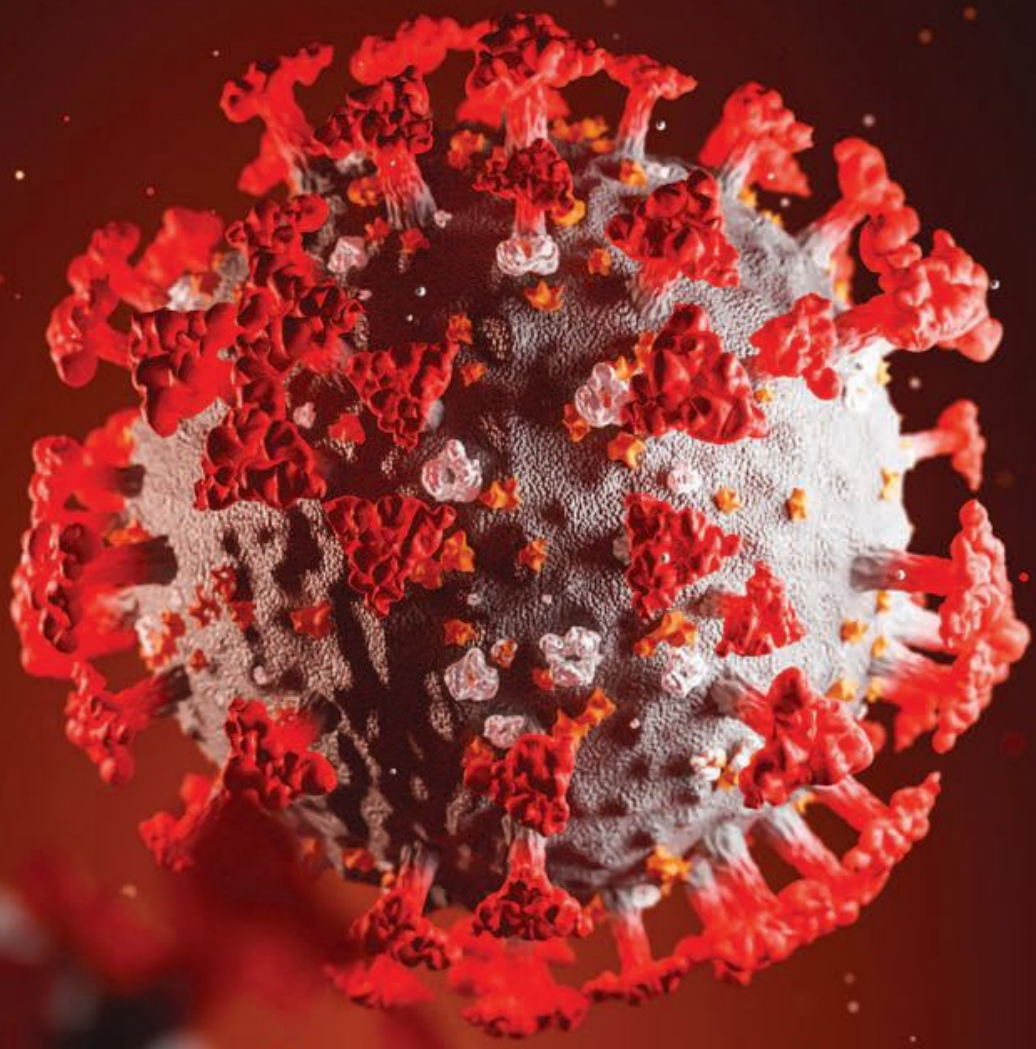
Missouri Medicine

The Journal of the Missouri State Medical Association www.msma.org/missouri-medicine March/April 2020



COVID-19

A Worldwide Pandemic

COVID-19 Teaches Hard Lessons
Imported Infections in the Midwest
China Dependence Threatens U.S. Drug Supply

MSMA Calls for Government Action
Life Expectancy & Deaths of Despair
Physician Well-Being in Times of Extreme Stress

SAINT LOUIS UNIVERSITY.

