descends to the introitus during [vaginal cuff] closure", the surgeon is starting with advanced apical prolapse. In addition to lack of agreement and guidance regarding clinically significant apical support loss, several factors may explain why ASPs are infrequently performed. First, although the Pelvic Organ Prolapse-Quantification (POP-Q) examination is the standard prolapse staging system used in the Female Pelvic Medicine and Reconstructive Surgery field for reporting outcomes, this assessment is not commonly used in clinical care outside the sub-specialty. One of the primary contributions of the POP-Q system was the standardized, independent evaluation of all three compartments (anterior, apical, and posterior) of the vagina. Because the POP-Q is not widely used, these three compartments may not be routinely and adequately assessed independently. Also, non-specialists may not commonly use the POP-Q because it has been described as "cumbersome" and "difficult to teach".

A second likely explanation for why apical support procedures are infrequently performed during hysterectomies is that no clinically useful and accepted definition of apical support loss exists. The currently available definitions are based on point C of the POP-Q. Point C is the distance from the hymen to the cervix or vaginal cuff (herein referred to as the vaginal apex) during maximum valsalva maneuver and is a negative number if the vaginal apex is above the hymen and a positive number if beyond the hymen.[37] The International Continence Society defines apical support loss as the vaginal apex descending to a point 2 cm lower than the total vaginal length.[38] This definition has come under scrutiny as being too stringent. Thus, in the seven-year outcomes paper of the NIH-Pelvic Floor Disorders Network extended Colpopexy and Urinary Reduction Efforts (eCARE) study, the authors revised the definition of apical support loss to descent of the vaginal apex to greater than one-third of total vaginal length.[39]

Given these discrepant definitions, our group performed a systematic review of surgical trials addressing apical vaginal prolapse to describe what surgeons used as "clinically significant" apical prolapse.[40] We screened 3,140 publications, reviewed 399 full-text articles, and identified 35 randomized controlled trials. We evaluated the study inclusion/exclusion criteria, definitions of success/failure, and study outcomes. Prolapse-related inclusion criteria were: 1) apical prolapse; 2) overall prolapse; or 3) both. Definitions of apical prolapse (relative to the hymen) included: 1) apical prolapse beyond -1 cm; 2) apical prolapse beyond +1 cm; 3) apical prolapse beyond 50% of total vaginal length; and 4) cervix/apex beyond 0 cm. Only 16 of the 35 studies required the presence of symptoms for inclusion. A measurement of the apical compartment (relative to the hymen) was used as a measure of surgical success or failure in fewer than half of the studies. Definitions for surgical success included: 1) prolapse better than stage 2 in each compartment; 2) prolapse above 50% of total vaginal length; 3) apical support better than two-thirds of TVL; 4) absence of prolapse beyond the hymen; and 5) point C at -5 cm or higher. Surgical failure was defined as: 1) apical prolapse at or beyond 0 cm; 2) apical prolapse at or beyond -1 cm; 3) apical prolapse beyond 50% of total vaginal length; and 4) recurrent apical prolapse surgery. We concluded that among randomized controlled surgical trials specifically designed to address apical vaginal support loss, definitions of clinically significant apical prolapse for study inclusion and surgical success or failure were either highly variable or absent and overall represent advanced apical support loss. In addition, the current literature provides limited evidence of consensus and little insight into current expert opinion.[40]

Given the lack of clinical guidelines and the low utilization of the POP-Q examination, our group sought to find a clinically useful and "easy" way to screen for apical vaginal prolapse. We performed receiver operator curve analyses on data from 462 women with stage 0-IV POP-Q examinations. We based our analyses on the following definitions of apical support loss: 1) the current ICS definition (vaginal apex descending to a point 2 cm lower than total vaginal length[38]), the current eCARE definition (apical descent lower than two-thirds of total vaginal length[39]), and 3) a POP-Q point C cut point associated with symptoms of POP (POP-Q point C = -5 cm).[41] Our analyses revealed that a measurement of the genital hiatus (GH, measured from mid urethral meatus to posterior forchette) predicts apical support loss based on these definitions. For all three definitions, we found that a GH >3.75 cm has a high sensitivity (79%–87%) for detecting "significant" apical support loss.[42] Thus, if a surgeon is considering a hysterectomy (either for prolapse or not for prolapse) and finds an enlarged genital hiatus over ~2 fingerbreadths, additional screening for apical support loss should be performed.[42]

Summary

Hysterectomy is the most common major gynecological procedure performed in women in the U.S. Uterovaginal

prolapse is the fifth most common diagnosis for hysterectomy. Unfortunately, surgeons rarely perform ASPs to re-establish support at time of hysterectomy not for prolapse for prevention of future prolapse. Additionally, surgeons performed ASPs in only a little over one-third of women undergoing hysterectomy for uterovaginal prolapse. The literature contains no consensus on what defines clinically significant apical support loss and when an ASP should be performed, and surgeons appear to not typically screen for apical support loss. While surgeons await evidence-based guidelines for both what defines significant apical support loss and when an ASP should be performed, they can use a patient's genital hiatus of >3.75 cm as a marker to further screen for significant apical vaginal support loss.

References

1. Wu JM, Hundley AF, Fulton RG, Myers ER. Forecasting the prevalence of pelvic floor disorders in US women. Obstet Gynecol 2009;114:1278-83.
2. Nygaard I, Barber MD, Burgio KL, et al. Prevalence of symptomatic pelvic floor disorders in US women. JAMA. 2008;300:1311.
3. Rortveit G, Brown JS, Thom DH, et al. Symptomatic pelvic organ prolapse: prevalenc and risk factors in a population-based, racially diverse cohort. Obstet Gynecol. 2007;109:1396.
4. Bradley CS, Nygaard IE. Vaginal wall descensus and pelvic floor symptoms in older women. Obstet Gynecol. 2005;106:759.
5. Olsen AL, Smith VJ, Bergstrom JO. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol 1997;89: 501-6.
6. Fialkow MF, Newton KM, Lentz GM, Weiss NS. Lifetime risk of surgical management for pelvic organ prolapse or urinary incontinence. Int Urogynecol J 2008;19:437-40.
7. Samuelsson EC, Arne Victor FT, Tibblin G, Svardsudd KF. Signs of genital prolapse in a Swedish population of women 20 to 59 years of age and possible related factors. Am. J. Obstet. Gynecol. 180, 299–305 (1999).
8. Jelovsek JE, Maher C, Barber MD. Pelvic organ prolapse. The Lancet 2007;369:1027-38.
9. Hendrix SL, Clark A, Nygaard I, Aragaki A, Barnabei V, McTiernan A. Pelvic organ prolapse in the Women's Health Initiative: Gravidity and gravidity. Am J Obstet Gynecol 2002;186:1160-66.
10. Swift S, Woodman P, O'Boyle A, et al. Pelvic Organ Support Study (POSST): The distribution, clinical definition, and epidemiologic condition of pelvic organ support defects. Am J Obstet Gynecol 2005;192:795-806.
11. Swift SE. The distribution of pelvic organ support in a population of female subjects seen for routine gynecologic health care. Am J Obstet Gynecol 2000;183:277-85.
12. Swift SE, Tate SB, Nicholas J. Correlation of symptoms with degree of pelvic organ support in a general population of women: What is pelvic organ prolapse? Am J Obstet Gynecol 2003;189:372-9.
13. Gutman RE, Ford DE, Quiroz LH, Shippey SH, Handa VL. Is there a pelvic organ prolapse threshold that predicts pelvic floor symptoms? Am J Obstet Gynecol 2008;199:1-12.
14. Ghetti C, Gregory T, Edwards R, Otto LN, Clark AL. Pelvic organ descent and symptoms of pelvic floor disorders. Am J Obstet Gynecol 2005;193:53-7.
15. Hodgson B. AAGL Practice Guidelines on the Prevention of Apical Prolapse at the Time of Benign Hysterectomy. Journal of Minimally Invasive Gynecology (2014) 21, 715-722.
16. Sung VW, Rogers ML, Myers DL, Akbari HM, Clark MA. National trends and costs of surgical treatment for female fecal incontinence. Am J Obstet Gynecol. 2007:197:652e1.
17. Handa VL, Blomquist JL, Knoepp LR, Hoskey KA, McDermott KC, Munoz A. Pelvic floor disorders 5-10 years after vaginal or Cesarean childbirth. Obstet Gyneco. 2011;118:777.
18. Health, United States, 2010: With Special Feature on Death and Dying. Hyattsville, MD: National Center for Health Statistics, 2011.
19. Wright JD, Herzog TJ, Tsui J, Ananth CV, Lewin SN, Lu YS, Neugut AI, Hershman DL: Nationwide trends in the performance of inpatient hysterectomy in the United States. Obstet Gynecol 2013, 122:233-41.
20. Aigmueller T, Dungl A, Hinterholzer S, Geiss I, Riss P. An estimation of the frequency of surgery for posthysterectomy vault prolapse. Int Urogynecol J. 2010;21:299–302.
21. Altman D, Falconer C, Cnattingius S, Granath F. Pelvic organ prolapse surgery following hysterectomy on benign indications. Am J Obstet Gynecol. 2008;198:572.e1–572.e6.
22. Blandon RE, Bharucha AE, Melton LJ 3rd, et al., Incidence of pelvic floor repair after hysterectomy: a population-based cohort study. Am J Obstet Gynecol. 2007;197:664.e1–664.e7.
23. Mant J, Painter R, Vessey M. Epidemiology of genital prolapse: observations from the Oxford Family Planning Association Study. Br J Obstet Gynaecol. 1997;104:579–585.
24. Forsgren C, Lundholm CT, Johansson AL et al. Vaginal hysterectomy and risk of pelvic organ prolapse and stress urinary incontinence. Int. Urogynecol. J. Pelvic Floor Dysfunct. 23, 43–48 (2012).
25. DeLancey JO. Anatomic aspects of vaginal eversion after hysterectomy. Am J Obstet Gynecol. 1992; 166:1717-1724.
26. Cruikshank SH, Kovac SR. Randomized comparison of three surgical methods used at the time of vaginal hysterectomy to prevent posterior enterocele. Am J Obstet Gynecol 1999;180:859–65.
27. Eilber KS, Alperin M, Khan A, Wu N, Pashos CL, Clemens JQ, Anger JT: Outcomes of vaginal prolapse surgery among female Medicare beneficiaries: the role of apical support. Obstet Gynecol 2013, 122:981-7.
28. Walters MD, Ridgeway BM: Surgical treatment of vaginal apex prolapse. Obstet Gynecol 2013, 121:354-74.
29. Green-top Guideline No. 46. Post-Hysterectomy Vaginal Vault Prolapse. RCOG/BSUG Joint Guideline, Royal College of Obstetricians and Gynaecologists, July 2015. https://www.rcog.org.uk/en/guidelines-research-services/guidelines
30. Lowder JL. Meister M, Sutcliffe S, Ghetti C, Wang L, Winger DG, Shepherd JP. Reestablishing apical support at time of hysterectomy not performed for prolapse. Unpublished data, manuscript in progress.
31. Ross WT, Meister MR, Shepherd JP, Olsen MA, Lowder JL. Utilization of apical vaginal support procedures at time of hysterectomy performed for benign conditions: a national estimated. Accepted for oral presentation to the American Urogynecologic Society Annual Scientific Meeting, 2016. Submitted to Am J Obstet Gynecol.
32. Bulletins–Gynecology ACoP (2007) ACOG practice bulletin No. 85: pelvic organ prolapse. Obstet Gynecol 110(3):717–729. doi:10.1097/01.AOG.0000263925.97887.72
33. Brubaker L, Glazener, Jacquetin B, Maher C, Melgrem A, Norton P, Rajamaheswari, Von Theobald P. (2009) Committee 15: Surgery for Pelvic Organ Prolapse. Continence. EdsAbrams, Cardozo, Khoury, Wein. Health Publication Ltd. ISBN 0-9546956-8-2.
34. Kantartzis KL, Turner LC, Shepherd JP, Wang L, Winger DG, Lowder JL. Apical support at the time of hysterectomy for uterovaginal prolapse. Int Urogynecol J Pelvic Floor Dysfunct 2015 Feb;26(2):207-12. doi: 10.1007/s00192-014-2474-y.
35. Toozs-Hobson P, Swift S. POP-Q stage I prolapse: Is it time to alter our terminology? (2014) Int Urogynecol J.25:445-446.
36. Harmanli O. POP-Q 2.0: its time has come! (2014) Int Urogynecol J.25:447-449.
37. Bump RC, Mattiasson A, Bo K, Brubaker LP, DeLancey JO, Klarskov P, et al. (1999) The standardization of terminology of female pelvic organ prolpase and pelvic organ dysfunction. Am J Obstet Gynecol 180:299-305.
38. Abrams P, Cardozo L, Gall M, Griffitsh D, Rosier P, Ulmsten U, Van Kerrebroeck P, Victor A, Wein A. (2003) The standardization of terminology in lower urinary tract function: report from the standardization sub-committee of the Intrenational Continence Society. Urol. 67:37-49.
39. Nygaard I, Brubaker L, Zyczynski H, Cundiff G, Richter H, Gantz M, Fine P, Menefee S, Ridgeway B, Visco A, Warren LK, Zhang M, Meikle S. (2013) Long-term outcomes following abdominal sacrocolpopexy for pelvic organ prolapse. JAMA 309(19): 2016-2024.
40. Meister MR, Siobhan S, Lowder JL. Definitions of apical vaginal support loss: a systematic review. Am J Obstet Gynecol. Accepted for publication Sept 7, 2016.
41. Dietz HP, Mann KP. What is clinically relevant prolapse? An attempt at defining cutoffs for the clinical assessment of pelvic organ descent. (2014) Int Urogynecol J. 25:451-455.
42. Lowder JL, Oliphant SS, Shepherd JP, Ghetti C, Sutkin G. Genital hiatus size is associated with and predictive of apical vaginal support loss. Am J Obstet Gynecol. 2016 Jun;214(6):718.e1-8.

Disclosure

None reported.

MM

Uterine Morcellation: Fact and Fiction Surrounding the Recent Controversy

by Brooke Winner, MD & Scott Biest, MD

New devices and techniques that allow surgeons to offer more women the benefits of a minimally invasive approach should be further investigated and encouraged.





Brooke Winner, MD, Division of Minimally Invasive Gynecological Surgery, Assistant Professor, and Scott Biest, MD, Director, Division of Minimally Invasive Gynecological Surgery, Associate Professor; both in the Department of Obstetrics and Gynecology, Washington University School of Medicine.
Contact: winnerb@wudosis.wustl.edu

Abstract

Minimally invasive surgery is commonly used for hysterectomies because of its many benefits over open surgery. Although small uteri can be removed whole in this approach, larger specimens must be morcellated. Power morcellation has come under scrutiny recently because of concerns that it can disseminate occult uterine sarcoma, other undiagnosed malignancies, and benign tissue. To limit uterine tissue dissemination, morcellation can be contained within a bag. In addition, a careful preoperative workup should be performed to minimize the risk of occult malignancy. New techniques that allow surgeons to offer more women a minimally invasive approach should be investigated and encouraged.

Introduction and Background

Minimally invasive gynecologic surgery has many benefits over open surgery, including lower blood loss, decreased pain, shorter hospital stay, faster recovery, and fewer wound, bowel, and thrombotic complications.[1-4] In addition, laparoscopic hysterectomies have a three-fold lower risk of mortality than open hysterectomies.[4] In a total laparoscopic hysterectomy, a small uterus can be removed whole through the vagina at the end of the procedure. If the uterus is large, or in cases of supracervical hysterectomy (the cervix is not removed) or myomectomy (when no colpotomy is available through which to extract the specimen), the tissue must be morcellated before extraction. Morcellation can be performed manually with a scalpel, either vaginally or through a mini-laparotomy incision, or laparoscopically with a power morcellator.[5]

The Problem

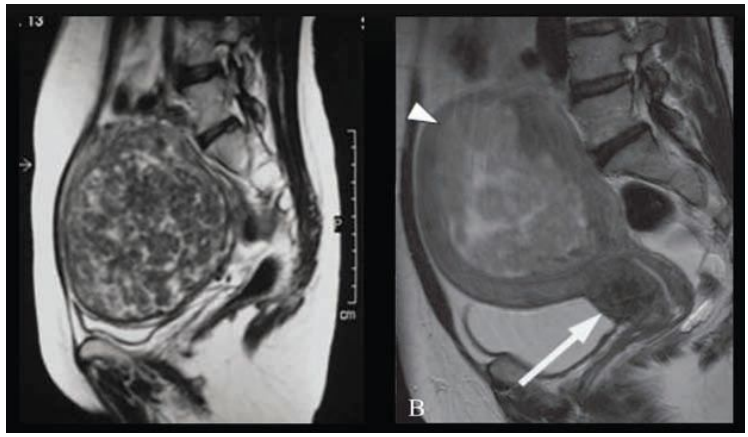
Power morcellation has come under scrutiny recently because of concerns regarding the dissemination of uterine tissue, particularly uterine sarcoma, throughout the abdomen. This concern was brought to public attention after a high-profile case in which an occult sarcoma was morcellated during a supracervical robotic hysterectomy for suspected benign fibroids at a Harvard-affiliated hospital in Boston. Coverage in the main-stream media was extensive, and in 2014 the Food and Drug Administration (FDA) issued a safety warning discouraging the use of power morcellation during hysterectomy and myomectomy.[6] In addition to concerns about disseminating sarcoma, other risks include dissemination of other malignancies, dissemination of benign tissue, direct damage to surrounding organs, and disruption of the pathologic specimen.[7-15]

Sarcoma

Uterine sarcomas, including stromal sarcoma and leiomyosarcoma,

are of particular concern because they can mimic benign fibroids and are difficult to diagnose preoperatively (see Figure 1). Fibroids cannot be biopsied directly due to concerns about bleeding and sampling error. Additionally, endometrial biopsy will only detect sarcoma 30-60% of the time (presumably when the sarcoma is eroding into the endometrium), so a negative biopsy does not rule out sarcoma.[16-17] One study showed that magnetic resonance imaging (MRI) in combination with serum levels of lactate dehydrogenase isoenzyme-3 predicted sarcoma[18], but that has not been replicated in other centers.

Figure 1
Uterine sarcomas are of particular concern because they can mimic benign fibroids and are difficult to diagnose preoperatively. The MRI image on the left is a fibroid. The image on the right is a sarcoma. Arrow on the right points to the uterus. Arrowhead on the right points to the sarcoma.



It is worth considering whether the benefits of minimally invasive surgery outweigh the risks of occult sarcoma. Previously, the risk of sarcoma was thought to be 1-2 per 1,000 patients.[19-24] However, the 2014 FDA analysis quoted a risk of 1 per 352.[6] Although this sounds like a much higher risk, all of these estimates fall within the same 95% confidence interval, and all equal a risk of less than 0.3%. Additionally, the FDA may have reported a higher rate for several reasons. First, the data were derived from nine single-institution studies from academic referral centers, which have higher rates of malignancy than in the community.[25-33] Second, the studies analyzed were from five countries, spanning several decades, with varying histopathologic criteria. Third, the studies included postmenopausal women and did not stratify for age. Fourth, no information about how many sarcomas were morcellated was included. Finally, and perhaps most importantly, the studies included women with sarcomas that were diagnosed preoperatively. Therefore, a reproductive-age woman presenting for a minimally invasive procedure with a negative preoperative workup may have a much lower rate of occult sarcoma than in the studies analyzed by the FDA.

Risk factors for sarcoma include age greater than 65 years, black race, tamoxifen use for more than five years, pelvic radiation, and a history of Lynch syndrome, hereditary leiomyomatosis, renal cell cancer, or childhood retinoblastoma.[34-41] Although a rapidly enlarging myoma is often cited as a risk factor for sarcoma, the evidence suggests this is not a reliable predictor.[42-43] For example, in one series of 1300 women undergoing surgery for presumed uterine myoma, the risk of sarcoma was 0.23% overall and 0.27% in those reporting rapid growth, a non-significant difference.[42]

The largest histologic subgroup of sarcoma is leiomyosarcoma. The overall survival is universally poor, and only 40% of patients are alive at five years.[34-35] Recurrence rates and survival outcomes are poor even in the setting of early stage disease. In a recent multi-institution study of women with stage I-II disease whose uteri were removed intact, 72% experienced a recurrence in the first 2.5 years after diagnosis, and median overall survival was only 52 months for the entire cohort.[44] However, there is evidence that morcellation of the sarcoma worsens the prognosis. Although the studies were all small, single-center, and retrospective, they reported that patients who underwent intraperitoneal morcellation of unsuspected leiomyosarcoma had a higher risk of recurrence and shorter progression-free survival than those who underwent en bloc resection.[44, 25, 45] The most recent of these studies demonstrated that those who underwent laparoscopic hysterectomy plus uncontained power morcellation had a higher risk of recurrence than those who underwent total abdominal hysterectomy (11 months vs. 40 months recurrence-free survival).[45]

Other Malignancies

Although most of the debate about uterine morcellation has centered around uterine sarcoma, cervical and endometrial cancers are more common. Because cervical and endometrial biopsies can reliably detect these malignancies preoperatively, the risk of occult dissemination should be low. However, after the 2014 FDA warning, Wright et al. published a new analysis in *The Journal of the American Medical Association* suggesting that dissemination of cervical and endometrial cancers is not as rare as previously thought.[46] The study used a large prospective database, accounting for 15% of all United States hospital admissions, to analyze the risk of occult malignancy in women undergoing morcellation at

Figure 2
Hand morcellation through a minilaparotomy incision, contained within a bag.

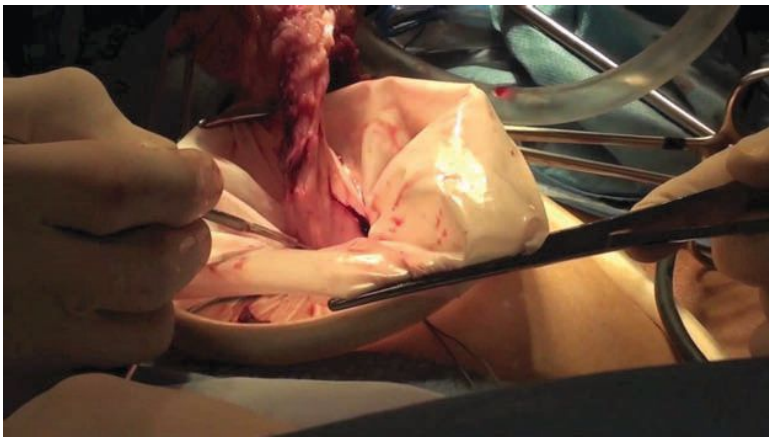
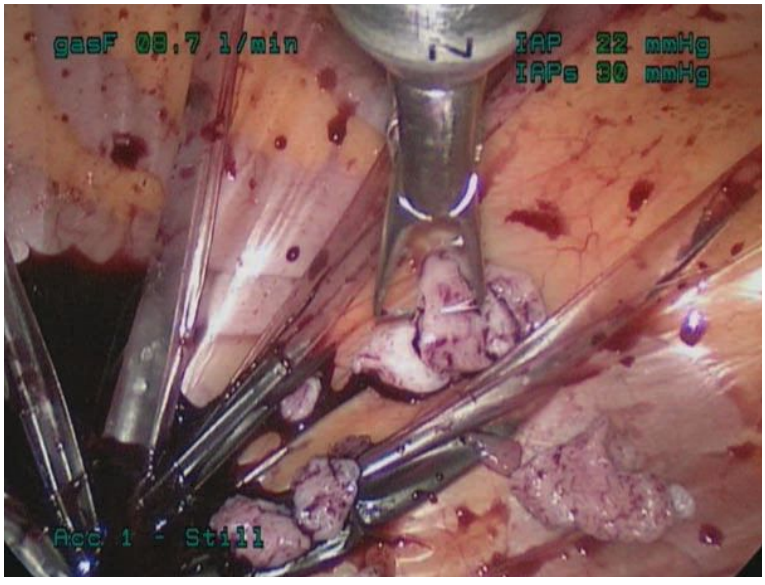


Figure 3
Power morcellation contained within an insufflated bag.



the time of their minimally invasive hysterectomy. In a cohort of 200,000 women undergoing minimally invasive hysterectomy, 15% underwent power morcellation. Of those, 1 in 368 had uterine cancer including all sarcoma and endometrial cancer. Because endometrial cancer is much more common than sarcoma, these data suggest that the FDA estimate of 1 in 352 for sarcoma alone is an overestimate. Additionally, the authors reported that 1 in 1,429 of those who underwent morcellation had some other gynecologic malignancy (cervical or adnexal), and 1 in 99 had endometrial hyperplasia. These findings highlight the importance of appropriate preoperative screening and workup, as most cervical and endometrial cancers should be detected preoperatively.

Another important component of this study was a subgroup analysis revealing that the rate of occult malignancy was highly variable by age. The rate ranged from 1 in 1,572 for women less than 40-years-old, to 1 in 33 for women greater than 65-years-old. However, 80% of women undergoing minimally invasive hysterectomy with morcellation in this cohort were under the age of 50. Therefore, average risk calculations, such as the 1 in 352 rate reported by the FDA, overestimate the risk of occult malignancy for the vast majority of these patients. Given these findings, age specific counseling regarding the rate of occult malignancy would be more appropriate.