Frontiers of Surgery

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

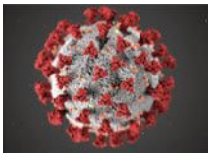
Donations may be sent to:
Missouri State Medical Foundation | P.O. Box 1028 | Jefferson City, MO 65102
Contact Patrick Mills at 800-869-6762 | Email pmills@msma.org

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

Missouri Medicine

The Journal of the Missouri State Medical Association - Since 1904

Volume 117 | Number 2 | March/April 2020 www.msma.org/missouri-medicine



MISSOURI MEDICINE SPECIAL REPORT: COVID-19

The Most Important Thing in a Pandemic? Don't Panic! Together, We Can Get Through This
by **John C. Hagan, III, MD** 80

MSMA Recommends "Shelter-In-Place" to Missouri Governor to Curb COVID-19 82

MSMA Urges Congress Independent Physician Financial Stability in Economic COVID-19 Relief Legislation 83

COVID-19 Teaches Hard Lessons
by Jin Wang, MD & Sharon Frey, MD 84

China's Coronavirus-Induced Paralysis Threatens U.S. Drug Supply Chain
by Henry I. Miller, MD & John J. Cohrssen, JD 86

Imported Infections in Rural Mid-West United States - A Report from a Tertiary Care Center
by Amy Meyer, **Hariharan Regunath, MD**, Christian Rojas-Moreno, MD, William Salzer, MD† & Gordon Christensen, MD† 89

The Need for an Integrated Approach to Well-Being in Healthcare
by **Lawrence M. Lewis, MD, Evan Schwarz, MD, Randall Jotte, MD** & Colin P. West, MD 95

The Role of Alcohol, Drugs, and Deaths of Despair in the U.S.'s Falling Life Expectancy
by Mark S. Gold, MD 99

MEDICAL | LEGAL

Physician Practice Cybersecurity Threats: Ransomware
by Christopher A. Budke & Peter J. Enko, JD 102

PERSPECTIVE

The Curse of Time
by **Charles W. Van Way, III, MD** 105

AS I SEE IT

Life Happens During Training
by **Lauren Umstattd, MD** 107

SCIENCE PERSPECTIVE

Gluten Free Diets – A Challenge for the Practicing Physician
by **Richard Hellman, MD** 119

MEDICAL SCHOOL REPORT

Saint Louis University School of Medicine and Vaccine Center Mobilize for COVID-19 Pandemic
by **Robert W. Wilmott, MD** 125

SCIENCE OF MEDICINE | FEATURE SERIES

Presented by Saint Louis University School of Medicine: Frontiers of Surgery

Punctuated Equilibrium: Surgical Innovation and an Evolutionary Theory
by Sameer Siddiqui, MD 127

The Role of Immunotherapy in Urologic Cancers
by Allison May, MD, Loren Roustio, BS & Zachary A Hamilton MD 128

Screening for Breast Cancer: What You Need to Know
by Kaitlin Farrell, MD, Debbie Lee Bennett, MD & Theresa L. Schwartz, MD 133

Plastic Surgery Innovation with 3D Printing for Craniomaxillofacial Operations
by Alexander Y. Lin, MD & Lauren M. Yarholar, MD 136

Surgical Management of Lymphedema
by Aurora M. Kareh, MD & Kyle Y. Xu, MD 143

Use of Robotic Technology in the Management of Complex Colorectal Pathology
by Claire Wunker, MD & Grace Montenegro, MD 149

SCIENCE OF MEDICINE MINISERIES

Colorectal Surgery Review for Primary Care Providers
by Rakesh Hegde, MD, John M. Trombold, MD & **José M. Dominguez, MD** 154

The Dangers of Vaping
by Peter Laucks, DO & **Gary A. Salzman, MD** 159

FROM YOUR ASSOCIATION

1 Picture = 1,000 Words 98
Book Review 110
Missouri Physicians Health Program 112
Correspondence 114
Alliance Report 116

www.msma.org/engage

momedical @momedicalassn mostatemedicalassociation momedical momedical

Missouri Medicine

The Journal of the Missouri State Medical Association - Since 1904

www.msma.org/missouri-medicine











About Missouri Medicine

In publication since 1904, the peer-reviewed, award-winning, bi-monthly *Missouri Medicine: The Journal of the Missouri State Medical Association,* is indexed by *Index Medicus*, MEDLINE, and PubMed. Complete issues archived at PubMed Central since 2010. Content appears on EBSCO Host Research databases.

With a large and respected editorial board and regular participation by Missouri's six medical schools on eight campuses, *Missouri Medicine* is among the nation's foremost state medical journals.

Articles are frequently cited in impact factor journals and regularly featured in the national media including: *Wall Street Journal, CSPAN-2, KevinMD, Outside Magazine, Runner's World, NBC News, General Surgery News, Ophthalmology Times,* and many others. Issues of *Missouri Medicine* are printed on acid-free paper with open access to digital issues available at www.msma.org/missouri-medicine-library.

Copyright & Postal Entry

Missouri Medicine, the Journal of the Missouri State Medical Association, is owned and copyrighted by the Missouri State Medical Association. Published at 113 Madison Street, Jefferson City, Missouri 65101. Printed by the Ovid Bell Press, Inc., Fulton, Missouri. 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. Annual subscription is included in membership dues; non-members pay $75.00.

Disclaimer

All articles, editorials, letters, and advertisements published represent the opinions of the authors and advertisers, and do not necessarily reflect the official policy or endorsement of the Missouri State Medical Association or the institution with which the author or product or service is affiliated unless clearly specified. *Missouri Medicine* reserves the right to make the final decision on all content and advertisements.

Missouri Medicine Editor

John C. Hagan, III, MD, FACS, FAAO

Managing Editor

Lizabeth R. S. Fleenor, BJ, MA

Contributing Editors & Publication Committee

Justin M. Albani, MD
Jessica D. Bauerle, 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

Allergy & Immunology: Jacqueline L. Reiss, MD
Anesthesiology: Kathy M. Perryman, MD
Cardiac Surgery: Michael C. Murphy, MD
Cardiology: Jerry D. Kennett, MD
Colon & Rectal Surgery: Jose M. Dominguez, MD
Dermatology: Jon A. Dyer, MD
Emergency Medicine: Mark T. Steele, MD
Endocrinology: Howard M. Rosen, MD
Family Practice: Michael L. O'Dell, MD
Gastroenterology: David H. Cort, MD
General Surgery: Joseph A. Corrado, MD
Hematology & Oncology: Stephanie L. Graff, MD
Hospital Medicine: Lancer G. Gates, DO
Infectious Disease: Eden M. Esguerra, MD
Internal Medicine: John S. Daniels, MD
Medical Genetics: Patricia I. Dickson, MD
Medical Student Section: Calli Morris, BS
Military Medicine: Michael S. Clarke, MD
Neonatology: Joshua E. Petrikin, MD
Nephrology: Gary G. Singer, MD
Neurology: Pradeep K. Sahota, MD
Neurosurgery: Keith M. Rich, MD
Obstetrics & Gynecology: Octavio R. Chirino, MD
Ophthalmology: John B. Holds, MD
Orthopaedics: Gregory R. Galakatos, MD
Otolaryngology: John F. Eisenbeis, MD
Pathology: Louis P. Dehner, MD
Pediatrics: Nancy J. Bunge, MD
Physical Medicine & Rehabilitation: Gregory M. Worsowicz, MD
Plastic Surgery: Edmond B. Cabbabe, MD
Preventive Medicine: James H. O'Keefe, MD
Psychiatry: Laine M. Young-Walker, MD
Public Health: Katherine R. Lichtenberg, DO
Pulmonary Medicine: Gary A. Salzman, MD
Radiology: John H. Niemeyer, MD
Resident & Fellow Section: Frances Mei Hardin, MD
Retired Physicians: Juan C. Corvalan, MD
Rheumatology: Anne E. Winkler, MD
Sports Medicine: Brian L. Mahaffey, MD
Statistics & Methodology: Christopher R. Carpenter, MD
Urology: Elizabeth A. Piontek, MD
Vascular Surgery: W. Kirt Nichols, MD
Women Physicians Section: Joanne Loethen, MD
Young Physician Section: Fola Fasuyi, MD