Additional Concerns

Other concerns of power morcellation include dissemination of benign tissues, disruption of the pathologic specimen, and direct damage to surrounding organs.[7-15] Dissemination of benign tissue has led to disseminated leiomyomatosis and iatrogenic endometriosis, which can result in pain or bowel obstruction and require reoperation.[8-14] Disruption of the pathologic specimen has made it difficult for pathologists to identify malignancy or depth of invasion.[7,15] Finally, injury from the rapidly rotating blade of the power morcellator has caused bowel and vascular injuries and has resulted in deaths; surgeon inexperience is cited as the key risk factor for direct injury. Although the focus of this debate has been on power morcellation, manual morcellation can also disseminate tissue and worsen prognosis in the setting of occult malignancy.[44]

Potential Solutions

As suggested by Wright et al. dissemination of many malignancies could be prevented with an appropriate preoperative workup. The workup should include a history and physical, up-to-date cervical screening, and an endometrial biopsy if indicated. In taking a complete history, special attention should be paid to description of bleeding patterns, menopausal status, and a personal or family history of cancer. A complete physical exam should include an accurate description of uterine size, which is

measured according to the size the uterus would reach at different gestational weeks during pregnancy. Special note should be made of prominent lower uterine segment or cervical myomas, as these may increase the chance that morcellation will be required. Cervical cytology screening should be up-to-date, and abnormalities evaluated via the American Society for Colposcopy and Cervical Pathology guidelines before scheduling surgery.[47] Endometrial sampling should be performed per the American College of Obstetrics and Gynecology guidelines, which include sampling for women with any abnormal bleeding if they are over 45-years-old or have other risk factors.[48,49] Although endometrial biopsy detects an endometrial malignancy up to 95% of the time, sarcoma is only detected 30-60% of the time, so a negative biopsy does not rule out sarcoma.[16,17,19] However, endometrial biopsy is still the best test to diagnose sarcoma preoperatively, so if morcellation is planned, a low threshold to biopsy should be used. Imaging such as ultrasound or MRI may be indicated for other reasons (assessing uterine size, mapping fibroid location, etc.) but has not been shown to be useful in diagnosing sarcoma preoperatively.

Even with a careful preoperative workup, some malignancies will be missed. Therefore, to limit both benign and malignant uterine tissue dissemination, morcellation can be contained within a bag. Several such techniques have been described. For example, specimens can be placed in a bag and morcellated by hand either through the vagina or through a minilaparotomy incision (see Figure 2). Alternatively, power morcellation can be performed inside a bag (see Figure 3).[5] In 2014 Cohen et al. described the safety and feasibility of power morcellation within a large insufflated containment bag, and then in a follow-up study demonstrated negative cytologic washings after morcellation in vitro.[50, 51] In 2015, Winner et al. found that morcellation within an insufflated bag took twenty minutes longer than uncontained morcellation, with no increase in complications.[52] And in 2016, Cohen et al. published a prospective *in vivo* study in which uterine tissue was stained with dye before morcellation, and the pelvis was inspected after morcellation.[53] Dye/tissue leakage was noted in 7 out of 76 cases, although the authors noted that most of the dye leakage was likely due to the method of introduction; actually spillage of tissue fragments was only noted in one case. Together, these studies indicate that power morcellation within a containment bag is feasible and effective, although efforts should be made to improve the technique. In 2016, the FDA approved the first bag for contained morcellation.[54]

Currently, the American College of Obstetrics and Gynecology (ACOG), the Society of Gynecologic Oncology (SGO), and the American Association of Gynecologist Laparoscopists (AAGL) all suggest bags as potential solutions to prevent dissemination of tissue.[55,56,57] However, ACOG and AAGL also warn that these techniques require advanced laparoscopic skill and that appropriate training and credentialing are important considerations.

Conclusions

Uterine morcellation is sometimes required to perform a hysterectomy via a minimally invasive approach. Morcellation has become controversial recently because of concerns regarding dissemination of occult malignancy. However, laparoscopic hysterectomy results in significantly less morbidity and mortality than open hysterectomy. Potential solutions include a careful preoperative workup and performing morcellation contained within a bag. New devices and techniques that allow surgeons to offer more women the benefits of a minimally invasive approach should be further investigated and encouraged.

References

1. Nieboer TE, Johnson N, Lethaby A, Tavender E, Curr E, Garry R, et al. Surgical approach to hysterectomy for benign gynaecological disease. Cochrane Database Syst Rev 2009 Jul 8;(3):CD003677. doi(3):CD003677.
2. Wright KN, Jonsdottir GM, Jorgensen S, Shah N, Einarsson JI. Costs and outcomes of abdominal, vaginal, laparoscopic and robotic hysterectomies. Journal of the Society of Laparoendoscopic Surgeons. 2012 Oct-Dec;16(4):519-524.
3. American Congress of Obstetricians and Gynecologists Committee Opinion No. 444: Choosing the route of hysterectomy for benign disease. Obstet Gynecol 2009 Nov;114(5):1156- 1158.
4. Wiser A, Holcroft CA, Tolandi T, Abenhaim HA. Abdominal versus laparoscopic hysterectomies for benign diseases: evaluation of morbidity and mortality among 465,798 cases. Gynecological surgery 2013;10:117-122.
5. Kho KA, Anderson TL, Nezhat CH. Intracorporeal Electromechanical Tissue Morcellation A Critical Review and Recommendations for Clinical Practice. Obstet Gynecol 2014;124:787–93
6. U.S. Food and Drug Administration. 2014; Available at: http://www. fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm393576. htm. Accessed 04/07, 2014.
7. Milad MP, Milad EA. Laparoscopic Morcellator-Related Complications. J Minim Invasive Gynecol 2013 Dec 9.
8. Larrain D, Rabischong B, Khoo CK, Botchorishvili R, Canis M, MageG. "Iatrogenic" parasitic myomas: unusual late complication of laparoscopicmorcellation procedures. J Minim Invasive Gynecol 2010 Nov-Dec;17(6):719-724.
9. Nezhat C, Kho K. Iatrogenic myomas: new class of myomas? J Minim Invasive Gynecol 2010 Sep-Oct;17(5):544-550.
10. Hilger WS, Magrina JF. Removal of pelvic leiomyomata and endometriosis five years after supracervical hysterectomy. Obstet Gynecol 2006 Sep;108(3 Pt 2):772-774.
11. Kho KA, Nezhat C. Parasitic myomas. Obstet Gynecol 2009 Sep;114(3):611-615.
12. Takeda A, Mori M, Sakai K, Mitsui T, Nakamura H. Parasitic peritoneal leiomyomatosis diagnosed 6 years after laparoscopic myomectomy with electric tissue morcellation: report of a case and review of the literature. J Minim Invasive Gynecol 2007 Nov-Dec;14(6):770-775.
13. Sepilian V, Della Badia C. Iatrogenic endometriosis caused by uterine morcellation during a supracervical hysterectomy. Obstet Gynecol 2003 Nov;102(5 Pt 2):1125-1127.

14. Donnez O, Squifflet J, Leconte I, Jadoul P, Donnez J. Posthysterectomy pelvic adenomyotic masses observed in 8 cases out of a series of 1405 laparoscopic subtotal hysterectomies. J Minim Invasive Gynecol 2007 Mar-Apr;14(2):156-160.
15. Kho KA, Nezhat CH. Evaluating the risks of electric uterine morcellation. JAMA 2014
16. Bansal N, Herzog TJ, Burke W, Cohen CJ, Wright JD. The utility of preoperative endometrial sampling for the detection of uterine sarcomas. Gynecol Oncol 2008 Jul;110(1):43-48.
17. Jin Y, Pan L, Wang X, Dai Z, Huang H, Guo L, Shen K, Lian L. Clinical characteristics of endometrial stromal sarcoma from an academic medical hospital in China. Int J Gynecol Cancer. 2010 Dec;20(9):1535-9.
18. Goto A, Takeuchi S, Sugimura K, Maruo T. Usefulness of Gd-DTPA contrast-enhanced dynamic MRI and serum determination of LDH and its isozymes in the differential diagnosis of leiomyosarcoma from degenerated leiomyoma of the uterus. Int J Gynecol Cancer 2002 Jul-Aug;12(4):354-361.
19. Leibsohn S, d'Ablaing G, Mishell DR,Jr, Schlaerth JB. Leiomyosarcoma in a series of hysterectomies performed for presumed uterine leiomyomas. Am J Obstet Gynecol 1990 Apr;162(4):968-74; discussion 974-6.
20. Parker WH, Fu YS, Berek JS. Uterine sarcoma in patients operated on for presumed leiomyoma and rapidly growing leiomyoma. Obstet Gynecol 1994 Mar;83(3):414-418.
21. Takamizawa S, Minakami H, Usui R, Noguchi S, Ohwada M, Suzuki M, et al. Risk of complications and uterine malignancies in women undergoing hysterectomy for presumed benign leiomyomas. Gynecol Obstet Invest 1999;48(3):193-196.
22. Reiter RC, Wagner PL, Gambone JC. Routine hysterectomy for large asymptomatic uterine leiomyomata: a reappraisal. Obstet Gynecol 1992 Apr;79(4):481-484.
23. Rowland M, Lesnock J, Edwards R, Richard S, Zorn K, Sukumvanich P. Occult uterine cancer in patients undergoing laparoscopic hysterectomy with morcellation. Gynecologic oncology 2012;127(1):S29.
24. Kamikabeya TS, Etchebehere RM, Nomelini, R S., Murta, E F. Gynecological malignant neoplasias diagnosed after hysterectomy performed for leiomyoma in a university hospital. European journal of gynaecological oncology 2010;31(6):651-3.
25. Seidman MA, Oduyebo T, Muto MG, Crum CP, Nucci MR, Quade BJ. Peritoneal dissemination complicating morcellation of uterine mesenchymal neoplasms. PLoS One 2012;7(11):e50058.
26. Leibsohn S, d'Ablaing G, Mishell DR,Jr, Schlaerth JB. Leiomyosarcoma in a series of hysterectomies performed for presumed uterine leiomyomas. Am J Obstet Gynecol 1990 Apr;162(4):968-74; discussion 974-6.
27. Parker WH, Fu YS, Berek JS. Uterine sarcoma in patients operated on for presumed leiomyoma and rapidly growing leiomyoma. Obstet Gynecol 1994 Mar;83(3):414-418.
28. Takamizawa S, Minakami H, Usui R, Noguchi S, Ohwada M, Suzuki M, et al. Risk of complications and uterine malignancies in women undergoing hysterectomy for presumed benign leiomyomas. Gynecol Obstet Invest 1999;48(3):193-196.
29. Reiter RC, Wagner PL, Gambone JC. Routine hysterectomy for large asymptomatic uterine leiomyomata: a reappraisal. Obstet Gynecol 1992 Apr;79(4):481-484.
30. Rowland M, Lesnock J, Edwards R, Richard S, Zorn K, Sukumvanich P. Occult uterine cancer in patients undergoing laparoscopic hysterectomy with morcellation. Gynecologic oncology 2012;127(1):S29.
31. Kamikabeya TS, Etchebehere RM, Nomelini, R S., Murta, E F. Gynecological malignant neoplasias diagnosed after hysterectomy performed for leiomyoma in a university hospital. European journal of gynaecological oncology 2010;31(6):651-3.
32. Sinha R. Hegde A, Mahajan C, Dubey N, Sundaram M. Laparoscopic myomectomy: do size, number, and location of the myomas form limiting factors for laparoscopic myomectomy? J Minim Invasive Gynecol. 2008;15(3):292-300.
33. Leung F, Terzibackian JJ. Re "The impact of tumor morcellation during surgery on the prognosis of patients with apparently early uterine leiomyosarcoma". Gynecol Oncol. 2012;124(1):172-173
34. Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z,Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2011, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2011/, based on November 2013 SEER data submission, posted to the SEER web site, April 2014.
35. Brooks SE, Zhan M, Cote T, Baquet CR. Surveillance, epidemiology, and end results analysis of 2677 cases of uterine sarcoma 1989-1999. Gynecol Oncol 2004 Apr;93(1):204-208.
36. Yildirim Y, Inal MM, Sanci M, Yildirim YK, Mit T, Polat M, et al. Development of uterine sarcoma after tamoxifen treatment for breast cancer: report of four cases. Int J Gynecol Cancer 2005 Nov-Dec;15(6):1239-1242.
37. Fang Z, Matsumoto S, Ae K, Kawaguchi N, Yoshikawa H, Ueda T, et al. Postradiation soft tissue sarcoma: a multiinstitutional analysis of 14 cases in Japan. J Orthop Sci 2004;9(3):242-246.
38. Stewart EA, Morton CC. The genetics of uterine leiomyomata: what clinicians need to know. Obstet Gynecol. 2006 Apr;107(4):917-21.
39. Tamoxifen and uterine cancer. ACOG Committee Option No. 336. American College of Obstetricians and Gynecologists. Obstet Gynecol 2006
40. Toro JR, Nickerson ML, Wei MH, Warren MB, Glenn GM, Turner ML, et al. Mutations in the fumarate hydratase gene cause hereditary leiomyomatosis and renal cell cancer in families in North America. Am J Hum Genet 2003 Jul;73(1):95-106.
41. Yu CL, Tucker MA, Abramson DH, Furukawa K, Seddon JM, Stovall M, et al. Cause-specific mortality in long-term survivors of retinoblastoma. J Natl Cancer Inst 2009 Apr 15;101(8):581-591.
42. Parker WH, Fu YS, Berek JS. Uterine sarcoma in patients operated on for presumed leiomyoma and rapidly growing leiomyoma. Obstet Gynecol 1994 Mar;83(3):414-418.
43. Baird DD1, Garrett TA, Laughlin SK, Davis B, Semelka RC, Peddada SD. Short-term change in growth of uterine leiomyoma: tumor growth spurts. Fertil Steril. 2011 Jan;95(1):242-6
44. Park JY, Park SK, Kim DY, Kim JH, Kim YM, Kim YT, et al. The impact of tumor morcellation during surgery on the prognosis of patients with apparently early uterine leiomyosarcoma. Gynecol Oncol 2011 Aug;122(2):255-259.
45. George S, Barysauskas C, Serrano C, Oduyebo T, Rauh-Hain AJ, Del Carmen MG, et al. Retrospective cohort study evaluating the impact of intraperitoneal morcellation on outcomes of localized uterine leiomyosarcoma <br/>. Cancer 2014;In press.
46. Jason D. Wright, MD; Ana I. Tergas, MD, MPH; William M. Burke, MD; Rosa R. Cui; Cande V. Ananth, PhD, MPH; Ling Chen, MD, MPH; Dawn L. Hershman, MD, MS. Uterine Pathology in Women Undergoing Minimally Invasive Hysterectomy Using Morcellation. JAMA. 2014;312(12):1253-125
47. Massad LS, Einstein MH, Huh WK, Katki HA, Kinney WK, Schiffman M, et al. 2012 Updated Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests and Cancer Precursors. Obstet Gynecol 2013 Apr;121(4):829-846.
48. American College of Obstetricians and Gynecologists. ACOG committee opinion no. 557: Management of acute abnormal uterine bleeding in nonpregnant reproductive-aged women. Obstet Gynecol 2013 Apr;121(4):891-896.
49. McPencow AM, Erekson EA, Guess MK, Martin DK, Patel DA, Xu X. Cost-effectiveness of endometrial evaluation prior to morcellation in surgical procedures for prolapse. Am J Obstet Gynecol 2013 Jul;209(1):22.e1-22.e9.
50. Cohen SL, Einarsson JI, Wang KC, Brown D, Boruta D, Scheib SA, Fader AN, Shibley T. Contained power morcellation within an insufflated isolation bag. Obstet Gynecol. 2014 Sep;124(3):491-7
51. Cohen SL, Greenberg JA, Wang KC, Srouji SS, Gargiulo AR, Pozner CN, Hoover N, Einarsson JI. Risk of Leakage and Tissue Dissemination With Various Contained Tissue Extraction (CTE) Techniques: An in Vitro Pilot Study. J Minim Invasive Gynecol. 2014 Sep-Oct;21(5):935-9
52. Winner B, Porter A, Velloze S, Biest S. Uncontained Compared With Contained Power Morcellation in Total Laparoscopic Hysterectomy. Obstet Gynecol. 2015 Oct;126(4):834-8.
53. Cohen SL, Morris SN, Brown DN, Greenberg JA, Walsh BW, Gargiulo AR, Isaacson KB, Wright KN, Srouji SS, Anchan RM, Vogell AB, Einarsson J. Contained tissue extraction using power morcellation: prospective evaluation of leakage parameters. Am J Obstet Gynecol. 2016 Feb;214(2):257.e1-6.
54. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm494650.htm
55. ACOG. Power Morcellation and Occult Malignancy in Gynecologic Surgery: A Special Report. May 2014.
56. SGO. Position Statement: Morcellation. December 2013.
57. AAGL. Morcellation During Uterine Tissue Extraction. May 2014.

Disclosure

None reported.

MM

Opioid Use Disorder and Pregnancy

by Frederick T. O'Donnell, MD & Daniel L. Jackson, MD

Advances in health information technology have given providers increased leverage in confronting the burden of substance use disorders.





Frederick T. O'Donnell, MD, (left), Assistant Professor of Clinical Anesthesiology, Department of Anesthesiology and Perioperative Medicine; Daniel L. Jackson, MD, (right), Assistant Professor of Clinical Obstetrics and Gynecology, Department of Obstetrics, Gynecology and Women's Health, University of Missouri Women's and Children's Hospital, Columbia, Missouri.
Contact: odonnellf@health.missouri.edu

Abstract

Over-prescription of opioid pain medications and increases in heroin use have contributed to the sharp rise in opioid-related hospitalizations and overdose deaths among young adults in the United States, including pregnant women. This has imposed substantial direct and indirect costs to our nation's health care system. Effective treatment with methadone and buprenorphine is available, but significant barriers to care may restrict access for many. Improved screening tools and expanded access to treatments for substance use disorders are keys to addressing the epidemic of opioid use disorder.

Introduction

Opioid Use Disorder (OUD), a problematic pattern of opioid use that causes clinically significant impairment or distress,[1] has become epidemic in the United States, due largely to the over-prescription of opioid pain relievers during the past two decades. Since 1999, the number of opioid prescriptions has quadrupled, as have the number of drug overdose deaths in the U.S., 60% of which involve opioids including heroin.[2,3] In 2014, opioids accounted for a record 28,647 overdose deaths in the U.S.[4] In that same year, heroin was involved in 338 of Missouri's 1,067 drug overdose deaths.[2] In 2012, U.S. physicians wrote 259 million opioid prescriptions, many for patients, including pregnant women, with chronic, non-cancer related pain.[5,6] Each year since 2013 more Americans, including Missourians, have died of drug overdoses than have died in motor vehicle crashes, with young adults aged 18-25 being affected the most.[7] The estimated annual cost of substance use disorders in the U.S., including direct health care costs, lost productivity, and costs related to violence and crime, is $442 billion.[8] Abuse of prescription drugs has become so prevalent that Federal, State, and local agencies, including the Surgeon General, have called on all physicians and public health agencies to improve prevention efforts, diagnosis and management strategies, and to modify prescribing practices in order to combat the growing problem of OUD in the United States.[9]

History

In the 1990s, there was renewed attention on the under-treatment of chronic pain as a public health problem in the United States. The Institute of Medicine report, *Relieving Pain in America*,[10] called for more frequent and comprehensive assessment of pain (the "5th vital sign") by physicians in all specialties, including primary care. Many physicians, inadequately trained in treating chronic pain, found themselves caught between overprescribing opioids and undertreating pain. Over the next decade, liberal prescribing practices and the aggressive marketing of long acting, extended release formulations of opioids (e.g., OxyContin™) had some unintended consequences. The increase in opioid prescribing coincided with increased rates of opioid addiction, overdose deaths and hospitalizations, and entry into drug treatment programs.[11] Practitioners, and the medical community in general, largely overestimated the efficacy of opioids in

treating chronic pain and underestimated their associated risks of addiction, overdose, and death. Although very effective for the short term treatment of acute pain with a low risk of addiction, [12] prolonged use of opioid analgesics (i.e., greater than six weeks) for chronic, non-cancer related pain is not efficacious for reducing pain scores or improving functionality or quality of life.[13] Further, the risk of addiction for patients on long term opioid therapy for chronic pain is estimated to be 26-35%.[14, 15]

In response to the epidemic of OUD, State and Federal agencies have tightened regulatory controls on the dispensing and sale of prescription pain medications. In October 2016, the DEA announced new regulations that will reduce the manufacture of some prescription opioids by 25-34% in 2017.[16] To assist efforts at the state level, the Centers for Disease Control and Prevention (CDC) has developed the "Prevention for States" program, which provides funding to states with innovative solutions to address prescription drug overdose and abuse. Twenty-nine states (Missouri is not included) have received a share of these funds to institute safer prescribing practices. Prescription Drug Monitoring Programs (PDMPs), electronic databases that track the statewide prescription and dispensing of controlled substances, have been instrumental in limiting opioid prescribing in some states. Laws requiring prescribers in New York and Tennessee to query their state's PDMP prior to prescribing opioid analgesics have been effective in reducing the number of patients filling multiple prescriptions for the same drugs ("doctor shopping").[17] Similar laws in Florida have stopped high volume pain clinics ("pill mills") from prescribing and dispensing large quantities of opioid analgesics to patients with no justifiable need for them. Since 2010, overdose deaths in Florida due to oxycodone have decreased by 50%.[18] Despite being in the second highest quartile of opioid prescriptions per 100 people, Missouri is the only state without a PDMP.[19]

Heroin

Although regulatory efforts to curtail opioid prescribing have reduced the supply of prescription opioids, demand by non-medical users remains high because of the experiences or feelings they cause. Increasingly since 2005, heroin has filled this void as an inexpensive, readily available, and easy-to-use alternative to prescription opioids. According to the 2015 U.S. National Survey on Drug Use and Health, over 300,000 American adults reported using heroin in the past year.[20] The number of overdose deaths from heroin increased from 1,878 in 2004 to 10,574 in 2014, and have tripled since 2010 when a tamper resistant formulation of OxyContin™ was introduced.[21] It is estimated that 80% of new heroin users abused prescription opioids prior to using heroin.[22] Over the past 30 years, the cost of a gram of heroin has gone from nearly $3,000 (U.S.) to less than $500.[23] One of the authors (FTO) has been told by a patient at the University of Missouri with OUD that a gram of pure heroin can be purchased for as little as $200 in Columbia, Missouri. The gram is then typically divided into 10 "hits" that are sold individually.

Management of Opioid Use Disorder

The diagnostic criteria for opioid use disorder include the development of tolerance, and a strong desire or urge to use opioids (craving) despite negative social, occupational, and financial consequences.[1] Patients who abruptly discontinue opioids, voluntarily or otherwise, after long term regular use are at risk for the physical and psychologic symptoms of acute opioid withdrawal, which include pain, autonomic hyperactivity, sweating, nausea, vomiting, diarrhea, anxiety, and insomnia. Withdrawal symptoms occur when opioids rapidly dissociate from their receptors in the brain and spinal cord. Avoidance of withdrawal symptoms is one reason that patients with opioid use disorder continue to use and misuse opioids, even though they may wish to stop.

The standard of care for treating opioid use disorder is medication-assisted treatment (MAT) that combines daily medically-supervised administration of FDA-approved medications with behavioral therapy and counseling.[24] MAT is effective in facilitating recovery from OUD, preventing relapses, improving social and occupational functioning, and in reducing criminal behavior and the spread of infectious diseases.[25] The most effective treatment for withdrawal remains opioid replacement therapy with long acting opioids such as methadone and buprenorphine. These medications prevent withdrawal symptoms and opioid cravings by continuous occupation of endogenous opioid receptors. Methadone, a full agonist at the endogenous *mu* opioid receptor, has long been the mainstay of treatment for opioid addiction. Methadone has a long half-life and is ideally suited for once daily oral dosing, but it carries the risks of respiratory depression and is among the most commonly implicated prescription opioids in overdose deaths.[26] Despite its risks, methadone has been shown to reduce mortality in patients with opioid use disorder by half.[27] Methadone is available only from federally-regulated specialty clinics approved to prescribe and dispense the drug to patients who meet strict inclusion criteria. Most states provide Medicaid coverage for methadone maintenance therapy, but most of the 17 states that do not are located in areas of the U.S. with high rates of OUD and heroin use (e.g., the South, Midwest, and Ohio River Valley).[28]

Unlike methadone, buprenorphine is only a partial agonist at the *mu* receptor. This partial activity prevents withdrawal, but also blocks the action of full opioid agonists taken concomitantly.[29] Buprenorphine is thus limited in its potential to cause sedation and respiratory depression, a

Figure 1.
The 4Ps Plus©

Parents • *Did either of your parents ever have a problem with alcohol or drugs?*
Partner • *Does your partner have a problem with alcohol or drugs?*
Past • *Have you ever drunk beer, wine, or liquor?*
Pregnancy • *In the month before you knew you were pregnant, how many cigarettes did you smoke?* • *In the month before you knew you were pregnant, how many beers/how much wine/how much liquor did you drink?* • *In the month before you knew you were pregnant, how much marijuana did you smoke?*

Reprinted with permission, NTI Upstream

safety advantage over methadone.[30] Buprenorphine is available as a rapidly dissolving sublingual tablet or buccal film, some formulations of which contain small amounts of the opioid antagonist naloxone (Narcan™) to deter intravenous injection of the drug. Compared to methadone, buprenorphine is not restricted to specialty clinics and is available by prescription from office-based physicians who are specially trained in treating opioid use disorder and have DEA approval to prescribe it. Although outpatient buprenorphine therapy is covered by Medicaid in all 50 states, it may be inaccessible in many areas due to a shortage of physicians licensed by the DEA to prescribe it.

Although both are effective, the choice between methadone and buprenorphine depends on individual patient factors such as proximity to treatment programs. Whenever long term opioid therapy is elected for, patients are encouraged to participate in educational programs as well as cognitive and behavioral therapy such as individual or group counseling and participation in self-help groups like Narcotics Anonymous. Although maintenance therapy with methadone or buprenorphine can be tapered down over time and in some cases discontinued altogether, most individuals require lifelong treatment as relapse rates are high.[31]

In addition to its proven efficacy, medication-assisted treatment of OUD is cost saving. Every dollar spent on treatment of substance use disorders saves $4 in health care costs and $7 in criminal justice costs.[32]

Pregnancy

Since 2002, the incidence of first time heroin use has doubled among women and among young adults aged 18-25 years, a demographic that includes many pregnant women.[33] According to the American College of Obstetrics and Gynecology, 1% of pregnant women report nonmedical use of opioid pain medications.[34] Pregnant women with opioid use disorder are at increased risk for adverse pregnancy outcomes including preterm labor, fetal death, growth restriction, and neonatal abstinence syndrome, which increased by 300% from 2000 to 2009.[35,36]

Universal screening for substance use disorders, including opioid use disorder, is recommended in pregnancy, and should occur at the initial prenatal visit and be performed again once per trimester for those who screen positive for past use. This should be done using a validated screening tool such as the 4Ps Plus questionnaire (see Figure 1),[37] an instrument to quickly identify obstetric patients at risk for misusing alcohol, tobacco, and illicit drugs, or the three question set of "In the past year how many times have you had more than four alcoholic drinks per day, used tobacco, or taken illegal drugs or used prescription drugs for non-medical purposes?".[38] Screening by means of a questionnaire is recommended over the use of universal urine drug screens, which have poor sensitivity and specificity for chronic use, and it is essential that the topic of substance use disorder be broached in a non-judgmental fashion. Care for women with opioid use disorder should be approached in a manner similar to that for women with other chronic conditions such as diabetes, chronic hypertension, obesity, or any of the myriad of maternal comorbidities that complicate pregnancy.

The goal of treating maternal OUD is to use the lowest possible dose of methadone or buprenorphine in order to eliminate cravings and withdrawal. While it has traditionally been taught that maternal withdrawal during opioid detoxification is harmful to the fetus, a recent publication by Bell, et al. challenges this notion.[39] Patients will frequently state a desire to wean off of MAT during pregnancy in order to minimize the risk of neonatal abstinence syndrome (NAS). We generally recommend against this approach due to the unacceptably high risk of relapse, which ranges from 35 to 75% depending on the intensity of outpatient therapy.

In regards to the fetus, maternal opioid use disorder carries significant risks. Maternal overdose and the associated risk of coma, aspiration, hypothermia, and cardiovascular collapse can be life threatening for the developing fetus. Neonates exposed to opioids *in utero* have a risk of neonatal abstinence syndrome (NAS) that is as high as 90%.[34]

NAS is characterized by neonatal irritability, temperature dysregulation, poor feeding, failure to thrive, and in some cases seizures. This condition may last for up to 10 weeks after delivery and may necessitate a prolonged NICU admission.[40] Some data suggests a lower rate of NAS with buprenorphine therapy as opposed to methadone, but this data is far from conclusive.[41] Although buprenorphine alone (Subutex™) has been traditionally preferred over buprenorphine-naloxone (Suboxone™) for pregnant women due to concerns about the fetal effects of naloxone, oral naloxone is biologically inert and a growing body of data supports the safety of buprenorphine-naloxone use in pregnancy.

The peripartum period is a particularly challenging time to provide care for women with OUD. Due to chronic opioid use and the development of tolerance, these individuals may require larger doses of pain medications than providers are typically accustomed to giving. This can lead to the patient being accused of 'drug seeking behavior' and her pain going untreated.

Our approach to caring for women on MAT at the time of delivery is to maximize the use of multimodal analgesia and to use regional anesthesia whenever possible. Neuraxial anesthesia (i.e., spinal or epidural) is the preferred method for both vaginal and cesarean delivery. Of note, there is no contraindication to intrathecal morphine in the setting of MAT use. In women with OUD undergoing vaginal delivery, we also treat pain with acetaminophen and NSAIDS and if necessary increase the dose of methadone or buprenorphine. In women who continue to have refractory pain, we will use adjunctive opioid therapy in the form of oral medication or patient controlled analgesia (PCA) as appropriate (intravenous or transdermal fentanyl in the setting of buprenorphine use) with early outpatient follow up with the patient's MAT provider.

Pregnant women on MAT with buprenorphine and methadone require careful attention in regards to medication interactions. The use of opioid agonist/antagonists such as butorphanol (Stadol™) or nalbuphine (Nubain™) is absolutely contraindicated in patients on methadone or buprenorphine due to the risk of precipitated withdrawal. Additionally, our practice is to avoid the concurrent use of full opioid agonists with buprenorphine. Because of buprenorphine's higher binding affinity for the *mu* receptor compared with full agonists (except fentanyl),[42] individuals undergoing induction of buprenorphine therapy must be free of opioids and in withdrawal before starting buprenorphine. In an individual with opioid dependence who has a full opioid agonist in her system and is therefore not in withdrawal, giving a dose of buprenorphine will result in the partial agonist buprenorphine displacing the full agonist from the *mu* receptors, which would in turn precipitate withdrawal due to the lower *mu* agonist activity of buprenorphine. Furthermore, an individual on long term buprenorphine therapy with refractory pain is unlikely to achieve adequate analgesia with typical *mu* receptor agonists (oxycodone, hydrocodone, morphine, etc) because large doses of these medications will be necessary to overcome the higher binding affinity of the buprenorphine.

As part of the treatment plan, it is essential to assure patients that the care team will do everything possible to manage the pain associated with labor and delivery and that the treatment of surgical pain will not increase the risk of relapse. If a patient enters prenatal care on MAT, it is recommended that the same provider continue to manage her MAT during pregnancy. In cases where MAT is initiated by an obstetric provider, arrangements should be made for continued treatment with MAT post-partum, which may entail cooperation with a methadone clinic, primary care provider, or addiction psychiatrist as appropriate. It is also important to arrange for consultation between the patient and the pediatricians or neonatologists who will be caring for the baby after delivery. The care of the child affected by maternal opioid use does not end at delivery and the patient should have an opportunity to ask questions regarding the post-partum care plan.

Although MAT with either methadone or buprenorphine is recognized as the standard of care for treating OUD during pregnancy, significant barriers to care exist and prevent more than half of pregnant women with OUD from receiving the recommended treatments.[43] Many women with OUD live in states where methadone is not covered under Medicaid, or live in areas where there are no physicians who are licensed to prescribe buprenorphine. Women in the criminal justice system are even less likely to receive standardized care for OUD. In addition to issues relating to accessibility and funding, women are significantly less likely to receive MAT (or even to seek prenatal care at all) in states that permit child abuse charges for illicit drug use during pregnancy. Although Tennessee is currently the only state in which a woman can face criminal charges for substance abuse during pregnancy, 18 states permit civil child abuse charges that may result in termination of parental rights. Missouri has no such laws and does not require drug testing or physician reporting of suspected substance use disorders during pregnancy.[28] Missouri is also one of only 12 states that offers pregnant women priority access to treatment programs for substance use disorders and does not impose limits on the dose or duration of buprenorphine therapy.

Future Directions

The opioid epidemic continues to shape Federal, State, and local health care policies on substance use disorders. The Comprehensive Addiction and Recovery Act, signed into law in

July 2016, provides new funding for measures to prevent and treat opioid use disorder, and such strategies must continue to evolve.

Prevention

Primary prevention of substance use disorders depends on effective prevention education. School and community-based prevention programs (e.g., *Communities that Care*) that teach skills to resist negative social influences have proven to reduce rates of initiation and escalation of alcohol, tobacco, and drug use among adolescents and young adults.[21] Many such programs, though effective, are underutilized and poorly implemented. It is estimated that only 8-10% of U.S. high schools utilize evidence-based programs to prevent substance misuse.[44] An emerging field within public health is improving the implementation and dissemination of evidence-based prevention programs at the community level, where they are most effective.

Despite some successful efforts to curtail the prescription and consumption of opioids, opioid pain relievers are still the most prescribed class of drugs in the United States.[45] Prescription drug monitoring programs have shown promise, but in many states they are underutilized because their use is voluntary.[46] A national PDMP, or interconnecting those of individual states could potentially prevent patients from crossing state lines to obtain and fill multiple prescriptions, but would require further investments in health information technologies and infrastructure. More widespread adoption of programs such as the *CDC Guideline for Prescribing Opioids for Chronic Pain* can help promote responsible and safe prescribing practices.

Another key aspect of preventing OUD is stemming the flow of heroin and illegally produced fentanyl, as well as counterfeit prescription opioids, into the United States. Most of the heroin sold in the U.S. comes from Mexico and South America, where it enters the Southwestern U.S. via established drug trafficking routes.[47] Heroin seizures at the border have tripled over the past five years. In response to this, the Office of National Drug Control Policy's 2015 National Drug Control Strategy includes a Southwest Border Counternarcotics Strategy to combat drug trafficking and organized criminal activity. Similar law enforcement strategies are in place at the U.S.-Canada and U.S.-Caribbean borders.

Treatment

Given the increasing burden of opioid use disorder in the U.S., we face the formidable public health challenge of expanding access to proven treatment modalities for people who need them most. It is estimated that only 1 in 10 persons with a substance use disorder receives medication-assisted treatment (MAT). It is therefore imperative to develop health care policies that make MAT more widely available and integrate it into existing general health care settings, thereby improving access to care and reducing the stigma of substance use disorders. The Office of National Drug Control Policy has advocated for therapeutic, rather than punitive, approaches to addressing opioid use disorder and treating it as a chronic medical condition rather than a moral failing or lack of willpower.

The 2010 Affordable Care Act (ACA) requires health care plans to provide coverage for mental health and substance use disorder services, one of the 10 designated categories of "essential health benefits".[21] However, a relative shortage of physicians who are certified to treat patients with OUD is a significant barrier to delivering care. The 2000 Drug Addiction Treatment Act increased the number of physicians permitted to prescribe buprenorphine for treating OUD by waiving the requirement to obtain a separate DEA registration for that purpose. In 2016, the Federal Substance Abuse and Mental Health Services Administration (SAMHSA) increased the buprenorphine-naloxone prescriber limit from 100 patients to 275 patients. However, fewer than 4% of office-based physicians in the U.S. are authorized to prescribe buprenorphine as part of MAT, and even fewer obstetricians can provide such care. According to SAMHSA, 215 physicians in Missouri are licensed to prescribe buprenorphine, including one of the authors (DLJ). Increasing prescribing capacity will be necessary to meet the increasing demand for OUD treatment. Information on obtaining a DEA physician waiver for prescribing buprenorphine is available at http://www.samhsa.gov/medication-assisted-treatment.

Another provision of the ACA allows states to expand Medicaid coverage to include individuals who qualify based on income, many of whom are affected by, or at risk for developing, substance use disorders including OUD. This expanded coverage includes mental health services and substance use disorder treatments in addition to general medical care. Missouri is one of 19 states not currently participating in the voluntary expansion of Medicaid. An estimated 3 million people who would qualify for expanded Medicaid coverage live in states that don't participate in Medicaid expansion.[48]

Advances in health information technology have given providers increased leverage in confronting the burden of substance use disorders. Telehealth, computerized Prescription Drug Monitoring Programs, and electronic medical records allow greater efficiency in treating patients with OUD and have much potential to expand OUD treatment services into areas where they are currently unavailable. Another barrier to providing treatment for OUD is a lack of reimbursement for screening and counseling services. To this end, the Office of National Drug Control Policy is pursuing initiatives to update

coding and increase reimbursement for Screening, Brief Intervention, and Referral to Treatment (SBIRT), an evidence-based practice to identify and treat OUD.

Conclusions

Though significant progress has been made on many fronts in the fight against the opioid epidemic, more research is needed in order to gain a better understanding of the determinants of addiction, effective prevention strategies, and ways to more effectively deliver treatment to those struggling with the many facets of opioid use disorder.

References

1. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, 2013. Washington DC. American Psychiatric Association.
2. Injury Prevention & Control: Opioid Overdose. CDC. https://www.cdc.gov/drugoverdose/. Accessed 09/24/16.
3. Betses M, Brennan T. Abusive prescribing of controlled substances -- a pharmacy view. N Engl J Med 2013;369:989-991.
4. Rudd, R. A., Aleshire, N., Zibbel, J. E., & Gladden, R. M. (2016). Increases in drug and opioid overdose deaths — United States, 2000–2014. MMWR, 64(50), 1378-1382.
5. CDC vital signs, July 2014. Opioid painkiller prescribing. Available at: http://www.cdc.gov/vitalsigns/opioid-prescribing/. Accessed 11/04/16.
6. Levy, B., Paulozzi, L., Mack, K. A., & Jones, C. M. (2015). Trends in opioid analgesic–prescribing rates by specialty, US, 2007–2012. American Journal of Preventive Medicine, 49(3), 409-413.
7. National Center for Health Statistics. Health, United States, 2015: With Special Feature on Racial and Ethnic Health Disparities. Hyattsville, MD. 2016.
8. National Drug Intelligence Center. (2011). National drug threat assessment. Washington, DC: U.S. Department of Justice.
9. U.S. Department of Health and Human Services (HHS), Office of the Surgeon General, Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health. Washington, DC: HHS, November 2016.
10. Pizzo P, Clark N, Carter-Pokras OD, et al. 2011. Relieving pain in America: A blueprint for transforming prevention, care. Education, and Research. OIM (Institute of Medicine).
11. Drug overdose deaths in the United States continue to increase in 2015. CDC. https://www.cdc.gov/drugoverdose/epidemic/index.html. Accessed 10/01/16.
12. Kunins HV, Farley TA, Dowell D. Guidelines for opioid prescription: why emergency physicians need support. Ann Intern Med 2013;158:841-842
13. Manchikanti L, Ailinani H, Koyyalagunta D, et al. A systematic review of randomized trials of long-term opioid management for chronic noncancer pain. Pain Physician. 2011;14:91-121.
14. Frieden TR, Houry D. Reducing the risks of relief—the CDC opioid-prescribing guideline. N Engl J Med 2013;374:501-1504.
15. Boscarino JA, Rukstalis MR, Hoffman SN, et al. Prevalence of prescription opioid-use disorder among chronic pain patients: comparison of the DSM-5 vs. DSM-4 diagnostic criteria. J AddictDis. 2011;30(3):185-94.
16. DEA puts quota on production of opioid painkillers. https://medlineplus.gov/news/fullstory_161326.html. Accessed 11/04/16.
17. Prescription Drug Monitoring Programs (PDMPs). CDC. https://www.cdc.gov/drugoverdose/pdmp/index.html. Accessed 11/04/16
18. CDC. Decline in drug overdose deaths after state policy changes—Florida, 2010-2012. MMWR 2014;63:569-74.
19. Patrick SW, Fry CE, Jones TF, et al. Implementation of prescription drug monitoring programs associated with reductions in opioid-related death rates. Health Affairs 2016;35:1324-32.
20. Center for Behavioral Health Statistics and Quality. (2016). Results from the 2015 National Survey on Drug Use and Health: Detailed tables. Rockville, MD: Substance Abuse and Mental Health Services Administration.
21. U.S. Department of Health and Human Services (HHS), Office of the Surgeon General, Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health. Washington, DC: HHS, November 2016.
22. Dart RC, Surratt HL, Cicero TJ, et al. Trends in opioid analgesic abuse and mortality in the United States. N Engl J Med 2015;372:241-248.
23. Compton WM, Jones CM, Baldwin GT. Relationship between nonmedical prescription-opioid use and heroin use. N Engl J Med 2016;374:154-163.
24. Schuckit MA. Treatment of opioid-use disorders. N Engl J Med 2016;375:357-368.
25. McLellan et al, The Effects of Psychosocial Services in Substance Abuse Treatment, JAMA, 1993 Apr 21;269(15):1953-9.
26. Ossiander EM. Using textual cause-of-death data to study drug poisoning. Am J Epidemiol. 2014 Apr 1;179(7):884-94.
27. Cousins G, Boland F, Courtney B, Barry J, Lyons S, Fahey T. Risk of mortality on and off methadone substitution treatment in primary care: a national cohort study. Addiction 2016;111:73-82.
28. Rinaldo, S. G., & Rinaldo, D. W. (2013). Availability without accessibility? State Medicaid coverage and authorization requirements for opioid dependence medications. American Society of Addiction Medicine. Available: www.asam. org/docs/default-source/advocacy/aaam_implications-for-opioid-addictiontreatment_final. Accessed: October 31, 2016.
29. Soyka M. New developments in the management of opioid dependence: focus on sublingual buprenorphine-naloxone. Subst Abuse Rehabil 2015;6:1-14.
30. Dahan A, Yassan A, Romberg R, et al. Buprenorphine induces ceiling in respiratory depression but not in analgesia. Br J Anaesth. 2006;96:627.
31. Hser YI, Hoffman V, Grella CE, et al. A 33-year follow-up of narcotics addicts. Arch Gen Psychiatry 2001;58:503-508.
32. Ettner, S. L., Huang, D., Evans, E., et al. (2006). Benefit-cost in the California treatment outcome project: Does substance abuse treatment "pay for itself"? Health Services Research, 41(1), 192-213).
33. CDC. Vital Signs: Demographic and substance use trends among heroin users—United States, 2002-2013. MMWR 2015;64:719-25.
34. Women, ACoG cfU and M. American Society of Addiction, ACOG Committee Opinion No. 524: Opioid abuse, dependence, and addiction in pregnancy. Obstet Gynecol 2012;119(5):1070-6.
35. Patrick SW, et al. Neonatal abstinence syndrome and associated health care expenditures: United States, 2000-2009. JAMA 2012;307(18):1934-40.
36. Saia KA, Schiff D, Wachman EM, et al. Caring for pregnant women with opioid use disorder in the USA: expanding and improving treatment. Curr Obstet Gynecol Rep 2016;5:257-263.
37. Chasnoff IJ, Hung WC. The 4P's Plus© Screen for Substance Use in Pregnancy. Chicago, IL: NTI Upstream, 2002. For permission please contact http://ntiupstream.com/contactnti.
38. McNeely, J., Cleland, C. M., Strauss, S. M., Palamar, J. J., Rotrosen, J., & Saitz, R. (2015). Validation of self-administered single-item screening questions (SISQs) for unhealthy alcohol and drug use in primary care patients. Journal of General Internal Medicine, 30(12), 1757-1764.
39. Bell, J., et al., Detoxification from opiate drugs during pregnancy. Am J Obstet Gynecol, 2016. 215(3): p. 374 e1-6.
40. Brady, K.L., Katie, Addiction and Substance Abuse. Clinical Updates in Women's Health Care, 2012. 11(1).
41. Noormohammadi, A., et al., Buprenorphine Versus Methadone for Opioid Dependence in Pregnancy. Ann Pharmacother, 2016. 50(8): p. 666-72.
42. Buprenorphine: an alternative to methadone. Med Lett Drugs Ther, 2003. 45(1150): p. 13-5.
43. Angelotta C, Weiss CJ, Angelotta JW, et al. A moral or medical problem? The relationship between legal penalties and treatment practices for opioid use disorders in pregnant women. Womens Health Issues 2016;26(6):595-601.
44. Ringwalt, C., Hanley, S., Vincus, A. A., Ennett, S. T., Rohrbach, L. A., & Bowling, J. M. (2008). The prevalence of effective substance use prevention curricula in the Nation's high schools. The Journal of Primary Prevention, 29(6), 479-488.
45. Levy, B., Paulozzi, L., Mack, K. A., & Jones, C. M. (2015). Trends in opioid analgesic–prescribing rates by specialty, US, 2007–2012. American Journal of Preventive Medicine, 49(3), 409-413.
46. Haffajee, R. L., Jena, A. B., & Weiner, S. G. (2015). Mandatory use of prescription drug monitoring programs. JAMA, 313(9), 891-892.
47. 2015 National Drug Threat Assessment Summary, DEA, DEA-DCT-DIR-008-16, Oct 2015; Drug Enforcement Administration Office of Intelligence; Department of Homeland Security Office of Intelligence and Analysis.
48. Garfield, R., Damico, A., & Cox, C. (2015). New estimates of eligibility for ACA coverage among the uninsured. Washington, DC: Kaiser Family Foundation.

Disclosure

None reported.

MM

Comparison of Family Medicine and General Internal Medicine on Diabetes Management

by Kimberly A. Zoberi, MD, Joanne Salas, MPH, Cassie N. Morgan, MSW & Jeffrey F. Scherrer, PhD

As the diabetes epidemic continues to grow in the United States, it is logical that family medicine physicians will see increasing numbers of patients with more severe type 2 diabetes.



Kimberly A. Zoberi, MD, (above), Joanne Salas, MPH, Cassie N. Morgan, MSW, and Jeffrey F. Scherrer, PhD, are in the Department of Family and Community Medicine, Saint Louis University School of Medicine.
Contact: zoberika@slu.edu

Synopsis

The majority of patients with type 2 diabetes are managed in primary care, either in family medicine (FM) or general internal medicine (GIM). Variances in training, beliefs and practice decisions between FM and GIM may result in differing approaches to diabetes management. This study found that differences do exist in the choice of treatment by FM vs GIM; however, these differences are driven by patient characteristics and does not result in glycemic control disparities.

Abstract

Background and Objectives

Approach to management of chronic health conditions differs between family medicine (FM) and general internal medicine (GIM). Differences might be due to beliefs, patient case mix, training, and/or experience. This study determined if FM and GIM diabetes management differences exist, and if so, resulted in better or worse glycemic control.

Method

Electronic medical record data from 2008-2013 were used to identify 976 patients (287 FM and 689 GIM) with type 2 diabetes and prescriptions for metformin. GEE-type regression models were computed to control for repeated measures and estimate the association between primary care specialty and glycemic control, defined as percent of patients with HgA1c<8.5 and average HgA1c. Covariates included demographics, comorbidities, smoking and health care utilization, and diabetes treatment.

Results

Compared to FM patients, significantly more GIM patients received a non-metformin medication (35.9% vs 47.2%) and insulin (16.4% vs 23.8%). After adjusting for covariates, FM patients had significantly lower HgA1c values (B = -.47; 95% CI: -0.68, -0.27) and were less likely to have an HgA1c>8.5 (OR=0.55; 95%CI:0.40-0.77). FM vs GIM patients did not differ in degree of HgA1c improvement over time.

Conclusions

FM patients vs GIM patients are less likely to receive a non-metformin and insulin medication. Differences in diabetes management likely correspond to degree of HgA1c control. Choice of treatment appears to reflect patient needs as both FM and GIM patients experienced equal improvement in HgA1c. Primary care specialty differences in beliefs and practices around diabetes management do not result in disparities in patient care.

Background

The majority of patients with type 2 diabetes are managed in primary care, either in family medicine (FM) or general internal medicine (GIM). Extant research indicates that FM providers differ from GIM in beliefs, attitudes and practice decisions in managing type 2 diabetes; however, this sparse literature is inconsistent.

A qualitative analysis of primary care attitudes toward diabetes management did not find differences between FM and GIM physicians.[1] Hayes and colleagues[2] stratified survey data by primary care specialty, comparing the beliefs of FM and GIM physicians regarding initiating insulin. While beliefs were mostly similar, a significant difference in beliefs was that FM physicians agreed more strongly than GIM that "most patients would not need to go on insulin if they would follow their physicians' recommendations."[2] Other studies have shown that actual practice decisions differ between FM and GIM physicians.[3] During a period of increasing use of oral anti-diabetic agents between 1990-2001, repeated surveys conducted in 1990, 1996, and 2001 indicated that the percent of FM patients receiving an oral anti-diabetic medication was consistently lower at each time point (36%, 31%, and 33%) than the percent of GIM patients receiving these medications (41%, 41%, and 39%).[3]

Attitudes toward care are partly formed by differences in training. FM providers receive twice as much behavioral medicine training as GIM providers and train in line with a biopsychosocial model while internal medicine physicians follow a pathophysiological model.[4] These differences influence the decisions providers make concerning diagnoses, labs, and medication orders.[4] Evidence of practice differences between FM and GIM have been reported for both typical primary care visits and specific conditions.[5-8]

Most important to determining evidence of practice differences is whether they impact patient outcomes. If FM providers encourage behavioral interventions and GIM physicians are quicker to turn to medications, these decisions could influence the course of diabetes and certainly contribute to the cost of care. To our knowledge, there is only one recent chart review study which found HgA1c control (<7%) was similar in FM and GIM patients (99.2% and 97.8%, respectively.[9] However this study did not include provider type in multivariate models with HgA1c control as the outcome. Therefore it is not known if patient characteristics and treatment differences between GIM and FM are associated with differences in HgA1c control.

The objectives of this study were to first determine if prescribing of non-metformin medications and insulin among patients, currently prescribed metformin, differed between FM and GIM physicians. Second, we compared change in HgA1c over time as a function of primary care specialty to determine if patient outcomes differed between FM and GIM care after controlling for patient characteristics and the treatment received. If differences in patient outcome exist, additional physician training and awareness of deficits is needed. On the other hand, a lack of difference in outcomes would suggest variation in treatment is due to patient need and not physician specialty training and philosophy.

Methods

Data were obtained from a Primary Care Patient Data (PCPD) Registry created from electronic medical records of FM or GIM clinic encounters between July 1, 2008 and July 31, 2013. The PCPD Registry includes data from ICD-9-CM codes, prescription orders, Current Procedural Terminology (CPT) codes, social and family history, demographics, laboratory orders, referrals, and vital signs. The PCPD contains 27,225 patients (FM=10,994 patients, GIM=16,231 patients) who had at least one encounter (e.g. office visit, procedure visit, or clinical support) during the study period. Encounters occurred in any of the three ambulatory care clinics staffed by FM (approximately 12-15 faculty) or any of the three ambulatory clinics staffed by GIM (over 100 faculty and residents). GIM and FM clinics were located at the same three locations, geographically dispersed throughout the St. Louis metropolitan area covering urban and suburban areas. Additional details of the PCPD and examples of its use for primary care research have been previously reported.[8,10-13] IRB approval was obtained for the creation and use of the PCPD Registry for research.