Editors Emeritus

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

Contact

Editor: John C. Hagan, III, MD / drjhagan3@gmail.com / 816-478-1230
Managing Editor: Lizabeth R.S. Fleenor / lfleenor@msma.org / 800-869-6762
Instructions for Authors: www.msma.org/missouri-medicine
Missouri Medicine Library: www.msma.org/missouri-medicine-library

ISSN 0026-6620 / Established 1904 / ©2020 Missouri State Medical Association

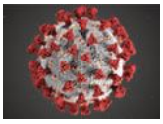


BIG FIRM RESOURCES. SMALL FIRM ATTENTION. YES, YOU CAN HAVE BOTH.

Moneta financial advisors are part of a team numbering 300+ with 200+ designations serving the MSMA and many of its members. Our large-firm resources are delivered with the personalized attention we are committed to deliver. Let us take care of your financial health and help grow your wealth.

Steve Finerty, Michael Carpenter and Rob Hehmeyer | monetagroup.com | 314.726.2300

© Moneta Group Investment Advisors, LLC an SEC registered investment advisor and wholly owned subsidiary of Moneta Group, LLC. Registration as an investment advisor does not imply a certain level of skill or training. Moneta is a service mark owned by Moneta Group, LLC, trademark application pending. All rights reserved.



The COVID-19 Pandemic of 2019-2020

The Most Important Thing in a Pandemic? Don't Panic! Together, We Can Get Through This

by John C. Hagan, III, MD

A vast opaque viral miasma obscures the future. We live from day to day, but we live. That alone is a victory.

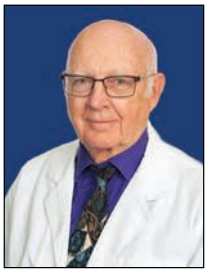
This morning (3/19/2020) I was told our distinguished, nationally known ophthalmology practice was complying with the recommendations of the American Academy of Ophthalmology for dealing with the COVID-19 Pandemic. Our huge practice is closed for all but emergent eye care and is doing no major surgery. For the first time in my life since about age 6, I don't have a part-time or full-time job. Like millions of other Americans and billions of others around the world, I'm stunned, dumbfounded and furloughed until it's safe to leave shelter and rebuild a normal world. My medical ophthalmology skills and my age do not allow me to assist our badly overworked colleagues in hospitals and emergency rooms. I will be sheltering in my home. Fortunately, Becky, my wife of 52 years, is great company; as is our loveable, lazy black cat Lizzy.

The greatest unknowns in the COVID-19 Pandemic are how much morbidity and mortality? How long the recovery for our U.S. healthcare system, our economy, and our national psyche? No one knows for sure. We are sailing through uncharted seas.

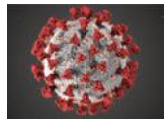
As with a vast multitude of others across our nation, my thoughts are turning to how we collectively shall ride this out. Professionally, what of our patients? Ophthalmology deals with an extraordinary large number of geriatric patients. Our practice has devised a unique system to deal with our patient's ongoing urgent and new emergency problems. We are implementing home health via phone, text, email, and telemedicine. I'm sure your practices are scrambling to do the same.

What about the U.S. economy? Will our individual and national collective wealth come back quickly? Will we have a recession? I don't have any answers. I'm asked by younger colleagues and patients if I've ever seen anything like this before? No, not at all! COVID-19 is a new paradigm; past history seems inapplicable. A vast opaque viral miasma obscures the future. We live from day to day, but we live. That alone is a victory.