Eligibility

The research design allowed patients to enter the cohort anytime between July 1, 2008 and July 31, 2013. Change in HgA1c values over time varied by patient with some having values for several years and other patients contributing several months of HgA1c laboratory results. For the present study, the cohort was restricted to patients 18 years and older (n=25,378) with type 2 diabetes (ICD-9 codes 250.x0, 250.x2; n=2,855) and at least two clinic visits during the observation period (n=2,634). Additionally, patients had to have no record

of insulin prescriptions on their first visit (n=2,412) and all patients must have been prescribed metformin to be eligible for analysis (n=1,227). These eligibility restrictions were used to limit the range of variability at the start of diabetes management. Patients with very modest hyperglycemia and dietary controlled diabetes were excluded because too much error and lack of follow-up data would be present. Finally, patients must have had at least one valid HgA1c value, resulting in a final sample of 976 patients (FM- 287 patients, GIM= 689 patients) with 2,404 HgA1c values.

Outcome

To determine if prescribing differences exist between FM and GIM, our first outcome was prescription of a non-metformin medication and insulin. To determine if prescribing differences resulted in different patient outcomes, we used HgA1c values as the outcome. We classified available HgA1c values as uncontrolled (>8.5%) or controlled (8.5% or lower). This threshold was chosen because it accommodates a higher HgA1c goal, which may be appropriate in elderly or fragile patients. Separate models were computed for percent of patients in HgA1c control over the observation time and for average HgA1c over time.

Diabetes Medications

The use of metformin, insulin, and non-metformin diabetic drugs were defined as any prescription from July 1, 2008 to July 31, 2013. The use of a non-metformin drug and insulin were treated as outcomes for the first part of the analytic approach and treated as covariates when modeling HgA1c values as an outcome.

Covariates

Covariates were selected to allow for drawing comparisons to demographic groups including age, race, and gender. To control for detection bias, we modeled volume of health care utilization. Last, to control for protective and risk factors related to diabetes outcomes, we adjusted for referral to dietary education, obesity, smoking, and the Romano adapted Charlson comorbidity index.[14] The comorbidity index is computed from ICD-9 codes for 17 health conditions associated with morbidity and mortality with higher scores pointing to greater morbidity and mortality. Descriptive information for specific comorbidities that may differ between physician groups and prescription outcomes was also assessed (e.g. retinopathy, neuropathy, nephropathy, cardiovascular disease, cerebrovascular disease, hypertension and hyperlipidemia).

Race was dichotomized into white versus non-white categories. Health care utilization was measured by the average number of clinic visits computed for each patient per month and was modeled as a binary variable measuring high utilizers (top 25th percentile of average clinic visits per month) vs non-high utilizers (lower 75th percentile). An electronic medical record indicator in which a patient was referred to dietary education was treated as a binary variable.

Obesity was defined by body mass index (30.0 kg/m^2 or above) and/or an ICD-9-CM diagnosis (278.00). Smoking status was obtained from patient social history and categorized as never, past, and current (for the study period).

Analytic Approach

Comorbidities and diabetic drug prescriptions were treated as prevalent conditions for 2008-2013. The prevalence of demographics and covariates were calculated and compared between FM (n=287) and GIM (n=689) patients, non-metformin drug (n=428) vs no non-metformin drug (n=548), and insulin (n=211) vs no insulin (n=765) using chi-square for categorical variables and independent sample t-tests for continuous variables. To measure the association between type of primary care specialty, glycemic control across all HgA1c values available during study period, and control for repeated observations of HgA1c within a patient, generalized estimating equations (GEE), and marginal multilevel linear models were used. These models account for multiple observations per patient over time by treating subject correlation of HgA1c over time as a nuisance parameter. GEE and marginal models describe changes in a population mean given covariates. Inferences from these models will help assess whether FM and GIM patients, on average, differ in HgA1c value or HgA1c control, regardless of time. Month was used as a continuous time indicator from 1 to 65, representing the months of available data in the PCPD Registry. An interaction term using month and specialty (specialty*month) assessed whether the course of HgA1c over time was similar among the patient specialties. Because there was no significant interaction, subgroup analyses are not presented. Multivariate adjusted models were created by adding all covariates to the crude model assessing the average association of patient specialty and HgA1c.

Table 1. Characteristics of FM and GIM patients with diabetes and at least 2 visits 2008-2013, age 18 and over, with at least one valid HgA1c value, by provider type (n=976)

Variable, % (n)	Overall (n=976)	FM (n=287)	GIM (n=689)	p-value
Age, mean (sd)	59.3 (11.8)	57.2 (12.0)	60.2 (11.6)	<.001
Non-white race	59.8 (584)	46.0 (132)	65.6 (452)	<.0001
Female	60.8 (593)	66.9 (192)	58.2 (401)	.011
High utilization (top 25%)	57.9 (565)	56.1 (161)	58.6 (404)	.464
Comorbidity Index, mean (sd)	2.5 (1.9)	2.1 (1.6)	2.7 (2.0)	<.0001
Neuropathy	19.6 (191)	20.6 (59)	19.2 (132)	.616
Nephropathy	5.9 (58)	3.8 (11)	6.8 (47)	.072
Retinopathy	4.5 (44)	2.4 (7)	5.4 (37)	.044
Cardiovascular disease	23.1 (225)	20.2 (58)	24.2 (167)	.173
Cerebrovascular disease	6.5 (63)	2.1 (6)	8.3 (57)	.0003
Hypertension	83.1 (811)	79.4 (228)	84.6 (583)	.049
Hyperlipidemia	68.0 (664)	65.5 (188)	69.1 (476)	.274
Obese	79.1 (772)	86.1 (247)	76.2 (525)	.001
Smoking Status				
Never	47.8 (466)	57.5 (165)	43.7 (301)	
Quit	28.9 (282)	22.6 (65)	217 (31.5)	<.001
Current	23.4 (228)	19.9 (57)	24.8 (171)	
Referral to dietary education	21.4 (209)	27.5 (79)	18.9 (130)	.003
Non-metformin prescription	43.9 (428)	35.9 (103)	47.2 (325)	.001
Insulin prescription	21.6 (211)	16.4 (47)	23.8 (164)	.010
Number of HgA1c values*	n=2,404	n=763	n=1641	
HgA1c, mean (sd)	7.9 (1.9)	7.5 (1.6)	8.0 (2.0)	<0.0001
% A1c >8.5	26.5% (637)	18.5% (141)	30.2 (496)	<0.0001
HgA1c level				
< 7.0	39.3 (944)	47.2 (360)	35.6 (584)	
7.0 to < 8.0	25.5 (614)	26.6 (203)	25.1 (411)	
8.0 to <9.0	12.8 (307)	11.4 (87)	13.4 (220)	.0001
9.0 to <10.0	8.4 (203)	5.8 (44)	9.7 (159)	
≥ 10.0	14.0 (336)	9.0 (69)	26.3 (267)	

*HgA1c values computed from number of laboratory values available from patients; p-value based on marginal GEE and multilevel linear models

Results

As shown in Table 1, of 976 patients with diabetes and receiving metformin, 59.8% were non-white, 60.8% female, and an average of 59.3±11.8 years of age. Older patients were disproportionately in GIM ($p<0.001$), as were non-white patients ($p<0.0001$). Female patients were more common in FM ($p<0.05$). GIM patients had a significantly greater comorbidity index score ($p<0.0001$) and were more likely to be current smokers ($p<0.001$), while the prevalence of obesity was greater among FM patients ($p=0.001$). GIM patients also had a higher prevalence of retinopathy ($p=.044$), cerebrovascular disease ($p=.0003$), and hypertension ($p=.049$). Patients were more often prescribed a non-metformin medication ($p=.001$) and insulin ($p=0.01$) if treated in GIM vs FM. Average HgA1c value was significantly ($p<0.0001$) higher in GIM patients compared to FM patients (8.0 vs 7.5), and a higher proportion of GIM, compared to FM, HgA1c values were >8.5 (30.2% vs 18.5%; $p<0.0001$).

Table 2. Characteristics of FM and GIM patients with diabetes and at least 2 visits 2008-2013, age 18 and over, with at least one valid HgA1c value, by non-metformin prescription and by insulin prescription (n=976)

	Non-metformin			Insulin		
Variable, % (n)	No (n=548)	Yes (n=428)	p-value	No (n=765)	Yes (n=211)	p-value
Age, mean (sd)	58.2 (11.8)	60.7 (11.7)	.001	59.6 (11.7)	58.2 (12.1)	.119
Non-white race	62.8 (344)	56.1 (240)	.034	58.6 (448)	64.5 (136)	.122
Female	59.7 (327)	62.1 (266)	.432	60.1 (460)	63.0 (133)	.445
High utilization (top 25%)	56.6 (310)	59.6 (255)	.345	53.6 (410)	73.5 (155)	<.0001
Comorbidity Index, mean (sd)	2.4 (1.8)	2.6 (2.0)	.108	2.3 (1.8)	3.2 (2.2)	<.0001
Neuropathy	17.9 (98)	21.7 (93)	.133	16.2 (124)	31.7 (67)	<.0001
Nephropathy	4.6 (25)	7.7 (33)	.039	4.6 (35)	10.9 (23)	.0006
Retinopathy	3.8 (21)	5.4 (23)	.249	3.3 (25)	9.0 (19)	.0004
Cardiovascular disease	22.8 (125)	23.4 (100)	.838	20.1 (154)	33.6 (71)	<.0001
Cerebrovascular disease	5.5 (30)	7.7 (33)	.158	4.7 (36)	12.8 (27)	<.0001
Hypertension	82.5 (452)	83.9 (359)	.563	82.5 (631)	85.3 (180)	.332
Hyperlipidemia	65.3 (358)	71.5 (306)	.040	66.1 (506)	158 (74.9)	.016
Obese	79.9 (438)	78.0 (334)	.471	78.7 (602)	80.6 (170)	.553
Smoking Status (08-13)			.117			
Never	49.1 (269)	46.0 (197)		48.4 (370)	45.5 (96)	
Quit	26.3 (144)	32.2 (138)		29.3 (224)	27.5 (58)	.367
Current	24.6 (135)	21.7 (93)		22.4 (171)	27.0 (57)	
Referral to dietary education	23.0 (126)	19.4 (83)	.174	20.0 (153)	26.5 (56)	.040
Insulin prescription	19.3 (106)	24.5 (105)	.051	--	--	--
Non-metformin prescription	--	--	--	42.2 (323)	49.8 (105)	.051
Number of HgA1c values*	n=1263	n=1141		n=1792	n=612	
HgA1c, mean (sd)	7.5 (1.8)	8.3 (1.9)	<.0001	7.5 (1.6)	9.0 (2.3)	<.0001
% HgA1c >8.5	18.4 (232)	35.5 (405)	<.0001	18.0 (322)	51.5 (315)	<.0001

Table 3. Marginal GEE and multilevel linear models, FM and GIM patients with diabetes and at least 2 visits 2008-2013, age 18 and over, with at least one valid HgA1c value (n=976 patients, n=2404 HgA1c values)

	HgA1c value, B (95% CI)		HgA1c > 8.5, OR (95% CI)	
	Crude*	Adjusted	Crude†	Adjusted
Intercept	8.05 (7.91, 8.19)	8.14 (7.45, 8.82)	---	---
Patient type				
FM	-0.58 (-0.81, -0.35)	-0.47 (-0.68, -0.27)	0.52 (0.39, 0.70)	0.55 (0.40, 0.77)
GIM	0.00	0.00	1.00	1.00
Month		0.007 (0.003, 0.01)		1.01 (1.00, 1.02)
Age, mean (sd)		-0.02 (-0.03, -0.007)		0.98 (0.97, 0.99)
Non-white race		0.36 (0.16, 0.56)		1.72 (1.28, 2.31)
Female		-0.13 (-0.34, 0.08)		0.81 (0.61, 1.09)
High utilization (top 25%)		-0.44 (-0.64, -0.24)		0.59 (0.44, 0.79)
Comorbidity Index, mean (sd)		-0.06 (-0.11, -0.01)		0.95 (0.88, 1.02)
Obese		0.13 (-0.11, 0.37)		1.20 (0.84, 1.73)
Smoking Status (08-13)				
Never		0.00		1.00
Quit		-0.25 (-0.48, -0.02)		0.60 (0.43, 0.85)
Current		-0.01 (-0.26, 0.23)		1.09 (0.78, 1.53)
Referral to dietary education		0.18 (-0.07, 0.42)		0.98 (0.71, 1.35)
Non-metformin diab drug RX		0.79 (0.59, 0.99)		2.85 (2.17, 3.73)
Insulin RX		1.55 (1.27, 1.82)		5.88 (4.29, 8.07)

* Interaction of month*patient type for HgA1c value, p = .354, † Interaction of month*patient type for HgA1c > 8.5, p = .422

The distribution of patient characteristics by prescription for a non-metformin medication and insulin is shown in Table 2. Non-metformin prescription was significantly associated with older age ($p<0.001$) and inversely associated with non-white race ($p=0.034$). Gender was not significantly associated with non-metformin prescription and no demographic variable was significantly associated with insulin prescription. High health utilization was not associated with non-metformin prescription, but those who were prescribed insulin were significantly more likely to be high utilizers ($p<0.0001$). Higher mean comorbidity

index scores were not associated with non-metformin prescription, but patients receiving insulin prescriptions had significantly larger mean comorbidity index score compared to patients not receiving an insulin prescription ($p<0.0001$). Only hyperlipidemia was positively associated with receiving a non-metformin prescription ($p=.040$) while neuropathy, nephropathy, retinopathy, cardiovascular disease, cerebrovascular disease and hyperlipidemia were associated with insulin prescription ($p<.05$). Obesity and smoking were not associated with prescriptions for non-metformin or insulin.

Referral to dietary education was not significantly associated with non-metformin prescription but was positively associated with prescription for insulin ($p=0.04$). A non-significant trend was observed for a positive association between receiving a prescription for a non-metformin medication and receiving a prescription for insulin. Last, average HgA1c and percent of HgA1c values >8.5% were positively associated with prescription for a non-metformin medication and for insulin ($p<0.0001$).

The first available HgA1c among all patients was examined (individual HgA1c not shown). Overall, 27.5% of patients had an initial HgA1c > 8.5 and average initial HgA1c was 7.9 (sd = 2.0). Among FM patients, 22.6% had an initial HgA1c > 8.5 compared to 29.5% of GIM patients ($p=.03$). Mean initial HgA1c for FM patients was 7.6 (sd = 1.8) compared to 8.1 (sd = 2.1) for GIM patients ($p=.001$). On average, among all HgA1c values across the study period (n = 2,404), 26.5% (n=637) were > 8.5 and the average HgA1c was 7.9± 1.9. Out of 763 HgA1c values for FM patients over time, 18.5% (n=141) were > 8.5 and the average HgA1c was 7.5±1.6. Out of 1,641 HgA1c values over time for GIM patients, 30.2% (n=496) were > 8.5 and the average HgA1c was 8.0 ±2.0.

The results from separate GEE and multilevel linear models are shown in Table 3. Both before and after controlling for covariates, the mean HgA1c was significantly lower among FM patients compared to GIM patients (beta=-0.47; 95% CI:-0.68, -0.27). Before and after controlling for covariates, the odds of having an HgA1c value > 8.5 was significantly lower among FM patients compared to GIM patients (OR=0.55; 95%CI:0.40-0.77). There was no significant interaction between time and primary care specialty for HgA1c value ($p=.354$) or percent HgA1c > 8.5 ($p=.422$); thus, FM and GIM did not differ in monthly course of HgA1c across the study period.

Discussion

Among 287 FM and 689 GIM patients with type 2 diabetes and receiving metformin, we observed significantly greater use of non-metformin medications and insulin in GIM patients. FM patients were more likely to be referred to dietary education compared to GIM patients. These practice differences are consistent with the fact that regardless of any time trend, GIM patients had on average higher HgA1c values and higher odds of HgA1c >8.5 than FM patients. However, in both FM and GIM patients, the differences in treatment decisions and practices did not result in worse or better outcomes in HgA1c levels over time.

Previous studies reporting lower rates of oral anti-diabetic medication prescribing by FM vs GIM physicians and prior evidence that FM providers' attitudes support a desire to avoid insulin are consistent with the current findings.[2,3] However, the present results indicate practice differences are likely driven by the degree of glycemic control at time of treatment initiation. Because FM and GIM patients had similar stability in HgA1c over time, differences in practice do not equate to differences in patient outcomes. GIM patients were older, had more comorbidities and higher HgA1c values, which likely pointed to the need for greater use of non-metformin medications and insulin, while the younger, less complicated FM patients with lower HgA1c values supports the logic of greater use of dietary education.

Our results are consistent with evidence that patient panel demographics play a role in variations of care between FM and GIM physicians. In a study of elderly patients with diabetes, Chin and colleagues[15] demonstrated that the patient populations treated by endocrinologists or GIM physicians had more comorbidities and diabetic complications than those treated by FM practitioners. This appears to be consistent with the findings of this paper. FM physicians typically see a younger population and a wider distribution of ages, even when patients < age 18 are excluded.[16,17]

There are several limitations to the present study. We are unable to measure adherence to medication because data did not include fill dates. This makes it impossible to estimate measures such as medication possession ratio. Likewise, referrals to dietary education do not allow measuring engagement with a dietician. We used a diagnosis of BMI>30 to define obesity but lacked data on duration of obesity, which may have had a stronger influence on HgA1c. Post-hoc analysis was run treating BMI as a continuous variable and the results were the same with no significant association between BMI and our outcome. Last, the patient sample is limited to an academic medical center in the Midwest and results may not apply to private practice settings or other demographic groups in the United States.

This paper demonstrates that GIM physicians are more likely than FM physicians to prescribe a non-metformin drug and insulin for patients with diabetes who are already taking metformin. Prescriptions for non-metformin medication were strongly associated with older age and higher HgA1c values, and insulin prescriptions were strongly associated with greater comorbidity and higher HgA1c values. Thus, factors associated with prescribing these medications also distinguish FM and GIM patients. As reviewed by Shackelton-Piccolo et al.,[4] training and philosophical orientation to medicine differs between FM and GIM, and beliefs about diabetes management and actual practice differences exist between these primary care specialties.[2,3] The present study supports the conclusion that these differences are likely due to patient characteristics typical of GIM vs FM patients. Most importantly, we found no evidence that patients fair better or worse in terms of glycemic control when treated by FM vs GIM providers.

As the diabetes epidemic continues to grow in the United States, it is logical that FM physicians will see increasing numbers of patients with more severe type 2 diabetes. Future research should return to the present analysis to determine if differences in treatment decisions and practices remain if the patient population with type 2 diabetes in FM begins to present with levels of hyperglycemia currently observed in GIM.

References

1. Helseth LD, Susman JL, Crabtree BF, O'Connor PJ. Primary care physicians' perceptions of diabetes management: a balancing act. J Fam Pract. 1999;48(1):37-42.
2. Hayes RP, Fitzgerald JT, Jacober SJ. Primary care physician beliefs about insulin initiation in patients with type 2 diabetes. Int J Clin Pract. 2008;62(6):860-868.
3. Wysowski DK, Armstrong G, Governale L. Rapid increase in the use of oral antidiabetic drugs in the United States, 1990-2001. Diabetes Care. 2003;26(6):1852-1855.
4. Schackelton-Piccolo R, McKinlay JB, Marceau LD, Goroll AH, Link CL. Differences between internists and family practitioners in the diagnosis and management of the same patient with coronary heart disease. Med Care Res Rev. 2011;68(6):650-666.
5. Noren J, Frazier T, Altman I, DeLozier J. Ambulatory medical care: a comparison of internists and family-general practitioners. New Engl J Med. 1980;302(1):11-16.
6. Ewing GB, Selassie AW, Lopez CH, McCutcheon EP. Self-report of delivery of clinical preventive services by U.S. physicians. Comparing specialty, gender, age, setting of practice, and area of practice. J Prev Med. 1999;17(1):62-72.
7. Higgins AY, Doubeni AR, Phillips KL, et al. Self-reported colorectal cancer screening of Medicare beneficiaries in family medicine vs internal medicine practices in the United States: a cross-sectional study. BMC Gastroenterol. 2012;12:23.
8. Brieler JA, Scherrer JF, Salas J. Differences in prescribing patterns for anxiety and depression between general internal medicine and family medicine. J Affect Disorders. 2015;172:153-158.
9. Rao DT, Sunio LK, Lo YJ, Gossain VV. Comparison of the adherence to the American Diabetes Association guidelines of diabetes care in primary care and subspecialty clinics. Journal of Diabetes and Metabolic Disorders. 2015; 14 (35): 1-7.
10. Devkota B, Salas J, Sayavong S, Scherrer JF. Use of an online patient portal and glucose control in primary care patients with diabetes. Popul Health Manag. 2016;19(2):125-131.
11. Hooks-Anderson DR, Crannage EF, Salas J, Scherrer JF. Race and referral to diabetes education in primary care patients with prediabetes and diabetes. Diabetes Educator. 2015;41(3):281-289.
12. Scherrer JF, Salas J, Brieler JA, Miller BJ, Meyer D, Schneider FD. Depression leads to incident vascular disease: Evidence for the relevance to primary care. Fam Pract. 2015;32(2):147-151.
13. Schoen MW, Salas J, Scherrer JF, Buckhold FR. Cholesterol treatment and changes in guidelines in an academic medical practice. Am J Med. 2015;128(4):403-409.
14. Romano PS, Roos LL, Jollis JG. Adapting a clinical comorbidity index for use with ICD9-CM administrative data: differing perspectives. J Clin Epidemiol. 1993;46(10):1075-1079; discussion 1081-1090
15. Chin MH, Zhang JX, Merrell K. Specialty differences in the care of older patients with diabetes. Med Care. 2000;38(2):131-140.
16. Kravitz RL, Greenfield S, Rogers W, et al. Differences in the mix of patients among medical specialties and systems of care: Results form the medical outcomes study. JAMA. 1992;267(12):1617-1623.
17. Bahn TJ, Cronau HR, Way DP. A comparison of family medicine and internal medicine experiences in a combined clerkship. Fam Med. 2003;35(7):499-503.

Disclosure

None reported.

MM

Chronic Lymphocytic Leukemia and the Side Effects of Therapy: 2017 Review

by Asim Ahmad, MD & Clint Daniel Kingsley, MD

There is no standard first line therapy and the choice of agent depends on numerous factors including but not limited to, patient's goals of therapy, patient's performance status, and the cytogenetics of the disease.





Asim Ahmad, MD, (left), Postdoctoral Fellow, and Clint Daniel Kingsley, MD, FACP, (right), MSMA member since 2006, Associate Professor of Medicine; both are in the Hematology/Medical Oncology Division, Department of Medicine, University of Missouri - Columbia School of Medicine.
Contact: kingsleyc@health.missouri.edu

Abstract

In recent years, the choice of therapies for symptomatic Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) have grown exponentially, with no single agreed upon standard first-line therapy. The choice of therapy is often dictated by goals of care, patient characteristics and tumor genetic abnormalities. The goal of this article is to familiarize the primary care provider with some of the most commonly used therapeutic modalities with attention to the side effect profile of these regimens.

Introduction

Chronic lymphocytic leukemia (CLL) represents an accumulation of lymphocytes that are functionally incompetent and usually arise from a monoclonal origin. It is considered identical to the mature B cell non-Hodgkin neoplasm, small lymphocytic lymphoma (SLL). CLL occurs primarily in the blood while SLL occurs primarily in the lymph nodes. CLL represents around 25 to 30 percent of leukemias in the United States, and is one of the most common leukemias in adults in western countries.[1] CLL is more common in men and tends to affect older adults, with a median age at diagnosis of 71.6 years.[2]

CLL can present with a wide array of symptoms, but the vast majority of patients are asymptomatic and are incidentally diagnosed when a routine blood count reveals absolute lymphocytosis. Only 5 to 10 percent of patients present with typical "B" symptoms of extreme fatigue fevers, unintentional weight loss, or drenching night sweats.[3] The most common physical finding is lymphadenopathy, and as alluded to earlier, the most common laboratory abnormality is lymphocytosis. (see Figure 1) The diagnosis is confirmed by an absolute B lymphocyte count greater than or equal to 5000/microL and demonstration of clonality of circulating B lymphocytes by flow cytometry of the peripheral blood.[3] Of note, a bone marrow aspirate and biopsy are not required for the diagnosis. (see Figures 2 and 3).

CLL represents a heterogenous disease with certain subsets not requiring treatment at time of diagnosis. With the potential exception of allogenic hematopoietic cell transplantation, CLL at the present cannot be cured. Numerous prospective trials have established that delayed treatment strategies result in similar long-term survival when compared to early treatment.[4] In general, therapy is indicated in the setting of "B" symptoms, Rai stage III or IV (Binet stage C) anemia or thrombocytopenia (see Table 1), autoimmune hemolytic anemia and/or thrombocytopenia that is poorly responsive to corticosteroid therapy, rapidly progressive disease manifested by a lymphocyte doubling time of less than six months, rapid enlargement of lymph nodes, spleen or liver, or recurrent episodes of infection.[5] The goal of therapy is to ameliorate symptoms and improve overall and progression free survival, which unfortunately drop precipitously as a patients stage of disease progresses (see Graph 1).

Figure 1
Lymphocytosis in peripheral blood due to CLL.
Photograph courtesy of Donald Doll

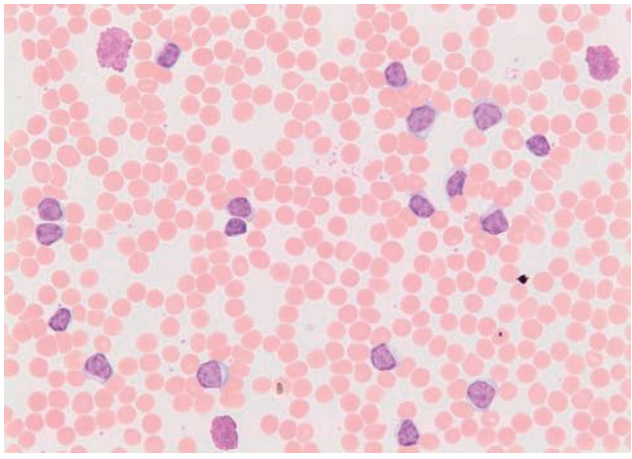


Figure 2
Lower power view of CLL marrow infiltration.
Photograph courtesy of Donald Doll, MD.

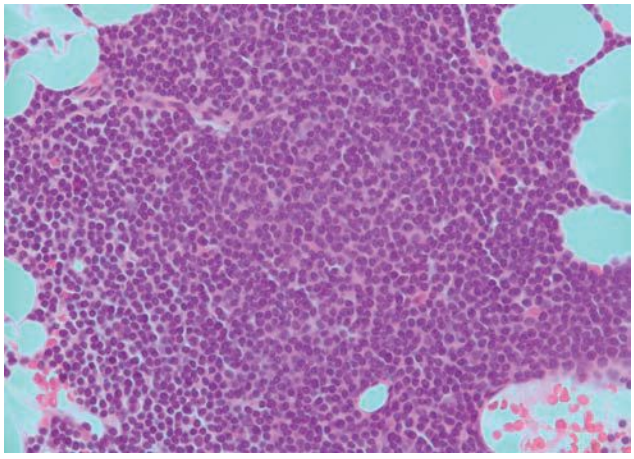
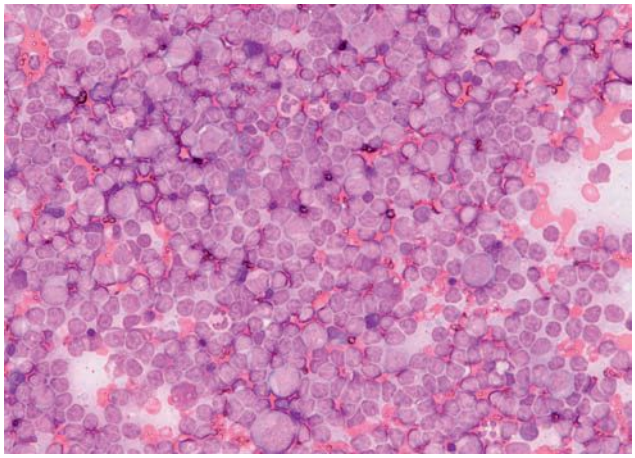


Figure 3
High power view of CLL marrow infiltration.
Photograph courtesy of Donald Doll, MD.



In recent years, the choice of therapies for symptomatic CLL/SLL have grown exponentially. There is no single agreed upon standard first-line therapy as most regimens have not been compared directly. The choice of therapy is often dictated by goals of care and patient characteristics. Importantly, certain genetic abnormalities, particularly, del(17p) or del(11q) require particular attention (see Graph 2). The goal of this article is to familiarize the primary care provider with some of the most commonly used therapeutic modalities with attention to the side effect profile of these regimens. Often, the CLL patient will present to their primary provider with signs/symptoms attributed to these drugs. We hope that by educating the provider regarding the most commonly used drugs, we can empower them to provide the best care possible for their patient.

Therapeutic Agents

Fludarabine, a purine analog, is often combined with rituximab, an anti-CD20 agent, and/or cyclophosphamide, an alkylating agent, for the treatment of young and fit patients with symptomatic CLL. Long term toxicity with this regimen is comprised mostly of myelotoxicity and infectious complications.[6] Severe neutropenia was noted in over 50% of patients in one study, but major and minor infections occurred in only 2.6 and 10 percent of cycles respectively.[7] Fludarabine is also associated with autoimmune hemolytic anemias and should be avoided in patients with a history of autoimmune hemolytic anemia or autoimmune thrombocytopenia. The treatment of autoimmune anemia/thrombocytopenia consists of prompt cessation of fludarabine and initiation of immunosuppressive agents including corticosteroids. Side effects of anti-CD20 monoclonal antibody therapy include reactivation of hepatitis B. All patients should be screened for hepatitis B infection and monitored during and after therapy for clinical or laboratory signs of hepatitis B. Progressive multifocal leukoencephalopathy is a rare but often fatal complication that can occur up to a year after therapy. Consider this disease in patients with new or worsening neurological symptoms and if progressive multifocal leukoencephalopathy is suspected, rituximab should be discontinued immediately.

Cyclophosphamide is rarely associated with hemorrhagic cystitis and interstitial pulmonary fibrosis. These regimens carry an increased risk of pneumocystis and herpes infections, and thus prophylaxis is recommended.

Bendamustine, an alkylating agent, is often combined with rituximab for treatment of CLL in patients with significant comorbidities, including decreased renal function.[8] Bone marrow suppression is common and may lead to febrile neutropenia and severe thrombocytopenia. Dermatological toxicity including Steven-Johnson syndrome and toxic epidermal necrolysis have been described and should

prompt urgent discontinuation of treatment. Bendamustine may cause reactivation of hepatitis B, CMV, herpes zoster or mycobacterium tuberculosis. Infectious prophylaxis or treatment may be considered before bendamustine administration.

Pentostatin, another purine analog, is often combined with rituximab and/or cyclophosphamide. It has been compared to fludarabine based regimens and was found to be equally efficacious.[9] Pentostatin based regimens are associated with more infections per cycle and more hospitalizations from infection when compared to fludarabine regimens. In general, one should wait for an infection to clear before proceeding with a pentostatin based therapy. CNS toxicity, hepatotoxicity, and pulmonary toxicity have all been described with higher doses of pentostatin than recommended, prompting a U.S. black boxed warning not to exceed the recommended dose.

Ibrutinib, a Bruton's tyrosine kinase inhibitor, is often used in older adults with untreated CLL as well as patients with del(17p) and those with relapsed/refractory disease. In patients with cardiac risk factors, atrial fibrillation and atrial flutter have been noted. Patients should be monitored periodically for symptoms of atrial fibrillation, and an ECG should be obtained if new onset dyspnea or other suggestive symptoms develop. Ibrutinib is associated with dizziness, fatigue and weakness. Patients should be cautioned about performing tasks requiring mental alertness. Diarrhea is also commonly observed and may warrant use of anti-motility agents. Though myelosuppression is common, patients may also get a transient lymphocytosis, especially upon initiation of therapy. New onset of neurological symptoms should prompt concern regarding intracranial hemorrhage as ibrutinib is also associated with increased bleeding events. Because of the increased bleeding risk, the risk-benefit of holding ibrutinib 3 to 7 days prior to and after surgery should be considered and will depend on the type of procedure and risk of bleeding. Numerous drug-drug interactions exist and should be monitored closely.

Chlorambucil, an alkylating agent, is an often used in the untreated elderly or medically-frail CLL patient. It is particularly attractive when certain comorbidities that may preclude the use of ibrutinib are present (history of severe bleeding, moderate hepatic impairment, or atrial fibrillation). It can be administered as monotherapy or in combination with anti-CD20 monoclonal antibodies. Common adverse effects include myelosuppression, increased seizure risk, and rarely severe skin reactions.

The anti-CD20 monoclonal antibody obinutuzumab is often combined with chlorambucil. In clinical trials, severe neutropenia has been observed with this combination. Patients with prolonged neutropenia of greater than one week time benefit from antimicrobial prophylaxis. Antifungal and antiviral prophylaxis should also be considered. Severe

Table 1. CLL Clinical Staging Systems.

Rai staging (1975)

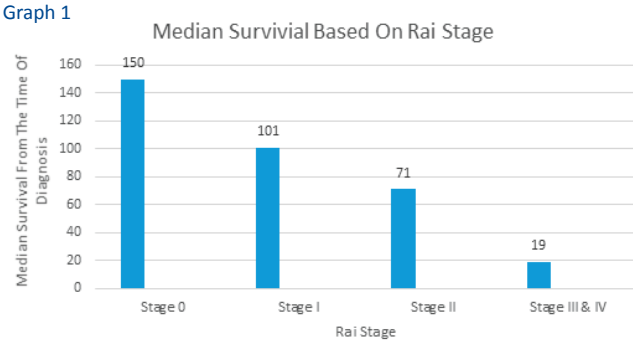
Stage	Lymphadeno-pathy	Hepatomegaly or Splenomegaly	Hemoglobin (g/dL)	Platelets (Platelets/µL)
0	None	None	>11	>100,000
I	>1	None	>11	>100,000
II		>1	>11	>100,000
III			<11	>100,000
IV				<100,000

Binet staging (1981)

Stage	Number of Involved Areas	Hemoglobin (g/dL)	Platelets (Platelets/µL)
A	<3	>10	>100,000
B	>3	>10	>100,000
C		<10	<100,000

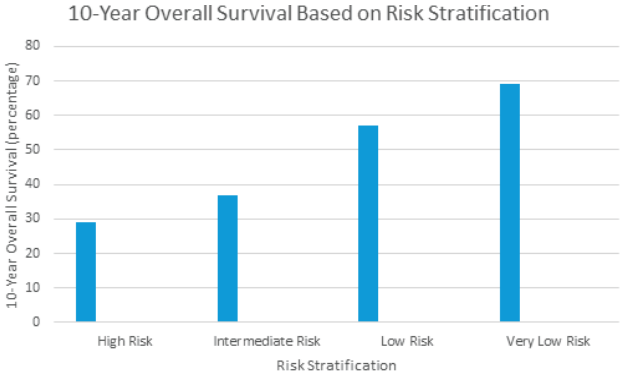
Source: Parker TL, Strout MP. Chronic lymphocytic leukemia: prognostic factors and impact on treatment. Discov Med. 2011;11(57):115-23.

Graph 1



Source: Rai KR, Sawitsky A, Cronkite EP, Chanana AD, Levy RN, Pasternack BS. Clinical staging of chronic lymphocytic leukemia. Blood. 1975;46(2):219-34.

Graph 2



High Risk - TP53 and/or BIRC3 abnormalities
Intermediate Risk - NOTCH1 and/or SF3B1 mutations and/or del11q22-q23
Low Risk - Harboring +12 or normal genetics
Very Low Risk - del13q14 only

Source: Rossi D, Rasi S, Spina V, et al. Integrated mutational and cytogenetic analysis identifies new prognostic subgroups in chronic lymphocytic leukemia. Blood. 2013;121(8):1403-12

thrombocytopenia has also been reported, sometimes within 24 hours of administration. Patients should be monitored for thrombocytopenia and treated with platelet transfusions when needed as fatal hemorrhagic events have been reported, more commonly during the first cycle of therapy. Fatal cardiovascular events have been noted, and patients with pre-existing cardiac comorbidities should be monitored closely, and antihypertensive agents could be held 12 hours prior to infusions due to the possibility of hypotension during infusions. Like rituximab, reactivation of hepatitis B can occur, and a U.S. black box warning exists for risk of progressive multifocal leukoencephalopathy.

Another anti-CD20 monoclonal antibody often combined with chlorambucil is ofatumumab. Like obinutuzumab, severe and prolonged cytopenias have been noted. Hepatitis B reactivation is a concern. Ofatumumab also carries a U.S. black box warning for progressive multifocal leukoencephalopathy. Bowel obstruction and abdominal pain has been reported. Patients presenting with abdominal pain should be assessed for bowel obstruction and treated appropriately.

Idelalisib, an oral inhibitor of phosphoinositide 3'-kinase delta, is combined with rituximab for the treatment of relapsed or refractory CLL. Idelalisib is associated with an increased risk of opportunistic infections. Manufacturer guidelines suggest prophylaxis for pneumocystis jirovecii pneumonia and monitoring for CMV infections. A U.S. black box warning exists for pneumonitis, and thus patients should be monitored for pulmonary symptoms and bilateral interstitial infiltrates. These findings should prompt interruption or discontinuation of medication. Idelalisib is associated not only with general diarrhea, but also a severe wasting diarrhea due to histologically proven colitis. This colitis generally occurs after 8 months of therapy. Treatment for this colitis involves cessation of idelalisib and use of systemic or local corticosteroids. Idelalisib can be safely restarted once the colitis subsides, albeit at a lower dose. Severe neutropenia occurred in close to one-third of patients on clinical trials. Blood counts should be monitored every two weeks for the first 3 months. Severe cutaneous reactions, including Steven Johnson syndrome have been reported. Patients should be monitored for dermatological toxicity and treatment discontinued with severe reactions. In addition to diarrhea, Idelalisib also carries a U.S. black box warning for serious intestinal perforations and hepatotoxicity and clinicians should investigate if patients present with new or worsening abdominal pain, chills, fever, nausea, or vomiting.

Venetoclax, an inhibitor of BCL2, is FDA approved for patients with CLL and del(17p) who have received one prior line of therapy. Myelosuppression is common and severe neutropenia occurred in almost half of patients. Antimicrobials and WBC growth factor support should be considered as good adjuncts. Since venetoclax can cause rapid reduction in tumor volume, tumor lysis syndrome is of significant concern, especially during the initial five-week dose escalation phase of treatment. Changes in blood chemistries consistent with tumor lysis syndrome may occur as early as six to eight hours after the first dose and require urgent management. Left untreated, renal failure and even fatalities have been reported. High tumor burden and decreased kidney function increase the risk of tumor lysis syndrome. Concomitant use of either a P-gp or CYP3A inhibitor also increases the risk of tumor lysis syndrome.

Conclusion

CLL represents a heterogeneous disease entity that typically presents as an asymptomatic rise in absolute lymphocyte count. When treatment is warranted, a wide array of therapies exists. There is no standard first line therapy and the choice of agent depends on numerous factors including but not limited to, patient's goals of therapy, patient's performance status, and the cytogenetics of the disease. We hope to highlight some of the most common regimens used in practice today as well as update providers about the most common toxicities associated with these drugs. Through this review, we hope providers are better able to recognize adverse side effects in their patients and either treat or refer sooner.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66(1):7-30.
2. Smith A, Howell D, Patmore R, Jack A, Roman E. Incidence of haematological malignancy by sub-type: a report from the Haematological Malignancy Research Network. Br J Cancer. 2011;105(11):1684-92.
3. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008;111(12):5446-56.
4. Chemotherapeutic options in chronic lymphocytic leukemia: a meta-analysis of the randomized trials. CLL Trialists' Collaborative Group. J Natl Cancer Inst. 1999;91(10):861-8.
5. Gribben JG. How I treat CLL up front. Blood. 2010;115(2):187-97.
6. Gill S, Carney D, Ritchie D, et al. The frequency, manifestations, and duration of prolonged cytopenias after first-line fludarabine combination chemotherapy. Ann Oncol. 2010;21(2):331-4.
7. Strati P, Wierda W, Burger J, et al. Myelosuppression after frontline fludarabine, cyclophosphamide, and rituximab in patients with chronic lymphocytic leukemia: analysis of persistent and new-onset cytopenia. Cancer. 2013;119(21):3805-11.
8. Eichhorst B, Fink AM, Bahlo J, et al. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. Lancet Oncol. 2016
9. Reynolds C, Di bella N, Lyons RM, et al. A Phase III trial of fludarabine, cyclophosphamide, and rituximab vs. pentostatin, cyclophosphamide, and rituximab in B-cell chronic lymphocytic leukemia. Invest New Drugs. 2012;30(3):1232-40.

Disclosure

None reported. **MM**

Missouri State Medical Association

159th ANNUAL CONVENTION



OFFICIAL MINUTES & REPORTS

March 31-April 2, 2017
Sheraton Kansas City Hotel at Crown Center
Kansas City, Missouri



Meet MSMA's 2017-2018 President

Warren C. Lovinger, Jr., MD
Nevada, Missouri

Contact: wclovinger@gmail.com

Warren C. Lovinger, Jr. MD, MACP, a board certified Internal Medicine physician from Nevada, Missouri, will serve as President of the Missouri State Medical Association in 2017-2018. He was formally installed in Kansas City, April 1, 2017, during MSMA's 159th Annual Convention.

Dr. Lovinger was born in Aberdeen, South Dakota, but moved with his family to Warrensburg, Missouri, at age four. He grew up on the campus of Central Missouri State University (now University of Central Missouri), where his father was the CMSU president.

After completing an undergraduate degree in Chemistry and Biology at CMSU, he received his MD from the Johns Hopkins University School of Medicine in Baltimore, Maryland, in 1977. Dr. Lovinger returned to St. Louis for his Internship and Residency in Internal Medicine at Barnes Hospital.

While in St. Louis, Warren met and married his wife, Marilyn. As newlyweds, they evaluated several communities in Missouri. They selected Nevada, a town of 10,000 in west central Missouri as the place for them to live, practice general internal medicine, and raise a family. Their children, Sarah Florio, MD, Thomas Lovinger, MD, Laura Lovinger, and Daniel Lovinger, MD, were all born and raised in Nevada, and continue to live in Missouri.

During Dr. Lovinger's 37 years in Nevada, he has been immersed in many aspects of the community. He served six terms on the Nevada R-5 Board of Education, was President of the Nevada Rotary Club, is an Elder in the Presbyterian Church, co-founder of Nevada's YMCA, and was honored as Nevada's Citizen of the Year in 1987.

His Internal Medicine practice has included outpatient, inpatient, long-term care, and cardiologic diagnostic services at Nevada Regional Medical Center. Dr. Lovinger is currently president of the NRMC medical staff, and has been president of the West Central Medical Society and the Missouri Society of Internal Medicine, as well as a Governor of the Missouri Chapter of the American College of Physicians. In 2011, he was elected to Mastership in the ACP, one of only 12 living in Missouri.

In their spare time, Warren and Marilyn enjoy traveling, gardening, and spending time with family—including their two grandchildren.

Goals for MSMA during his tenure as President include:

- Promotion of renewed pride and professionalism in our medical community—recognizing that being a physician is not just a job, but a calling and lifestyle in which we have daily opportunities to serve others.
- Recognizing the contribution of our rural colleagues, who often serve for many years in relative isolation with limited support. Dr. Lovinger is planning to visit as many of Missouri's 114 counties (and their physicians) as possible during his presidency.
- Encouraging early interactions between the youngest and oldest members of our medical community by establishing a medical student mentoring program with participating MSMA members across the state.

MM

Marsha Conant to Lead Medical Alliance

Marsha Conant
St. Joseph, Missouri

Contact: msmaalliance@gmail.com



Marsha Conant, St. Joseph, was installed as the 93rd President of the Missouri State Medical Association Alliance, (MSMAA), April 1, 2017, in Kansas City.

A Missourian her entire life, she was born and raised in St. Joseph where she attended primary school and graduated from Central High School. She received her Bachelor's Degree in Elementary Education at Missouri Western State University where fate smiled and the love of her life became her husband, James Conant. Marsha said, "The difficult challenges that are unique to being married to a medical student, post-graduate student, and practicing physician made for an interesting 44 years of married life." She and Jim have been blessed with four wonderful children, and in June and July of 2016, with their first grandchildren, two amazing little girls.

After graduation, her first job was teaching second grade. Once her husband began the practice of medicine, her services were required at his office where she filed insurance, filled in when the nurse was off, and served as office manager. This helped her to understand the stresses, frustrations, and daily grind to which physicians are subjected. They never left the office until every patient was seen, and they never turned away a sick or injured individual.

Her family has always been her first priority. Striving to assist her husband, her children, and especially her new grandchildren has been a guiding precept in Marsha's life. Her mother was diagnosed with Alzheimer's, and they were honored to have her spend her last years in their home. After a myocardial infarction in 2010, from which she has made a complete recovery, exercise and a healthy diet are paramount in her agenda. Marsha's other interests include traveling, reading, genealogy, crossword puzzles, and volunteering at both the local food kitchen and at her Temple, where she leads services several times a year.

Thrice she has been elected president of her local medical society Alliance, once in Jefferson County on the east side of the state and twice in Buchanan County on the west side. Marsha has represented Missouri at the Southern Medical Association Alliance where she served for many years as the councilor. Attendance at the annual and interim meetings of the Organized Medical Staff Section of the AMA has provided an excellent education on medicine and its evolution into the twenty-first century. A member of MSMAA for approximately 37 years underscores her appreciation of the vital importance of organized medicine. Remember, it is only together that we can effectively fight for the "House of Medicine" and support the medical family.

MM

MSMA Alliance
Missouri State Medical Association
Physician Families Advocating for a Healthy Missouri

State of the Association: Presidential Address

by Ravi Johar, MD, 2016-2017 MSMA President

It has been my pleasure to have served as your president for the past year. My duties have been extremely gratifying and rewarding, especially my travels to the various component organizations around the state. You should be proud that your Missouri State Medical Association is widely recognized as the voice of medicine in Missouri.

It would be appropriate, at this time, to give you the headlines from the Missouri State Medical Association.

MSMA is involved in more legislative issues than any other organization in the state; everything from scope of practice to tobacco, and tort reform to Medicaid expansion. Keep yourself updated by reading the weekly *Legislative Report*, which members receive during the legislative session.

MSMA is also involved in a wide range of federal government issues, including lobbying federal authorities on the proposed Anthem/Cigna and Aetna/Humana mergers, brand and generic drug prices, the Department of Veterans Affairs APRN rule, the new non-discrimination/ language translation services rule, meaningful use hardship exemptions, MACRA, and many others.

I, along with MSMA staff, attended a number of local component society meetings across the state. From Maryville to Poplar Bluff, and from Hannibal to Joplin, your leadership and staff make themselves available to every component society, no matter how large or small.

MSMA boasts an outstanding group of member physicians who represent you and your patients in the AMA House of Delegates.

In AMA-related news, we are excited and extremely proud that one of our very own, David Barbe, MD, a past MSMA President, was chosen as President-Elect of the AMA in June of 2016. He will take office in June of 2017. This is an extraordinary accomplishment and a blessing, knowing that we will all be so well represented at the upper tier of the AMA's leadership.

Your MSMA staff and leadership are constantly striving to bring more value to your membership. I want to highlight a few items.

In addition to its regular duties, your MSMA staff also provides top-rate administrative services for several statewide medical specialty societies, and maintains liaison with a large number of external governmental and private-sector committees, task forces, boards and commissions.

Missouri Medicine, MSMA's outstanding scientific journal, is free to you with your membership. Many of you know it has won awards and it now published in digital format that you can download from MSMA's website.

In addition to the honors the journal has won, last year the University of Missouri Press offered to publish as a book a series of *Missouri Medicine* articles on near-death experiences. We signed a contract for that, and the book is available for purchase outside at our Membership station.

MSMA also offers you free CME at this meeting every year, and we are glad you are here to advantage of that. We also accredit 28 entities to offer CME, many of which participate in joint providerships across the state.

Other membership benefits you enjoy is our partnership with:

- Moneta, an outstanding financial services firm.
- Resolve Physician Agency, which offers a wide range of career services, all at a discount to MSMA members.
- CCPA Purchasing Partners gives you access to up-front discounts on a variety of medical and office supplies.
- DocbookMD offers you a secure, HIPAA-compliant tool to send messages, patient information, images, and more to your MSMA colleagues through an application on your smart phone.
- Medical Waste Services offers MSMA members significant savings on medical and biohazard waste removal and treatment services.

Our most recent partners include LifeLock, a leading provider of identity theft protection; Officite, a medical practice website development and internet marketing provider; and MedJet Assist, a medical transport service.

Other great offers include the Missouri Drug Card, PQRS Registry services, collection services, coding and billing resources, and even travel arrangements, all with special rates and savings for MSMA members. You can see MSMA membership saves you far more than your membership dues.

Other outstanding programs affiliated with the MSMA include the Missouri State Medical Foundation. You will hear that report later.



David Barbe, MD, President Elect to the American Medical Association, addressed the Sunday House of Delegates session.



Above, Dr. Johar stands with the 2016-2017 MSMA Alliance President Jana Wolfe.

Below, MSMA Past Presidents Jeff Copeland, MD, (left), and John Stanley, MD, (right) enjoy the Presidential Inauguration.

Your Missouri Physicians Health Program is widely considered one of the most successful of its kind in the nation. Last year the program served more than 100 physicians who are dealing with chemical, emotional, or behavioral issues.

Your Missouri Medical Political Action Committee is one of the most respected and effective PACs in the state. Your membership and participation is essential to our political effectiveness.

Your MSMA Insurance Agency was formed by MSMA and is directed by physicians to serve you and your practice.

The MSMA Alliance boasts 250-plus dedicated and enthusiastic physician spouses who work tirelessly to promote a health Missouri.

The Center for Patient Safety is dedicated to being the leader in providing solutions and resources to reduce medical errors and improve patient safety.

The MSMA is YOUR organization, and your officers and staff welcome your thoughts on how best to serve you and your fellow members.

On behalf of the staff and the entire MSMA membership, I want to express undying gratitude for your officers, councilors, committee members, and other leaders who give so much of their time and resources for the betterment of the Association and patient care in Missouri. They are nothing short of extraordinary. **MM**



Dwell on the Positive

by Warren C. Lovinger, Jr., MD
2017-2018 MSMA President



Dr. Johar hands over the reigns of MSMA to Dr. Lovinger.

I would like to thank all of you for attending this evening's event. I would like to especially thank my family, friends, and coworkers from Nevada for being here. I will ask each of you to stand as I introduce you: Marilyn, my wife of 37 years; our children: Dr. Sarah Florio and husband Rev. Andrew Florio, Dr. Tom Lovinger and wife Dr. Kate Lovinger; Laura Lovinger and Christian Hornhuber; Dr. Dan Lovinger and wife Mariette Lovinger; the two wonderful ladies who have been my nurses during the past 35 years – Ruthanne McCoy, and Verna Jaross RN; the administrator of Nevada Regional Medical Center – Mr. Kevin Leeper; all of my physician colleagues from Nevada; and our excellent musicians. To all of you—thanks very much—I am very proud of you!

As I begin my address—let me make a confession: I am an eternal optimist! I always try to look at the good side of an individual, an issue, or a situation. I find that this attitude helps things go better—or at least makes me feel that they did. Current events in our country, which are fraught with negativity and divisiveness, suggest that we could all benefit from a large dose of happiness! We, as physicians, have a special opportunity to think and act positively as we interact with patients, peers, and our communities.

This does not mean that everything is perfect in our profession and society. Indeed, it is hard to say nice things about such daily irritants as overloaded schedules, prior authorizations, and uncooperative EMRs. It is also hard to excuse bureaucratic overreach, insurance non-payment, and pushy coworkers.

Yet, I believe that we are at our best as individual physicians and a medical profession when we dwell on the positive. Our actions and attitudes should set a good example and lead to beneficial results. As a long time Rotarian, I have come to appreciate and utilize the Rotary 4 Way Test of what we say and do: 1) Is it the truth? 2) Is it fair to all concerned 3) Will it build goodwill and better friendships? 4) Will it be beneficial to all concerned?

Let me give some examples of the helpfulness of the 4 Way Test from a physician's perspective.

How we approach patients: I always try to tell my patients the truth, even if it hurts. I believe this is fair to the patient and me. Sometimes I get push-back, but this is when a Presbyterian adage is helpful. We "agree to disagree agreeably." Hopefully, my patients know that they can trust me as we seek their benefit when discussing appropriate therapy and interventions.

How we interact with coworkers: We, as physicians, should be depended on to promote the truth. We should be "evidence based." This usually allows us to complement and encourage our coworkers, but sometimes requires gentle correction. This is ultimately fair to all, and promotes goodwill and friendship in the form of stronger care teams.

Of course, intellectual honesty and professionalism always benefits the patients we care for.

Transparency: Patients deserve to be told the truth about expected costs, benefits, and side effects of medications, diagnostic procedures, and episodes of care—whether in the office or hospital. This is fair to them and their families as they weigh the value of a health service. This type of advocacy builds goodwill and trust, while benefiting all of us as caregivers and receivers. This is not unique to the healthcare industry. I recently saw a paper napkin from Southwest Airlines that defined "Transfarency" as their corporate goal.

As physicians, we are enormously blessed with the opportunity and mandate to help others. We should be advocates for our patients, our communities, and our profession. We have the privilege of doing this in our offices, our hospitals, and other places we practice. The Missouri State Medical Association is made up of caring physicians who strive for the common good and societal benefit.



Dr. Lovinger and his family at the Presidential Inauguration.

Our organizational advocacy includes such important current issues as: 1) Healthcare access for all Missourians, 2) Continued availability of affordable insurance coverage, 3) Confronting the opioid epidemic with needed tools such as an effective PDMP, 4) Advocating for appropriate scopes of practice among allied health providers, 5) Advancing our youngest colleagues—medical students and residents—through a program of mentoring. I hope that all of you here this evening will participate as mentors to medical students in a pilot program that MSMA and the University of Missouri-Columbia will be initiating this summer.

We live in exciting but also uncertain times for our profession. The advent of an Obama-care replacement, the MACRA system of outcome based physician compensation, consolidation within healthcare systems, and the inexorable trend toward physicians begin employees—all present many challenges to us as individuals and for organized medicine. Yet, I believe that when all else fails, we do best by maintaining professionalism, telling the truth, promoting goodwill, and striving for solutions that benefit all involved.

As most of you know, I have lived and practiced solo Internal Medicine for over 35 years in a rural Missouri community of 8400 one hundred miles south of here—Nevada. Other than Dr. Dave Barbe, I am the most rural President that MSMA has had for many years. Places like Nevada are well kept secrets, as they truly promote quality of life, sense of community, and opportunities for leadership. But, it can be lonely as a rural physician. Community expectations are very high—often with limited access to medical peers and support mechanisms that would be taken for granted in urban and suburban medical communities.

I think it is important that we in the Missouri State Medical Association do all that we can to reach out to our rural colleagues who have often been serving their communities for many years in relative isolation. Missouri is a vast and diverse state-stretching more than 500 miles from Maryville in the northwest to Kennett in the boot heel.

I have an ambitious goal for my year as MSMA President to visit all 114 counties and the city of St. Louis—hopefully meeting with practicing physicians and MSMA members while there. You can just call me the "Traveling Doc." Hopefully, Marilyn will be able to accompany me on most of my travels, and I will keep you informed of our progress in Missouri Medicine.

I want to again thank all of you for being here tonight as friends, family, and fellow members of the Missouri State Medical Association. I am truly honored by the opportunity to represent you and work with our great MSMA staff as we dwell on the positive in promoting the medical profession of our state. **MM**

Recipients of the 50-Year Physician Pin

Twenty-two career physicians earned their 50-Year Physician Pin during the MSMA Presidential Inauguration from MSMA President Ravi Johar, MD. After the Installation, many celebrated at the reception. Below is the listing of all pin recipients.

- Lillard Ashley, Jr., MD, Lee's Summit, MO
- Wallace P. Berkowitz, MD, St. Louis, MO
- Gerald Claycomb, MD, Chesterfield, MO
- Carlos Deleste, MD, St. Louis, MO
- Nillima Ghosh, MD, St. Louis, MO
- Ted Groshong, MD, Columbia, MO
- Edward R. Habert, MD, Destin, FL
- Judith Ho, MD, St. Louis, MO
- Anne A. Idiculla, MD, Denver, CO
- Yasuo Ishida, MD, St. Louis, MO
- Chul Kim, MD, Poplar Bluff, MO
- Harry L. Knopf, MD, St. Louis, MO
- Russell R. Kraeger, MD, St. Louis, MO
- William Lampros, MD, Town & Country, MO
- Charles Luetje II, MD, Olathe, KS
- Hugh Lundman, MD, Battlefield, MO
- Larry Marti, MD, Rolla, MO
- Edward O'Brien, Jr., MD, Kirkwood, MO
- Donald E. Philgreen, MD, Kansas City, MO
- Gary Ratkin, MD, St. Louis, MO
- Stanley E. Thawley, MD, St. Louis, MO
- Gus Wetzel II, MD, Clinton, MO



Ted Groshong, MD, receives his 50-Year Physician Pin during the Presidential Inauguration from Dr. Johar.



From left, Alliance Vice President of Legislation Kirk Doan, President Marsha Conant, and Recording Secretary Diana Corzine enjoy the MSM Foundation fundraiser.

MM

House of Delegates Votes on Resolutions

Resolution #1 – Recognize Sleep Awareness Week in the State of Missouri

Substitute Resolution #1 Adopted

Resolved, that MSMA support legislation to recognize Sleep Awareness Week as the week between the first and second Sundays of March in the state of Missouri.

Resolution #2 – AMA To Support Pharmaceutical Pricing Program in U.S.

Amended Resolution #2 Adopted

Resolved, that the MSMA's AMA delegation present a resolution that the AMA prioritize its support for CMS to negotiate pharmaceutical pricing for all applicable medications covered by CMS.

Resolution #3 – Ban on Direct-to-Consumer Advertising by Pharmaceutical Companies

Resolution #3 Not Adopted

Resolved, that Missouri State Medical Association partner with the AMA by strongly calling upon the AMA to now actively pursue that ban on the direct-to-consumer pharmaceutical company advertising and not just support it.

Resolution #4 – Support for International Medical Graduates in Response to Executive Order 13769

Substitute Resolution #4 Adopted

Resolved, that the MSMA issue a statement of support for all international medical graduates who wish to train and practice in the U.S. and who meet U.S. training and accreditation standards.

Resolution #5 – Out of Network Co-pays

Substitute Resolution #5 Adopted

Resolved, that MSMA staff research the frequency and effects of patients paying higher out-of-network cost-sharing when their out-of-network physician is receiving in-network rates, and report that information to MSMA Council to determine if further action is necessary.

Resolution #6 – Pharmacy Notification

Substitute Resolution #6 Adopted

Resolved, that MSMA support the establishment of a direct access statewide prescription drug monitoring program (PDMP).



Reference Committee A: from left, David Pohl, MD, St. Louis; Caitlin Curcuru, Kansas City; Brian Andrews, MD, O'Fallon, Chair; Stephen Halpin, MD, Hannibal; and Adam Grumke, MD, Kansas City.



Reference Committee B: from left, Megan Clark, MD, Columbia; I. J. Singh, MD, St. Louis; Douglas Wallace, MD, Cape Girardeau, Chair; and Charles Canver, MD, Osage Beach.

Resolution #7 – Comprehensive Review of CME Process

Resolution #7 Adopted

Resolved, that the Missouri State Medical Association request that the American Medical Association do a comprehensive review of the CME process on a national level, with the goal of decreasing costs and simplifying the process of providing CME.

Resolution #8 – Certified Translation Services

Substitute Resolution #8 Adopted

Resolved, that the Missouri State Medical Association, in collaboration with the American Medical Association, work to relieve the burden of the costs associated with translation services implemented under Section 1557 of the Affordable Care Act.



From left, Parliamentarian Jo-Ellyn Ryall, MD, Vice Speaker Sam Page, MD, and Speaker Lancer Gates, DO, manage the MSMA House of Delegates.



From left, Keith Ratcliffe, MD, Jim Blaine, MD, and Alex Hover, MD, catch a break between General Sessions.



MSMA members listen to testimony during the MSMA Reference Committees.

Resolution #9 – Peer to Peer Reviews

Substitute Resolution #9 Adopted

Resolved, that MSMA support legislation to require insurance companies to have an actively practicing physician, who is board certified in the same specialty as the patient's physician, to participate in the peer-to-peer stage of Missouri utilization review appeals process.

Resolution #10 – Claim Payment Adjustments

Resolution #10 Adopted

Resolved, that the Missouri State Medical Association work with the appropriate parties to require each insurance claim to be independently evaluated.

Resolution #11 – Medical Coverage for Dental Conditions

Referred to MSMA Council

Resolved, that the Missouri State Medical Association support Medicaid medical benefit coverage for the treatment of dental conditions that complicate or exacerbate systemic medical disease, and request that our AMA delegates pursue a similar resolution.

Resolution #12 – Insurance Contract Revisions Requiring Opt-in Agreement

Resolution #12 Adopted

Resolved, that the Missouri State Medical Association work with the Missouri Department of Insurance and appropriate parties to require that any unilateral alterations to an insurance contract be sent by certified mail, and further be it

Resolved, that the physician must opt-in to agree to any changes or additional networks.

Resolution #13 – Decreasing Screen Time and Increasing Outdoor Activity to Offset Myopia Onset and Progression in School Children

Resolution #13 Adopted

Resolved, that the Missouri State Medical Association will support the efforts of the American Academy of Pediatrics and American Academy of Ophthalmology to educate, promote public awareness, and promote guidelines to reduce the incidence and burdens of myopia to physicians, public health agencies and schools, and encourage the American Medical Association to do likewise.

Resolution #14 – Past Presidents Committee

Resolution #14 Adopted

Resolved, that the MSMA Bylaws be amended to create a new standing committee composed of MSMA's Past Presidents by adding the following new provision to Chapter VII, Section 1. of said Bylaws:

"The Committee of Past Presidents shall consist of the MSMA Past Presidents who are members of the Association and who volunteer to serve on the Committee. The Committee shall provide the MSMA Council and House of Delegates with advice on such matters as may be necessary to advance the Association's mission and causes." MM

Awards: Legislative

Each year MSMA recognizes a legislator or two who has demonstrated unusual support for our profession and our patients. Over the years we have applauded some truly outstanding individuals. And this year is no exception. This year MSMA honored Senator David Sater.

Senator David Sater represents the 29th Senatorial district, which is located in southwest Missouri and includes Table Rock Lake and the city of Branson.

After serving eight years in the House of Representatives, he was elected to the Senate in November 2012, and quickly earned the respect and admiration of his colleagues on both sides of the aisle.

For the past three years, Senator Sater has served as Chairman of the important Senate Seniors, Families and Children Committee. In this position, he controls legislation that addresses many of MSMA's public health concerns. The legislation in his committee significantly impacts physicians and the practice of medicine.

This year, Senator Sater is the sponsor of MSMA's Predetermination of Benefits bill, which would give patients more accurate healthcare price transparency.

Senator Sater has come to medicine's aid countless times during his service in the General Assembly. He was a firm supporter of our commonsense tort reform measure, which restored the noneconomic damage cap in medical malpractice lawsuits.

Equally as important, he is a stalwart protector of the practice of medicine when other health care professionals attempt to expand their scope of practice. He has been a tireless advocate for physicians. In the past, Senator Sater has supported MSMA policies ranging from physician licensing to MO HealthNet reimbursement to insurance issues.



MSMA's Legislative Award is presented to Senator David Sater by Dr. Johar.

Senator Sater regularly seeks the advice of MSMA on important healthcare issues at the Capitol, and shares that information with his colleagues and the members of his committee.

Whether it is big issues, like tort reform and scope of practice, or the less visible ones, like vaccinations and access to affordable medications, Senator Sater has been a terrific supporter of Missouri physicians and their patients.

Awards: Arthur Gale Freedom of Expression



John Holds, MD, (center) receives the annual "Arthur Gale, MD, Freedom of Expression Award," presented by 2016-17 MSMA President Ravi Johar, MD, (left), and Arthur Gale, MD (right).

MSMA presents the Arthur Gale freedom of Expression Award, on behalf of its Journal, *Missouri Medicine*. It is awarded annually to the author of the best commentary article published in *Missouri Medicine*, in honor of Arthur Gale, MD, one of the Journal's Contributing Editors and MSMA member since 1976.

The 2016 recipient of this award is Dr. John Holds, of St. Louis, Missouri. His article, "Is Health Care Reform a Gathering Storm for Doctors?" was published in the March/April 2016 issue.

Dr. Holds, an MSMA member since 1991, is a Clinical Professor of Ophthalmology and Otolaryngology/Head and Neck Surgery at Saint Louis University, a former president of the Missouri Society of Eye Physicians and Surgeons, and current legislative chair for that organization.

This prestigious and monetary award is offered to encourage MSMA physicians to submit personal perspective essays on issues that are topical and provocative. **MM**

Sponsors & Exhibit Partners

MSMA thanks the following Sponsors and Exhibit Partners who supported the Annual Convention through educational grants.

- **Doximity**
- **Indiana University, Kelley School of Business**
- **Mentor**
- **MSMA Health Education Foundation**
- **MSMA Insurance Agency**
- **ProAssurance**
- **MoDocs**
- **MSMA Insurance Agency**
- **MPM-PPIA**
- **Norcal Mutual Insurance Company**
- **MO DHSS Bureau of Vital Records**
- **National Diabetes Prevention Program**
- **CCPA Purchasing Partners**
- **MGMA Missouri**
- **Allertech Laboratories**
- **Medical Waste Services**
- **Missouri Drug Card**
- **Board of Registration Healing Arts**
- **Moneta Group**
- **Air Force Health Professions**
- **Doximity**
- **MedPro Group**
- **Sanofi**
- **Pfizer**
- **MO Telehealth Network/Show-Me Echo**
- **SNC Squared**
- **SumnerOne**
- **Officite**
- **Hawthorn Physician Services Corp**
- **Premier Specialty Network**

MM

Credentials & Appointments

The 159th Annual Convention of the Missouri State Medical Association was held at the Sheraton Kansas City Hotel at Crown Center, March 31-April 2, 2017. Lancer Gates, DO, Kansas City, Missouri, presided as Speaker of the House of Delegates. Parliamentarian was Jo-Ellyn Ryall, MD, St. Louis.

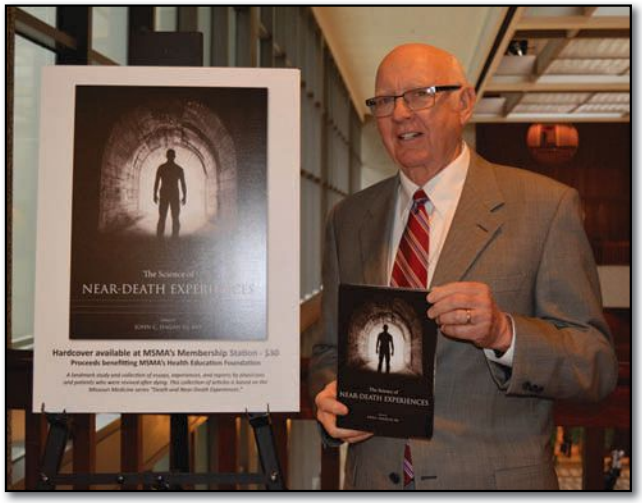
The Committee on Credentials announced that there were 8 Officers, 14 Councilors, and 42 Delegates in attendance for the Opening Session of the House of Delegates.

This report and the minutes of the 158th Annual Convention as published in the May/June 2016 issue of *Missouri Medicine* were approved.

At the Second Session of the MSMA House of Delegates, the Committee on Credentials reported that there were 9 Officers, 17 Councilors, and 107 Delegates in attendance.

Reference Committee A members were Brian Andrews, MD, O'Fallon, Chair; Stephen Halpin, MD, Hannibal; Adam Grumke, MD, Kansas City; David Pohl, MD, St. Louis; and Ms. Caitlin Curcuru, Kansas City. Reference Committee B members were Douglas Wallace, MD, Cape Girardeau, Chair; Charles Canver, MD, Osage Beach; Megan Clark, MD, Columbia; and I.J. Singh, MD, St. Louis.

The MSMA Nominating Committee members were: 1st District - Robert Corder, MD, St. Joseph; 2nd District - Stephen Halpin, MD, Hannibal; 3rd District - Edmond Cabbabe, MD, St. Louis; 4th District - Martin Willman, MD, St. Louis; 5th District - Lisa Thomas, MD, Columbia; 6th District - William Haynie, MD, Butler; 7th District - Marc Taormina, MD, Lee's Summit; 8th District - Ellen Nichols, MD, Joplin; Organized Medical Staff Section - James Conant, MD, St. Joseph; Young Physician Section - Sarah Florio, MD, Lee's Summit; Resident and Fellow Section - Daniel Young, MD, St. Louis; and Medical Student Section - Hannah Bucklin, St. Louis. **MM**



Kansas City physician John Hagan, MD, showcases a new book of essays from Missouri Medicine on "The Science of Near-Death Experiences.

MSMA Elects Leadership

MSMA Officers

President
Warren Lovinger, MD, Nevada
President Elect
Joseph Corrado, MD, Mexico
Secretary
Brian Biggers, MD, Springfield
Treasurer
David Pohl, MD, St. Louis
1st Vice President
William Turner, MD, Nevada
Honorary Vice President
Nathaniel Murdock, MD, St. Louis
Honorary Vice President
Kirby Turner, MD, Poplar Bluff
Immediate Past President
Ravi Johar, MD, St. Louis
Speaker
Lancer Gates, DO, Kansas City
Vice Speaker
Sam Page, MD, St. Louis

Councilors

Chair, MSMA Council
James DiRenna, Jr., DO, Gladstone (7th Dist)
Vice Chair, MSMA Council
George Hruza, MD, Chesterfield (3rd Dist)
1st District
Robert Corder, MD, St. Joseph
2nd District
John Memken, MD, Hannibal
3rd District
Elie Azrak MD, Chesterfield
Robert Brennan, MD, St. Louis
Michael Stadnyk MD, Chesterfield
4th District
Kevin Weikart, MD, Lake Saint Louis
5th District
George Hubbell, MD, Osage Beach
6th District
David Kuhlmann, MD, Kansas City
7th District
Betty Drees, MD, Kansas City
Lancer Gates, DO, Kansas City
8th District
Alexander Hover, MD, Springfield
Mathew Stinson, MD, Springfield
9th District
Lirong Zhu, MD, Rolla
10th District
Charles Lawson, MD, Poplar Bluff
Organized Medical Staff Section
Peggy Barjenbruch, MD, Mexico
International Medical Graduate
Sri Devi Kolli, MD, St. Louis
Young Physician Section
Ramona Behshad, MD, Chesterfield
Resident & Fellow Section
Nathanial Nolan, MD, Columbia
Medical Student Section
Shivani Singh, Fenton

Vice Councilors

1st District
Robert Weigand, MD, St. Joseph
2nd District
Sandra Ahlum, MD, Hannibal
3rd District
Inderjit Singh, MD, Chesterfield
4th District
Keith Ratcliff, MD, Washington
5th District
Lisa Thomas, MD, Columbia
6th District
Benjamin Wilson, MD, Nevada
7th District
Marc Taormina, MD, Lee's Summit
8th District
Ellen Nichols, MD, Joplin
9th District
David Barbe, MD, Mountain Grove
10th District
Sharon Wallace, MD, Cape Girardeau
Organized Medical Staff Section
James Conant, MD, St. Joseph
International Medical Graduate
Ramona Aitken, MD, St. Louis
Young Physician Section
Sarah Florio, MD, Lee's Summit
Resident & Fellow Section
Mihir Brahmbhatt, MD, Columbia
Medical Student Section
David Goodson, Columbia



Stephen Halpin, MD, Hannibal, provides testimony during the Reference Committees.

AMA Delegates & *Alternate Delgates

Edmond Cabbabe, MD, St. Louis
James Conant, MD, St. Joseph
Ted Groshong, MD, Columbia
Rebecca Hierholzer, MD, Leawood, KS
William Huffaker, MD, St. Louis

*Elie Azrak, MD, Chesterfield
*Michael O'Dell, MD, Kansas City
*Charles Van Way, MD, Kansas City
*Nathaniel Murdock, MD, St. Louis
*Shannon Tai, Lisle, IL, Student

AMA Regional Student Alternate Delegates
Jared Lammert, Columbia
Ariel Carpenter, Columbia

AMA President-Elect
David Barbe, MD, Mountain Grove

Alliance

President
Marsha Conant, St. Joseph
President Elect
Gill Waltman, St. Louis

Summary of Council Actions: 2016-2017

Meeting of March 20, 2016 – St. Louis

Ravi Johar, MD, St. Louis, President, presided. Warren Lovinger, MD, Nevada, was elected President Elect. Rob Schaaf, MD, St. Joseph, was elected Chair. Joe Corrado, MD, Mexico, was elected Vice Chair. Brian Biggers, MD, Springfield, was elected Secretary. David Pohl, MD, St. Louis, was elected Treasurer.

Meeting of July 17, 2016 – Jefferson City

MSMA President, Ravi Johar, MD, reported that he had attended the annual meetings of the Iowa Medical Society and the Tennessee Medical Association. Dr. Johar also attended the Tri-County Medical Society meeting in Augusta, Mo., and is planning several Fall visits to additional component societies.

In other news, MSMA is working on a partnership with the Kansas Medical Society to create a statewide health information exchange/data analytics program in Missouri. And MSMA is now providing administrative services for the Missouri College of Emergency Physicians.

Legislative Affairs

Dr. Johar directed the Council's attention to MSMA's 2016 Legislative Review. He pointed out that advocacy is one of the most important services MSMA provides its members, and encouraged Council members to share the Review with their non-member colleagues.

The Legislative Committee made recommendations to Council on several resolutions referred from the 2016 MSMA House of Delegates. The Council voted to not adopt Resolution #1, "License Parity for IMGs," which sought licensure parity between United States and international medical graduates. The Council also voted to not adopt Resolution #5, "Non-Compete Clauses," which urged MSMA to pursue legislation to prohibit non-compete clauses in employed physician contracts. Instead, the Council reaffirmed the current MSMA policy which supports the elimination of non-compete clauses between physicians and non-profit hospitals. And the Council adopted Resolution #9, "Nurse Practitioners," which calls on MSMA to advocate for putting nurse practitioners under the jurisdiction of the Board of Healing Arts, the same as practicing physicians.

Commission on Medical Economics

The Council approved the Commission's recommendation on another resolution from the MSMA House of Delegates: Resolution #13, "Parental Leave." There was discussion about the potential economic and health implications of modifying various aspects of the federal Family and Medical Leave Act (FMLA). The resolution calls on MSMA to support expanding FMLA coverage to employers with 10 employees (instead of the current 50), and to employees with 1,000 hours of work history (instead of 1,250). It also would extend the length of allowable leave from 12 to 24 weeks, and make that leave paid, rather than unpaid. The resolution was referred to the AMA for further study.

Membership

The MSMA Membership Committee reported that prospect members were sent news of MSMA's successful efforts on the proposed Aetna-Humana merger. That message, showing what MSMA does for its members, appears to have resonated with members and non-members alike. A Member-Get-a-Member campaign is set to launch in October and run through April of 2017. Members will receive a $15 reduction in dues for every new member they recruit, with a limit of ten new members ($150).

MSMA Insurance Agency

Ronnie Staggs from MSMA Insurance Agency shared information on a new product, Private Client, from Nationwide. More information on this will be provided to MSMA members in the coming weeks.

Continuing Education

Sandra Ahlum, MD, reported that the Committee on Continuing Education had reviewed evaluations on speakers at the 2016 Annual Convention, and is getting ideas for future speakers from that input. Topics under consideration for next year's convention are primary care patient engagement, physician burn-out, opioid abuse, and ABIM-MOC. The Commission will continue to survey hospitals that provide CME themselves.

Missouri Physicians Health Program

Bob Bondurant reported the MPHP has been asked to help with some hospital wellness committees, and encourages systems to reach out to MPHP for help with those efforts. Mr. Bondurant commented that the treatment of substance abuse and suicide prevention were early goals for the Program, but now problems of stress and burn-out are increasingly common. He asks MSMA members to reach

out to their colleagues and encourage them to contribute to MPHP.

AMA Report

Congratulations were offered to David Barbe, MD, upon his election in June as AMA President Elect.

Dr. Barbe will be the fifth AMA President from Missouri, and the first Missourian elected in ninety years.

Appointments

Rob Schaaf, MD, Council Chair, made the following appointments as Councilor Advisors to Commissions: Commission on Medical Economics – Alexander Hover, MD; Commission on Continuing Education – Peggy Barjenbruch, MD; Commission on Public Affairs – Joseph Corrado, MD; and Physicians Health Committee – Lisa Thomas, MD.

Councilor District Reports (selected)

District #3

George Hruza, MD, reported on the Cortex Center for Emerging Technologies. He stated the St. Louis Metropolitan Medical Society has set up an Innovation Committee to help collaborate with the biotechnology incubators in the area. He also reported that the 14th Annual Hippocrates Lecture, "From Volume to Value … to Values," will take place on October 27 in Maryland Heights.

District #5

Dr. Corrado reported that the state Certificate of Need program has approved development of a new 72-bed psychiatric hospital in Columbia.

District #8

Dr. Hover gave an update on the medical school partnership the MU School of Medicine has formed with the CoxHealth and Mercy Systems in Springfield. He also stated that the AMA Alliance materials on opioid abuse/addiction are designed to be used in the community, and will be posted on the Greene County Medical Society website. He encouraged members to seek opportunities to use them in their communities.

Organized Medical Staff Section

Dr. Barjenbruch discussed recent revisions to the requirements for reporting to the National Practitioner Data Base. Under the new rules, any leave of absence from a hospital or other reporting entity is considered a "surrender of privileges," and thus subject to reporting, including leave for the birth of a child.

Alliance

Alliance President Jana Wolfe reported on plans for the September's Fall Conference, February's "Day at the Legislature," the "Drugs are Not for Me" campaign, and plans for the 2017 Annual Meeting in Kansas City. She also reported on attending six installations of several local Alliance presidents and co-presidents during May and June. She encouraged member spouses to join and to follow the Alliance on Facebook and Twitter.

Eleven Alliance members attended the AMA Alliance Annual Meeting in Chicago in June. Missouri Alliance Past President Barbara Hover showcased materials and a DVD on the Opioid Abuse/Addiction campaign.

Meeting of October 16, 2016 – Jefferson City

At MSMA's October Council Meeting held in Jefferson City, Association leadership urged members to follow the recent HHS non-discrimination rule that most physicians need to observe. Non-discrimination policies must be posted in a conspicuous place in physician offices, and a notice must likewise be posted stating that language services are provided at no cost to the patient. MSMA developed forms that members can use to comply. Find them on MSMA's website at www.msma.org/aca-nondiscrimination-rule.

Advocacy

In other advocacy efforts, MSMA has opposed the proposed merger of Aetna with Humana, including formal comments at a hearing of the Department of Insurance in May. The Department issued a ruling that blocked that merger in Missouri. The two insurance companies have sued to overturn that ruling, and the case is now pending before the 19th Circuit Court in Cole County. In July, the U.S. Department of Justice filed suit in U.S. District Court, District of Columbia, to block both the proposed Aetna-Humana and Anthem-Cigna mergers.

The Council heard a brief update on federal affairs in Washington, D.C., including a CMS report on MACRA rules and regulations. Council members also received an update on the 2016 veto session, which included the override of SB 608, related to health care cost transparency.

A report on the Assistant Physician licensure regulations indicated the Board of Healing Arts has published the final rules, and will likely begin accepting applications in 2017.

Members are encouraged to sign up for Physician of the Day in the Capitol in 2017, and to sponsor a medical student shadow for that project.

MSMA Insurance Agency

MSMA members needing health insurance for their office staff, or professional liability insurance for their practice, can call the Agency to receive more information at 573-635-0320.

Continuing Education

Peggy Barjenbruch, MD, Councilor Advisor to the CME Commission, reported the plans for General Sessions at the 2017 Annual Convention. The Commission received provider updates: SSM St. Mary's - Jefferson City, Esse Health, and the St. Louis STD/HIV Prevention Training Center.

Membership

John Stanley, MD, encouraged Councilors to review the list of new members in their districts, welcome them, and thank them for joining.

The billing for 2017 dues has just begun, and hundreds of members have already renewed. Membership certificates are now optional, resulting in a savings on printing and postage. Members can sponsor a Missouri medical student for $8 per year, either designating a particular student or leaving the line blank for a generic sponsorship.

Participating members can earn discounts on their MSMA dues as a reward for recruiting new members. Various recruitment resources are available on the MSMA website. Successful recruiters will be recognized on-line and during meetings.

Physicians Health Committee

Bob Bondurant, Missouri Physicians Health Program Executive Director, encouraged physicians to advocate on behalf of MPHP to support the program through their practice and/or hospital.

AMA

Edmond Cabbabe, MD, reported that the AMA delegation will attend the 2016 Interim Meeting in Orlando, Florida, November 11-15.

Dr. Cabbabe reported that MSMA is well represented in the AMA leadership at the Interim Meeting: David Barbe, MD, AMA President Elect; Jerry Kennett, MD, AMA Council on Legislation; and Charles Van Way, MD, AMA Rules and Credentials Committee.

District Reports (selected)
District #3

George Hruza, MD, reported that the St. Louis Metropolitan Medical Society (SLMMS) is conducting a physician survey on insurance company performance. SLMMS' annual Hippocrates Lecture on October 27 focused on the transition to value-based health care. SLMMS has partnered with the American Cancer Society on its campaign to get 80% of people screened for colorectal cancer by 2018.

District #4

Kevin Weikart, MD, reported that the St. Charles-Lincoln County Medical Society is in its eleventh year of awarding MSM Foundation scholarships.

District #7

James DiRenna, DO, reported that at the Kansas City Medical Society's annual gala a number of awards were presented, and there was a great discussion on the history of medicine during wartime. A Top Golf event was given in appreciation for volunteer physicians, who have donated $65 million in care over ten years.

District #8

Brian Biggers, MD, reported that the Greene County Medical Society will host a candidate forum prior to the elections. Greene County Medical Society recommended Matthew Stinson, MD, to fill the District 8 Councilor position vacated by David Redfern, MD.

District #10

The Cape Girardeau Area Medical Society announced a dermatology symposium will be held on December 3.

Alliance

MSMA Alliance President Jana Wolfe and President-Elect Marsha Conant attended the North Central Alliance meeting in Indianapolis. Council members were encouraged to give to the Holiday Sharing Card in support of the Alliance Foundation Scholarship fund. Members who donate by November 15 will be recognized in Missouri Medicine and the Show Me Alliance News.

The Alliance Foundation Fundraiser for the 2017 Annual Convention will be revealed at the January Council meeting. Joseph Corrado, MD and his blues band will provide musical entertainment that evening. Donna Corrado, the Alliance Director of Membership, provided a membership application in the Council folders. Council members were encouraged to have their spouses sign up.

The Alliance had its fall conference in Branson, and members heard presentations on opioid abuse, attempts at marijuana legalization, and human trafficking.

Meeting of January 15, 2017 – Jefferson City

The MSMA Council Meeting was cancelled due to inclement weather.

Reports of the Delegate Handbook: 2016-2017

Secretary

The Missouri State Medical Association had 4,180 members as of the December 2016 audit. This was a net decline of 356 members from our membership of 4,536 as of the December 2015 audit. Following is a breakdown according to classification.

Year	Students	Residents	Active	Honor	Total
2015	1,047	98	2,936	455	4,536
2016	916	130	2,692	442	4,180
	-131	+32	-244	-13	+356

Number of member deaths reported during 2016 totaled 22.

The Committee on Nominations, which is appointed by the President, from the House of Delegates, must submit nominations for the following offices:

President Elect to fill the expired term of Warren Lovinger, Jr., MD, Nevada.

Three Vice Presidents to fill the expired terms of David Bean, DO, Florissant; William Reynolds, MD, Springfield; and Greg Terpstra, DO, Potosi.

A Speaker and Vice Speaker to fill the expired terms of Lancer Gates, DO, Kansas City, Speaker, and Sam Page, MD, Creve Coeur, Vice Speaker. Both are eligible for re-election to their current positions.

Three Delegates and Two Alternate Delegates to the AMA to fill the vacancies created by the expiration at the conclusion of the 2017 Annual Convention of the terms of Delegates: James Conant, MD, St. Joseph; Rebecca Hierholzer, MD, Leawood, KS; William Huffaker, MD, St. Louis; and Alternate Delegates: Dr. Warren Lovinger, Jr., MD, Nevada, and Mr. Matt Faubion, Columbia. The new-two year terms will begin at the conclusion of the 2017 MSMA Annual Convention and end at the conclusion of the 2019 MSMA Annual Convention.

The terms of the following Councilors will expire in 2017: 2nd District – Sandra Ahlum, MD, Hannibal; 3rd District – Robert Brennan, Jr., MD, St. Louis, and Michael Stadnyk, MD, Chesterfield; 4th District – Kevin Weikart, MD, Lake St. Louis; 6th District – David Kuhlmann, MD, Kansas City; 7th District – Betty Drees, MD, Kansas City; 8th District – Alexander Hover, MD, Ozark; 10th District – Charles Lawson, MD, Poplar Bluff; Organized Medical Staff Section – Peggy Barjenbruch, MD, Mexico; Young Physician Section – Ramona Behshad, MD, Chesterfield; Resident and Fellow Section – Nathanial Nolan, MD, Columbia; and Medical Student Section – Kartik Sreepada, Kansas City.

The terms of the following Vice Councilors will expire in 2017: 2nd District – John Memken, MD, Hannibal; 4th District – Martin Willman, MD, St. Peters; 6th District – Benjamin Wilson, MD, Nevada; 8th District – M. Ellen Nichols, MD, Joplin; 10th District – Sharon Wallace, MD, Cape Girardeau; Organized Medical Staff Section – James Conant, MD, St. Joseph; Young Physician Section – Sarah Florio, MD, Lee's Summit; Resident and Fellow Section – David Jung, MD, Columbia; and Medical Student Section – Shivani Singh, Fenton.

Delegates shall meet during the Annual Convention to elect the Councilors and Vice-Councilors for their respective districts and sections. The election shall be certified to the House of Delegates on the prescribed form which will be furnished.

The entire session will be held at the Sheraton Kansas City Hotel at Crown Center, Kansas City, Missouri. The House of Delegates will hold its First Session on Friday, March 31, 2017, at 8:00 a.m. and the Second Session on Sunday, April 2, 2017, at 8:15 a.m.

Registration facilities will be open on Thursday, March 30 at 3:30 p.m.; Friday, March 31 at 6:30 a.m. and Saturday, April 1, at 6:30 a.m. Registration will be in the Ballroom Level Foyer.

Treasurer

The report of the Treasurer is covered in the Financial Statement which is published in the May/June issue of *Missouri Medicine*.

Executive Vice President

The report of the Executive Vice President is covered in President's State of the MSMA speech on page 202.

Alliance

The MSMA Alliance's first board meeting was held in April 2016, with President Jana Wolfe and Vice Presidents planning their programming for the upcoming year.

With the theme, "Growing Missouri's Alliance", we are focusing on a Strategic Task Force, and revising our mission, vision, core values, membership, communication, programming and board affairs.

Our legislative priorities mirror MSMA's including the misguided legalization of marijuana, opioid abuse/addiction, and human exploitation/trafficking.

Alliance members attend the AMA Alliance Annual Meeting in Chicago, the MSMA Alliance Fall Conference on September 21-22 in Branson, the North Central Alliance Meeting on October 14-16 in Indianapolis, and the Southern Medical Alliance Conference on November 3-5 in Chattanooga.

The Holiday Sharing card raised thousands of dollars in funding for the Missouri State Medical Foundation and the MSMF Alliance Scholarship Fund.

The Alliance's Winter Board Meeting/Annual Alliance Advocates for Health Care Day at the Legislature was held February 21-22 in Jefferson City. Discussion included the slate of officers for 2017-2018, an update on legislative activities, proposed bylaws changes, and communication and membership updates.

The MSMA Alliance is looking forward to its 92nd Annual Meeting Friday, March 31 & April 1 in Kansas City. MSMA and the MSMA Alliance are proud to present on Friday, March 31, 1:30-3:00 p.m., the journalist, author and storyteller, Sam Quinones, who will share the haunting tale of opiate abuse in the heartland.

Following Mr. Quinones' presentation, the MSMA Alliance is bringing a "very special" fun-filled, entertaining hour with the "Wings of Love" proprietor, renowned "Bird Lady," Yvonne Patterson-Burbach and many of her beautiful, exotic birds. Free to MSMA, Alliance and meeting guests, ALL are invited to attend this exciting event.

Join us at the Alliance's "A Night with the Blues," the Foundation Fundraiser and Dinner on Friday, March 31, beginning at 7:00 p.m., chaired by Kathy Weigand. Enjoy an evening with *Blues Highway*, a 5-person blues ensemble that includes MSMA's own Joe Corrado, MD, on bass and Gene Thomas, DO, on lead guitar. Music from Blues greats BB King, Muddy Waters, and Stevie Ray Vaughn will provide a feast for your ears, with delicious food and fantastic drawings for great prizes, while raising funds for the Missouri State Medical Foundation.

We thank the MSMA for its invaluable contributions to its Alliance.

Commission on Continuing Education

The Commission reviewed and approved the following accreditation actions:

Reaccreditations

- Phelps County Regional Medical Center-Rolla, MO
- St. Anthony's Medical Center-St. Louis, MO

Progress Reports

The following entities submitted Progress Reports that were approved by the Commission:

- North Kansas City Hospital-Kansas City, MO
- Mercy Hospital Springfield-Springfield, MO
- Mercy Hospital St. Louis-St. Louis, MO
- St. Louis STD/HIV Prevention Training Center-St. Louis, MO
- SSM St. Mary's Hospital-Jefferson City, MO

Activity Review

The following entity had an on-site review of a live activity:

- Esse Health-St. Louis, MO
- Mosaic Life Care-St. Joseph, MO

2016 Annual Convention

The Commission planned and approved the 2016 Annual Convention CME Program for 17.75 hours of AMA PRA Category 1 creditsTM. Additionally, four of the General Sessions were approved for the American Board of Internal Medicine Maintenance of Certification Points.

Following the Annual Convention, attendees were able to participate in an online survey that measured outcomes based on questions designed by the Commission.

Providers Withdrawing From Accreditation in 2016

In 2016 the following entities withdrew from accreditation:

- Ozarks Medical Center-West Plains, MO
- Bothwell Regional Health Center-Sedalia, MO

Annual Maintenance Fee Increase

After keeping the Annual Maintenance Fee at $1050 for seven years, the Commission felt it necessary to increase the fee assessed to each Missouri provider. The Commission approved an annual maintenance fee increase for all Missouri accredited providers to be implemented in January of 2017.

Updated Markers of Equivalency

The ACCME updated the Markers of Equivalency that govern the actions of accredited State Medical Societies. The Commission adopted the updated document.

MSMA Accredited Providers

The Missouri State Medical Association currently accredits twenty-eight entities statewide.

Outreach and Educational Offerings

MSMA staff hosted new staff trainings at MSMA headquarters in 2016.

Benita Stennis, MSMA staff, attended the state medical society meeting sponsored by the ACCME and AMA and reported back to the Commission on issues and trends relevant to CME. Additionally, staff participated in the ACCME's monthly noon conference calls.

Membership

MSMA closed out the 2016 membership year with 2,692 active physician members, which is an 18 percent market share of physicians licensed with a Missouri address; 916 medical student members; 130 resident/fellow members; and 442 retired physician members. AMA reported a total of 2,290 active members from Missouri in 2016. Because of the drop in numbers on a national level, MSMA has had to forfeit one delegate slot in the AMA House.

On the state level, MSMA recruited 194 new members in 2016. More than 100 took advantage of the half-price offer in July, 2016. That offer coincided with MSMA's successful effort to block a proposed merger of insurance giants, Aetna and Humana. We included a message about that to non-member prospects.

As of January 30, 2017, MSMA counted 1,823 active members for 2017. We've picked up some new members in their first, second, and third years of practice who responded to a postcard mailing with an image of MSMA Councilors congratulating them on being newly-licensed in Missouri. This included a link to www.msma.org/big-wins, highlighting our success in the legislature and introducing our preferred partners.

When physicians join MSMA, they get a personal phone call from MSMA staff, a member ID card in the mail, and a series of introduction e-mails. Member certificates are mailed upon request. We encourage existing members to embrace those who are new to organized medicine, and to take advantage of the opportunity to recruit new members and receive a dues discount for every new member you recruit. Details about the Member-Get-a-Member Campaign are outlined at www.msma.org/member-get-a-member.

The local component medical societies statewide have appreciated their visits from MSMA President Ravi Johar, MD, this year. Also of great value have been the presentations given by Missouri Physicians Health Program in healthcare facilities, resident programs and throughout campuses at the medical schools. MSMA staff is collaborating with the AMA membership department on a member recruitment campaign highlighting AMA President Elect David Barbe, MD. We are coordinating with members from inactive local component medical societies who want to revitalize their societies, as well.

Physicians now have the option to sponsor a student membership when they join or renew their dues. In addition to that, MSMA is implementing a student mentorship program. We encourage Councilors, Delegates, physician leaders, members – all of the above – to volunteer as a mentor through Haley Wansing, hwansing@msma.org.

MSMA is proud to have such amazing leadership and members. Please read about them, acknowledge their accomplishments in each issue of Missouri Medicine, and tune in to our Facebook page: www.facebook.com/momedical.

Missouri Physicians Health Program

This has been a busy year as indicated by the number of referrals and the numerous Missouri physicians that were assisted. The MPHP provides a variety of services. This includes consultation, intervention, referral for treatment, monitoring and advocacy. The consultive service is especially active. Hospital administrators, physicians, colleagues and family members call the Program Coordinator or Clinical Coordinator to make a referral, discuss a potential referral or brainstorm about the necessity of making a referral. Information is often requested about how to identify problems, what services are available and how to handle issues of impairment should they occur. Many hours are required to meet their needs. The MPHP provides a safe and knowledgeable venue for any question or concern about physician health.

Missouri State Medical Association Insurance Agency

Your MSMA Insurance Agency is an independent insurance agency that offers professional insurance consultation to all Missouri physicians. The Agency offers policies primarily for professional liability and health, but also covers workers compensation, business office coverage, disability, and life.

The board of the Insurance Agency reviews budget and financial statements at each quarterly meeting. Agency financial statements are audited and consolidated into the MSMA financials.

The board is supportive of the Agency and encourages all MSMA members to contact the Agency for a competitive health insurance or professional liability insurance bid.

Missouri State Medical Foundation

Your Missouri State Medical Foundation loaned $100,000 to Missouri medical school students in 2016. The Foundation has loaned almost $12 million to over 3,000 Missouri medical students since beginning in 1961.

In addition to continuing to make student loans, the

Foundation is annually funding eight $2,500 MSMA Scholarships at each of the six Missouri medical schools totaling $120,000 in 2016.

The Foundation has also assisted with the creation of scholarship funds by local medical societies and the MSMA Alliance by providing $5,000 matching grants.

The current financial strength of the Foundation is due to the strong support received from the MSMA and the MSMA Alliance.

Commission on Medical Economics

The MSMA Medical Economics Commission addressed MSMA Resolution #13 (2016) which was referred to the MSMA Council by the House of Delegates.

Resolved, that MSMA support increasing employee eligibility under the Family and Medical Leave Act of 1993 by expanding the mandate to all employers with 10 employees or more within 75 miles, and be it further

Resolved, that MSMA support increasing employee eligibility under the Family and Medical Leave Act of 1993 by expanding the mandate to cover all employees who have worked at least 1000 hours in the past 12 months, and be it further

Resolved, that MSMA support promoting longer parental leave by amending the Family and Medical Leave Act of 1993 to increase the minimum length of protected parental leave to 24 weeks, and be it further

Resolved, that MSMA support amending the Family and Medical Leave Act of 1993 to mandate paid protected leave rather than unpaid leaved, and be it further

Resolved, that the MSMA forward this resolution to the 2016 AMA House of Delegates.

The Commission discussed the resolution and its potential impact on Missouri physicians. After considering a number of factors the Commission recommended a substitute resolution which the MSMA Council subsequently adopted and forwarded to the AMA meeting in November 2016. The resolution was passed by the AMA House of Delegates with the underlined additions and the removal of the second resolved statement.

Resolved, That our American Medical Association encourage the study of the health implications among patients if the United States were to modify one or more of the following aspects of the Family and Medical Leave Act:

- a reduction in the number of employees from 50 employees;

- an increase in the number of covered weeks from 12 weeks; and

- creating a new benefit of paid parental leave. (Directive to Take Action)

~~Resolved, That our AMA study the effects of FMLA expansion on physicians in varied practice environments. (Directive to Take Action)~~

The MSMA Council approved this report July 17, 2016.

Publications Committee

Volume Number 113 of *Missouri Medicine* showcased national authors and featured ground-breaking scientific articles. This volume published four issues featuring "theme" articles and two issues featuring a variety of scientific topics and micro-series. It contained 496 pages and 52 scientific articles. The Journal received a record number of scientific manuscripts for peer-review and continued regular departments.

Your current *Missouri Medicine* is peer-reviewed, indexed by MEDLINE, The National Library of Medicine, and linked to PubMed. We are included in EBSCOhost databases, the largest premium online information resource for researchers.

The University of Missouri Press will publish our near-death experiences articles in book form prior to the MSMA Annual Convention in late March 2017. The title is "The Science of Near-Death Experiences." The response to the Death/Near-Death Experiences series has been exceptional and papers have been cited or reprinted in several books. *Missouri Medicine* continues to receive reprint requests from around the world, the most recent being Spain and China. Articles based on *Missouri Medicine* papers appeared in General Surgery News, and all major Missouri newspapers. Due to an administrative problem all our scientific content has not been linked with PUBMED Central. This is a great disappointment given how much time and effort we put into the approval process. MSMA is working with PUBMED Central to establish linking. All content has for many years been indexed at PUBMED. We received a satisfactory number of unsolicited articles; acceptance rate is about 75%.

In 2016, our Journal presented its third Arthur Gale Freedom of Expression Award to physician Timothy Woods, MD, Springfield. It is to be presented annually to the author of the best commentary article published in Missouri Medicine, in honor of Arthur Gale, MD, one of the Journal's Contributing Editors and MSMA member since 1976.

Our thanks to the Editorial Board for their good work: Drs. David Fleming, Art Gale, William Reynolds, Charles Van Way, III, Justin Albani, Jeffrey G. Copeland, and newly added Betty Drees. Added experts in 2016-2017: Susan Berdy, MD (Allergy & Immunology), Jose M. Dominguez, MD (Colon & Rectal Surgery), and Gary Singer, MD (Nephrology). An Editorial Board Recognition Program was implemented in 2016 and many of the Editorial Board properly received recognition and awards.

Missouri Medicine provides reprinted papers for several prestigious medical specialty magazines and journals, and also selectively reprints articles from the medical component societies in Missouri and from national publications appropriate for our audience.

The Publication Committee Chair and Editor, John C. Hagan, III, MD, and Managing Editor, Lizabeth Fleenor, appreciate the many contributions of the MSMA, Alliance members, and others who have contributed to Missouri Medicine. The Committee appreciates the Association's continued support of the Journal. By any objective criteria, *Missouri Medicine* is among the top five state medical society journals in the United States.

Young Physicians Section

The Young Physician Section (YPS) will be meeting again at the 2017 Annual Convention. This will be the third consecutive year for a YPS meeting and the second consecutive year for an educational presentation. The 2016 presentation was entitled Protecting Your Biggest Asset, You. Speakers from the MSMA Insurance Agency and Moneta discussed insurance needs and financial concerns.

During 2016 YPS held a webinar on physician contracts presented by Resolve Physicians Agency. We hope to hold additional webinars in 2017 to encourage more interaction. YPS also has developed web pages within the MSMA website to provide more information about the section and as a resource to store the handouts and recordings from the educational sessions being held.

Resident and Fellow Section

The Resident and Fellow Section (RFS) continues to be active in the MSMA and AMA. Our resident member Dr. Lauren Umstattd, PGY-2 in Otolaryngology at MU, attended the national interim meeting this year in Orlando, FL. She reported on a vigorous RFS meeting that included discussion on MACRA, the new TruthInRx campaign (which is a program the AMA has established to promote drug price transparency), and gun violence in the US.

The RFS also convened their house of delegates to vote on RFS policy. Adopted resolutions include promoting the study of opioid production cuts, educating physicians and patients on the potential harms of nicotine replacement products, and supporting public and private payers covering all aspects of family planning, including elective pregnancy termination. Lengthy discussion was also had on the recently proposed ACGME changes to common program requirements. Ultimately, the group decided to refer the issue for more study, while collaborating with the AMA Committee on Medical Education, to obtain additional information of potential impacts of said changes.

On a local level, the RFS continues to work on membership and engagement with Missouri residents and fellows – a notoriously busy cohort. We have been actively communicating with members and non-members and are currently seeking avenues to better engage residents and fellows in ways that meet their time constraints. Should you have any thoughts, questions, or concerns regarding the MSMA Resident and Fellow Section, please reach out to me at nolann@health.missouri.edu.

Medical Student Sections

A.T. Still University – KCOM

The A.T. Still University - KCOM MSMA-MSS Chapter welcomed the class of 2020 during their first week, with a booth at the Taste of Kirksville event. The Chapter this year has expanded by several new members across the four graduating classes of KCOM students. In December, we partnered with the Red Cross to host a blood drive where we were able to help the Red Cross bring in 72 donors who donated 65 pints of blood. This spring should bring exciting events such as an interactive case presentation with Matthew Hardee, DO, an ethics panel with Dean Margaret Wilson, DO, and another blood drive. We look forward to bringing more events to our members and exploring new opportunities in the coming years.

We would like to thank Larry Ciesemier, DO, our faculty advisor, and also the MSMA- MSS Division for their continued support of our organization. We are thankful for this fall's success and are excited to see what the future has to offer.

Kansas City University of Medicine & Biosciences

The Kansas City University of Medicine & Biosciences (KCU) MSMA-MSS Chapter began the academic year with a "How to Survive Medical School" event for the incoming class. During this welcome event, students learned study skills and tricks. Additionally, MSMA-MSS officers explained the benefits of becoming a member and answered student questions. The event was a success; half of the 100 first-year students who attended decided to enroll in MSMA-MSS at our school's recruitment fair. Our chapter currently has over 300 members, making it the largest student organization at KCU. Our chapter continues to grow with every event we host.

This year, our organization has focused on giving back to families in need throughout the Kansas City area. We have been volunteering bimonthly at Ronald McDonald Houses across the area and have already donated a collective 200 service hours. Volunteers have worked to collect donated food products which are used to prepare delicious snacks for

families staying at Ronald McDonald Houses during trying times in their lives.

In addition to service work, our chapter welcomed Dr. Ravi S. Johar, MD, MSMA President, as well as Haley Wansing, MSS Staff Liaison, to campus in December to speak to members regarding current issues affecting physicians and students throughout Missouri. Our members discussed the effects of mandating a statewide prescription drug monitoring system, expanding Telehealth to rural areas, and raising awareness/prevention of medical student suicide. We also discussed the potential effects that the newly-elected Trump administration could have on the ACA. The meeting was enlightening and served to further our understanding and interest in addressing tort reform.

Along with our colleagues in the Student Osteopathic Medical Association and the Missouri Association of Osteopathic Physicians and Surgeons, we are currently preparing for our annual "Surviving Clerkships" panel. Third- and fourth-year KCU students have been invited to share their rotation experiences. This event was attended by 200 students last year, and we are hoping to have even larger participation this year. We are also looking forward to upcoming events, including the MSMA Annual Convention in Kansas City and the AMA meeting in Chicago.

Saint Louis University

The Saint Louis University MSMA-MSS welcomed the Class of 2020 during orientation week with a chapter lunch presentation on AMA, MSMA and SLMMS. We again introduced students to MSMA with tables at the Electives and Activities Fair and the Student Interest Group Fair during the first few weeks of school. In September, Dr. Johar spoke to us about the role of organized medicine in health policy and his experiences with MSMA. Later in the fall, Christopher Libby, AMA-MSS President, presented to students on finding success in medical school.

This year our chapter continued its strong commitment to serve the St. Louis community. We coordinated student involvement in the Health Protection and Education Services Clinic at University City Public Library, providing free screenings to 50 patients on the third Saturday of each month. The chapter developed a new tutoring program, "Take Two Tutoring," with the St. Louis Juvenile Detention Center where volunteers will host biweekly math and reading sessions. Finally, several of our chapter officers worked to plan the Missouri M1 Conference for first-year students from across the state. With MSMA's support, SLU will host 150 Missouri M1s at the conference later this spring.

Beyond SLU, our chapter participated in the larger MSMA and AMA organizations. Shivani Singh, a third-year student, served as MSMA-MSS Vice Councilor. Three of our members attended the 2016 MSMA Annual Convention. Nationally, our chapter sent delegates to AMA Annual in June and AMA Interim in November. This spring, we will host events to raise awareness about health policy on campus, and hold our annual fundraiser supporting the Institute for Family Medicine. We plan to initiate new fundraising opportunities to support greater participation in conventions, and continue to represent Saint Louis University in MSMA and AMA. We look forward to another great year in 2017.

University of Missouri

The MSMA-MSS at University of Missouri-Columbia started off the year with a recruitment table at the orientation week activities fair. We continued this effort with a luncheon meeting to provide information on the benefits and rewards of organized medicine. We were able to recruit many new students to join and get excited about opportunities within the MSMA and AMA.

In September, we partnered with the Boone County Medical Society (BCMS) to co-host a Q&A Panel with Mizzou Residency Directors. In October, we hosted the Government Relations and Advocacy Fellow (GRAF), who spoke about the functions of the AMA and avenues for medical students to get involved. At our annual Halloween party fundraiser, we raised and donated $900 to MedZou, the free student-run clinic at Mizzou.

For Advocacy Week, Mizzou focused on raising awareness about the national opioid epidemic. Several of our chapter officers tabled over lunch to encourage students and faculty to sign the Surgeon General's "Turn the Tide" pledge. As an extension of this, Meghna Srinath and Jared Lammert drafted a letter to John Oliver of "Last Week Tonight" in response to his spot on the opioid epidemic, urging him to do a follow-up segment on Missouri's lack of a PDMP. As in the past, Mizzou has continued to have strong attendance at national conferences and representation in state and regional leadership.

In March, four first-year students attended the Medical Student Advocacy and Region Conference (MARC) and lobbied on Capitol Hill for maintaining PSLF programs and GME funding. Later that month, several students attended the MSMA Annual Convention in St. Louis, where Matt Faubion was elected MSMA

Alternate-Delegate and Meghna Srinath was elected as MSMA-MSS Secretary. In June, several students attended the Annual Meeting in Chicago, where Sonia Boodram was elected as the Region 2 Membership and Recruitment Chair. In November, a contingent of four students attended the Interim Meeting in Orlando, where Ariel Carpenter and Jared Lammert were elected as Region 2-MSS Delegate and Alternate-Delegate, respectively.

Upcoming events include: Lobby Day in Jefferson City, MARC in D.C., MSMA Annual Convention in KC, BCMS General Meeting with Dr. Barbe and Chapter Officer Elections for 2016-2017.

University of Missouri – Kansas City

The UMKC Chapter of the MSMA-MSS has had another successful year reaching out to members in the medical school and local community. Our main goals this year are to expand on last year's monthly meeting and service events.

Our first recruitment event was in August on the undergraduate campus, promoting the organization to the general student body and incoming younger classmen. We appreciated the presence of Haley Wansing, MSMA-MSS Liaison, and current AMA members, who were able to illustrate the benefits of being a member. We also have an annual winter recruitment event at the Hospital Hill campus to promote the organization to the incoming third-year class in our unique six-year program, as well as the MD-only students who recently joined the program. Overall, our Chapter continues to grow through these events and promotions.

Our Chapter also continues to be involved on the national and local levels. In November, we sent five students to the AMA Interim Meeting in Orlando, where a variety of resolutions were discussed and new connections were formed with members from across the nation. We also have Chapter members that also serve as State MSS Officers, including Kartik Sreepada (Councilor), Timothy Chow (Treasurer), and Muhhamed Alikhan (Vice-Chairperson).

This past semester, we had many events, including a two-part event with the UMKC-Psychiatry Interest Group and UMKC-Internal Medicine Interest Group to have a screening of the movie "13th" and discuss health concerns in the prison population. We also had events to discuss the resolution writing process and how we can be more involved in regard to the Save GME project and the national opioid epidemic.

This year, we continue to involve our chapter with community service. We participated in our fourth "KC Fun-and-Fitness Day," a community-wide health fair. Our Chapter is also working with many other organizations in the medical school and local community, such as KC Prep to inspire high school students to pursue careers in medicine. We hope to continue expanding our Chapter with another exciting year ahead.

Washington University

The Washington University Chapter had another successful year training tomorrow's physician-advocates and healthcare leaders. We began the year with a very successful recruiting event during the First Year activities fair. We followed this up with well-attended lunch talks by SLMMS President Dr. Samer Cabbabe and AMA-MSS Chair Christopher Libby.

We have continued to focus on giving future physicians the skills to advocate for their patients. We hosted multiple lobby days last year and look to continue the tradition this year, with events planned for March and April. We have continued to foster strong legislative partners and look to continue working with them in the coming legislative session.

Our chapter is engaged on the Local, State, and National level. Hannah Bucklin, one of the incoming chapter chairs, was recently appointed as the SLMMS Student Board Member for 2017. Craig Yugawa currently serves as the MSMA-MSS chair and helped to arrange the recent MSMA Lobby Day. WUSM sent 6 students to the AMA Interim Meeting and several WUSM members serve on AMA standing committees and in Region 2 positions.

We are dedicated to changing healthcare policy for the better. One of our WashU submitted resolutions on Parental Leave was advanced to the AMA House of Delegates during the Interim Meeting. A couple of our students testified in support of Rep. Frederick's Compassionate Medical Education Act. We are continuing our partnership with the WashU Law School's Health Law Interest Group and hope it will produce resolutions and propose legislation in the future.

The WashU MSS chapter is focused on training the future physician-leaders of tomorrow and remains committed to host programming that gives them the skills necessary to bring about positive change in multiple roles. We are working to provide our members with candidate training and advocacy experiences that will help them as they leave WashU. We are grateful for the last year's success and hopeful for the future of our program going forward.

MM

MSMA House of Delegates and Council Vote on New Polices

(HOD) Prescription Drug Monitoring Program

MSMA supports the establishment of a direct access statewide prescription drug monitoring program.

(HOD) Peer to Peer Insurance Reviews

MSMA calls for insurance companies to have an actively practicing physician, who is board certified in the same specialty as the patient's physician, to participate in the peer-to-peer stage of Missouri utilization review appeals process.

(Council) Medical Marijuana

MSMA believes there is evidence that suggests marijuana and its related derivatives may have therapeutic benefits for patients with certain medical conditions. As such, MSMA calls on the Food and Drug Administration and the Drug Enforcement Administration to promptly revise marijuana's current classification as a Schedule I controlled substance in order to facilitate evidence-based, scientifically-valid clinical research to evaluate its efficacy and safety.

Missouri State Medical Association Financial Statement

Statement of Financial Position
December 31, 2016

ASSETS

CURRENT ASSETS:		
Cash and Cash Equivalents	$	642,913
Short-Term Investments		9,596,917
Accounts Receivable		4,350
Prepaid Expenses		28,013
Total Current Assets		10,272,193
FIXED ASSETS:		
Land		83,000
Building and Improvements		605,078
Furniture and Equipment		275,831
Less: Accumulated Depreciation		(845,358)
Total Net Fixed Assets		118,551
OTHER ASSETS:		
Note Receivable - MSMA Ins. Agency		209,610
Investment in Subsidiary - MSMA Insurance Agency		(8,334)
Long-Term Investments		2,391,562
Total Other Assets		2,592,838
TOTAL ASSETS	$	12,983,582

LIABILITIES AND NET ASSETS

CURRENT LIABILITIES:		
Accounts Payable and Accrued Expenses	$	10,957
Accrued Vacation		64,624
Funds Held for Others		19,647
Deferred Revenue		28,478
Deferred Dues		600,046
Total Current Liabilities		723,752
NON-CURRENT LIABILITIES:		
Non-Qualified Deferred Compensation Agreement		464,003
Pension Benefit Liability		4,027,144
Total Non-Current Liabilities		4,491,147
Total Liabilities		5,214,899
NET ASSETS:		
Unrestricted		7,768,683
Total Net Assets		7,768,683
TOTAL LIABILITIES AND NET ASSETS		$ 12,983,582

Missouri State Medical Foundation Financial Statement

Statement of Financial Position
December 31, 2016

ASSETS		LIABILITIES AND NET ASSETS	
CURRENT ASSETS:		**LIABILITIES:**	
Cash	$ 451,528	Funds Held for Others	$ 187,963
Investments	101,303		
Notes Receivable - Current	283,844	**TOTAL LIABILITIES**	187,963
Accrued Interest	144,765		
Total Current Assets	981,440		
EQUIPMENT:			
Office Equipment	1,091		
Software	10,692		
Less: Accumulated Depreciation	(11,274)		
Total Net Fixed Assets	509		
NON-CURRENT ASSETS:			
Investments	3,938,066		
Total Non-Current Investments	3,938,066		
Notes Receivable - Long Term	1,730,681	**NET ASSETS:**	
Allowance for Doubtful Accounts	(193,880)	Unrestricted	6,268,853
Notes Receivable - Long Term (Net)	1,536,801		
TOTAL ASSETS	$ 6,456,816	**TOTAL LIABILITIES AND NET ASSETS**	$ 6,456,816

Missouri Physicians Health Program Financial Statement

Statement of Financial Position
December 31, 2016

ASSETS		LIABILITIES AND NET ASSETS	
CURRENT ASSETS:		**CURRENT LIABILITIES:**	
Cash and Cash Equivalents		Accounts Payable	$ 6,649
Cash - Checking	$ 110,590	Accrued Payroll Tax	175
Cash - McIntosh Fund	54,242	Accrued Vacation	13381
Mutual Funds - McIntosh Fund	12,492	Total Current Liabilities	20,205
Certficates of Deposit	120,000		
Accounts Receivable	201,182	**NET ASSETS:**	
Allowance for Doubtful Accounts	(18,500)	Unrestricted	478,761
Accrued Interst	8		
Total Current Assets	480,014	**Total Liabilities and Net Assets**	$ 498,966
NON-CURRENT ASSETS:			
Investments - McIntosh Fund	9,775		
Property and Equipment			
Office Furniture and Equipment	49,922		
Less: Accumulated Depreciation	(40,745)		
Net Property and Equipment	9,177		
Total Non-Current Assets	18,952		
TOTAL ASSETS	$ 498,966		

2017 Annual Convention Attendance

Delegates	*110*
Members	*121*
Exhibitors	*46*
Staff	*22*
Guests	*159*
Officers	*9*
Councilors/Vice	*29*
Alliance	*50*
Total	*508*

(Actual numbers will not balance due to overlaps in positions served.)

Officers
Bean, David, DO
Biggers, Brian, MD
Gates, Lancer, DO
Johar, Ravi, MD
Lovinger, Jr., Warren, MD
Page, Sam, MD
Pohl, David, MD
Stanley, John, MD
Terpstra, Gregory, DO

Councilors
Ahlum, Sandra, MD
Behshad, Ramona, MD
Brennan, Jr., Robert, MD
Corrado, Joseph, MD
DiRenna, Jr., James, DO
Drees, Betty, MD
Gates, Lancer, DO
Hover, Alexander, MD
Hruza, George, MD
Hubbell, George, MD
Kuhlmann, David, MD
Nolan, Nathaniel, MD
Schaaf, Rob, MD
Sreepada, Kartik
Stadnyk, Michael, MD
Weikart, Kevin, MD
Zhu, Lirong, MD

Vice Councilors
Barbe, David, MD
Conant, James, MD
Corder, Robert, MD
Florio, Sarah, MD
Nichols, M. Ellen, MD
Singh, Shivani
Slocum, Stephen, MD
Taormina, Marc, MD
Thomas, Lisa, MD
Wallace, Sharon, MD
Willman, Martin, MD
Wilson, Benjamin, MD

Delegates
District 1
Buchanan County Medical Society
Conant, James, MD
Corder, Robert, MD
Weigand, Robert, MD

District 2
Northeast Missouri Medical Society
Bukstein, Michael, MD
Halpin, Stephen, MD
Johnson, Lent, MD

District 3
St. Louis Metropolitan Medical Society
Arnold, Donald, MD
Bean, David, DO
Butler, David, MD
Cabbabe, Edmond, MD
Cabbabe, Samer, MD
Corder, James Collins, MD
Goodhope, Karen, MD
Huffaker, William, MD
Johar, Ravi, MD
Klix, Mary, MD
Lund, Jr., Herluf, MD
Murdock, Nathaniel, MD
Page, Sam, MD
Pohl, David, MD
Ryall, Jo-Ellyn, MD
Shariff, Anjum, MD
Singh, Inderjit, MD
Slocum, Stephen, MD
Thomasson, Jeffrey, MD
Wild, Alan P. K., MD

District 4
St. Charles-Lincoln Medical Society
Andrews, Brian, MD
Copeland, Jeffrey, MD
Glaser, Jeffrey, MD
Sill, William, DO
Tyree, Thomas, MD
Willman, Martin, MD

Tri-County Medical Society
Chalk, David, MD
Raney, Michael, MD
Ratcliff, Keith, MD

District 5
Audrain County Medical Society
Taylor, Steve, MD

Boone County Medical Society
Brown, Michael, MD
Cunningham, Milamari, MD
Friedman, Michael, MD
Groshong, Ted, MD
Hillard, Alan, MD
Landrum, Alice, MD
Thomas, Lisa, MD
Winn, Hung, MD

Lake of the Ozarks Medical Society
Canver, Charles, MD

District 6
West Central Medical Society
Haynie, William, MD
Turner, Amanda, MD
Turner, William, MD
Wilson, Benjamin, MD

District 7
Kansas City Medical Society
Allen, Thomas, MD
Butin, Richard, MD
Doane, John, MD
Erkmann, John, DO
Hagan, III, John, MD
Hahn, Jr., Frederick, MD
Hierholzer, Rebecca, MD
Kelly, Jim, MD
Laiben, Gregg, MD
Mammen, Joshua, MD
McCandless, Bridget, MD
Montello, Sam, MD
O'Dell, Michael, MD
Perryman, Kathy, MD
Potts, Donald, MD
Rues, Larry, MD
Salanski, Stephen, MD
Stanley, John, MD
Striker, Adam, MD
Sun, Tony, MD
Taormina, Marc, MD
Van Way, III, Charles, MD
Youmans, Ronald, MD

District 8
Greene County Medical Society
Bentley, Anthony, DO
Biggers, Brian, MD
Blaine, James, MD
Corry, Francis, MD
DelCampo, Louis, MD
Knowlton, III, Norman, MD
Petersen, Larry, MD
Swearengin, Timothy, DO
Taylor, Marsha, MD
Wolfe, James, MD

Ozarks Medical Society
Hamilton, William, MD

Southwest Medical Society
Nichols, M. Ellen, MD

District 9
Mid-Missouri Medical Society
Fasuyi, Omofolarin, MD

South Central Counties Medical Society
Barbe, David, MD

District 10
Cape Girardeau County Area Medical Society
Jung, Christopher, MD
Jung, J. Marshall, MD
Moore, Andrew, MD
Wallace, Sharon, MD

Mineral Area Medical Society
Terpstra, Gregory, DO

Medical Student Section
St. Louis University
Kim, Ellen
Tai, Shannon

University of Missouri-Columbia
Boodram, Sonia
Yasin, Junaid

University of Missouri-Kansas City
Patel, Nilbhi
Varghese, Mana (delegate Sunday)
Veeramachaneni, Hima (delegate Friday)

Washington University
Bucklin, Hannah
Lynn, Mitchell

Kansas City University of Medicine
Medvec, Andrew

A.T. Still Osteopathic School of Medicine
Purviance, Adam
Sarmiento, Shaun

Resident and Fellow Section
Brahmbhatt, Mihir, MD
Clark, Megan, MD
Grumke, Adam, MD
Loethen, Joanne, MD
Umstattd, Lauren, MD
Young, Daniel, MD

Young Physician Section
Florio, Sarah, MD

Delegates-At-Large
Medical School Deans
Delafontaine, Patrice, MD

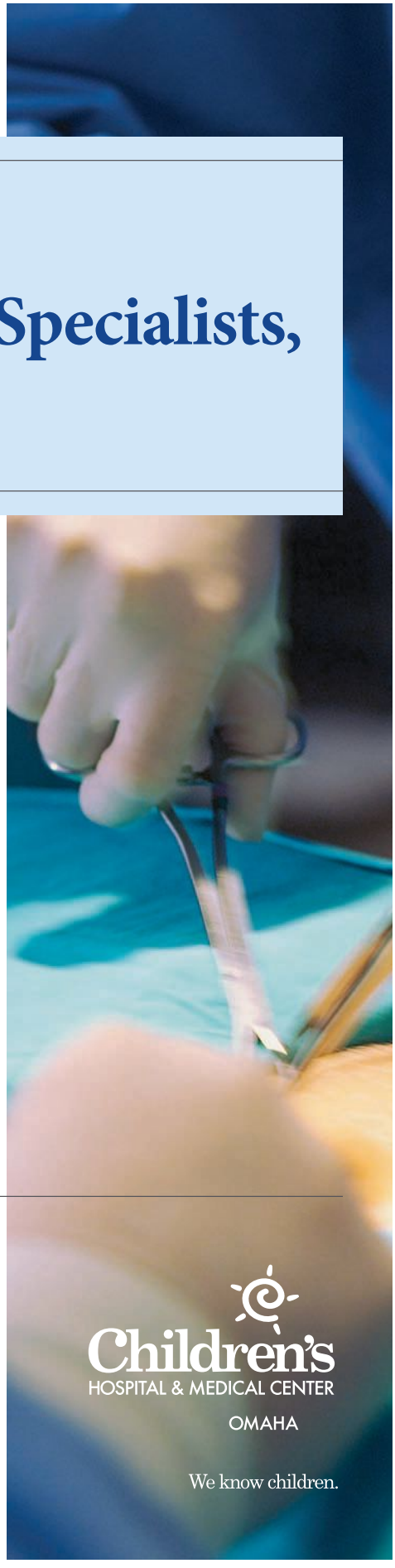
Past Presidents
Barbe, David, MD
Cabbabe, Edmond, MD
Copeland, Jeffrey, MD
Hahn, Jr., Frederick, MD
Johnson, Lent, MD
Knowlton, III, Norman, MD
Slocum, Stephen, MD
Stanley, John, MD
Thomasson, Jeffrey, MD
Wolfe, James, MD
Youmans, Ronald, MD

Vice Speaker
Page, Sam, MD

Members
Ahlum, Sandra, MD
Ajans, Z. A., MD
Andelin, Clark, MD
Andrews, Thomas
Atluri, Hima
Baber, William, MD
Batterson, James, MD
Behshad, Ramona, MD
Berkowitz, Wallace, MD
Berndt, Scott
Boschert, Mark, MD
Boulware, Robert, MD
Brennan, Jr., Robert, MD
Buchanan-McCanse, Barbara, MD
Cabbabe, Amy, MD
Campbell, Neal, MD
Carpenter, Ariel
Casey, Matthew, MD
Caughron, Samuel, MD
Chang, Chia-Wai David, MD
Colbert, Stephen, MD
Conway, Bob, MD
Cook, Tarah, MD
Cooper, Blake, MD
Corder, Patricia, MD
Corrado, Joseph, MD
Cullen, Reba, MD
Curcuru, Caitlin, MD
Curtis, Anna
Daus, Arthur Steven, MD
Delafontaine, Patrice, MD
DiRenna, Jr., James, DO
Dixon, Dave, MD
Drees, Betty, MD
Dunn, Catherine, MD
Ekman, Steven
Fakhoury, Donald, MD
Fleming, James, MD
Gardner, Joe, MD
Gates, Lancer, DO
Gondring, Bill, MD
Goodson, David
Hagen, John, MD
Heimburger, Richard, MD
Hoeman, Michael, MD
Hover, Alexander, MD
Howard, Barbara, MD
Hruza, George, MD
Hubbell, George, MD
Jackson, Ken, MD
Jani, Akash
Jones, Robert, MD
Kenney, Richard, DO
Kim, Chul, MD
Kiyanclar, Mehmert, MD
Kuennen, Scott, MD
Kuhlmann, David, MD
Lamb, Jerry, MD
Lammert, Jared
Lin, Jim, MD
Long, Curtis, MD
Lovinger, Thomas, MD
Lovinger, Daniel, MD
Lovinger, Jr., Warren, MD
Luetje, II, Charles, MD
Maitz, Carlos, MD
Manalaysay, Alvin, MD
Maples, AnnaMaria
Marietta, William, MD
Marti, Larry, MD
Mataverde, Philip, DO
McJunkin, Jonathan, MD
McMillen, James, MD
Metlis, Schuyler, MD
Miller, Ramona, DO
Montes, Arturo, MD
Moore, John, MD
Morton, Wayne, MD
Muscato, Mary, MD
Muscato, Joseph, MD
Myers, Carl, MD
Nolan, Nathaniel, MD
Norregaard, Thorkild, MD
Olomon, Angela, DO
Papreck, K. Thomas, MD
Patterson, Jonathan, MD
Rajcher, Wilma, MD
Reintjes, Steve, MD
Renner, Greg, MD
Reusch, James, MD
Roark, Lisa, MD
Sarma, Subbu, MD
Satterly, Matthew, MD
Schaaf, Rob, MD
Segal, Arelene, MD
Serota, Pearl, MD
Sescleifer, Anne
Sheeran, Paul, MD
Sincox, Charles, MD
Singh, Shivani
Southwick, Christopher, MD
Sreepada, Kartik
Srivastava, Hirsch
Stadnyk, Michael, MD
Stewart, Larry, MD
Threlkeld, Kevin, MD
Triplett, Daniel, MD
Ursick, Joe, MD
Volker, Cassie, MD
Wallace, Douglas, MD
Watson, Richard Alan, MD
Waynie, William, MD
Weikart, Kevin, MD
Weissend, Eric, MD
Welch, Mary Katherine, MD
Wetzel, II, Gus, MD
Wilbers, Raymond, MD
Wongskhaluang, Marjorie, MD
Woods, William, MD
Yugawa, Craig
Zhu, Lirong, MD

MM

One Number Accesses **Our Pediatric Surgical Specialists,** *Any* Problem, Anytime.



1.855.850.KIDS (5437)

PHYSICIANS' PRIORITY LINE

Your 24-hour link to pediatric specialists for physician-to-physician consults, referrals, admissions and transport service.

ChildrensOmaha.org

BEST CHILDREN'S HOSPITALS
U.S.News & WORLD REPORT
RANKED IN 3 SPECIALTIES
2016-17

CARDIOLOGY & HEART SURGERY

GASTROENTEROLOGY & GI SURGERY

ORTHOPEDICS

Children's
HOSPITAL & MEDICAL CENTER
OMAHA

We know children.



Coverage for Affluent Homes

Experience the peace of mind that comes from working
with an insurance professional who understands your unique needs.

MSMA Insurance cares for physicians and covers their personal and professional needs.

Contact Ronnie Staggs | 866-676-2467 | www.msma.biz | rstaggs@msma.biz

MSMA
Missouri State Medical Association
Insurance