We are pleased to present this issue of *Missouri Medicine* put together with considerable difficulty after MSMA cancelled their annual meeting. As in all our previous production crises, I commend Liz Fleenor our talented and dedicated managing editor. This issue features some unique insights into the COVID-19 pandemic as well as more familiar and comfortable cutting-edge scientific medicine from St. Louis University School of Medicine, Department of Surgery. We especially want to thank Sameer Siddiqui, MD, SLU Surgical Chair, Scientific Feature Series coordinator and Sharon Frey, MD of the SLU Department of Infectious Diseases for the excellent article on COVID-19 she prepared while under an enormous clinical work load. We thank all contributing authors for last-minute updates and rushed turn-around of galley proofs.



John C. Hagan, III, MD, FACS, FAAO, MSMA member since 1975, is a Kansas City, Missouri, ophthalmologist and *Missouri Medicine* Editor since 2000. He is a multi-year Diamond Contributor to MMPAC.
Contact: drjhagan3@gmail.com



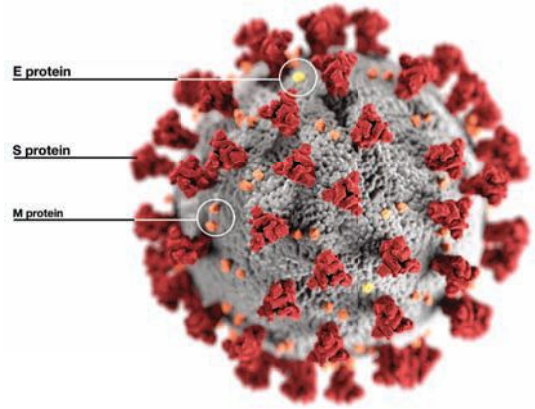
If stress is getting to you, read the article on physician well-being and how COVID-19 will affect the physician population. Let us learn from this crisis. Don't miss the Henry Miller, MD, article on how U.S. reliance on China for essential drugs must be corrected.

As a country, this teaches us we need to be more self-sustaining, making and creating more necessities here in the US. We need new and renovated factories with more skilled trade workers, electricians, welders, carpenters, plumbers that are fairly paid and respected for their vital skills. Also, STEM (science, technology, engineering, mathematics) and practical, essential, employable majors should be emphasized. Let's get practical. Let's get real.

Remember this, COVID-19 is not the Bubonic Plague; it's not the 1918 Spanish Flu, but it is a handful. Working together we will get through this, as individuals, as a profession, and as a proud resilient and more self-sufficient nation.

For the millionth time: wash your hands frequently and keep your distance. At this moment, more than ever, cleanliness is next to godliness.

That being said our thoughts, prayers, and ineffable admiration goes out to physicians, nurses, healthcare workers, first responders, and others working overtime and at personal peril to keep our hospitals and urgent, emergent, and essential healthcare functioning. Same to all police, fire, and essential services and industries workers. Together, we can get through this!



This illustration, created at the Centers for Disease Control and Prevention (CDC), reveals ultrastructural morphology exhibited by coronaviruses. Note the spikes that adorn the outer surface of the virus, which impart the look of a corona surrounding the virion, when viewed electron microscopically. In this view, the protein particles E, S, and M, also located on the outer surface of the particle, have all been labeled as well. A novel coronavirus, named Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), was identified as the cause of an outbreak of respiratory illness first detected in Wuhan, China in 2019. The illness caused by this virus has been named coronavirus disease 2019 (COVID-19).
Source: CDC Public Health Library

Should We Have Seen This Coming?

University of Hong Kong Predicted Future Coronavirus Problems in 2007

Clinical Microbiology Reviews published in October 2007, "Severe Acute Respiratory Syndrome Coronavirus as an Agent of Emerging and Reemerging Infection" by Vincent C. C. Cheng, Susanna K. P. Lau, Patrick C. Y. Woo, and Kwok Yung Yuen, State Key Laboratory of Emerging Infectious Diseases, Department of Microbiology, Research Centre of Infection and Immunology, The University of Hong Kong, Hong Kong Special Administrative Region, China.

ABSTRACT: The presence of a large reservoir of SARS-CoV-like viruses in horseshoe bats, together with the culture of eating exotic mammals in southern China, is a time bomb. The possibility of the reemergence of SARS and other novel viruses from animals or laboratories and therefore the need for preparedness should not be ignored.

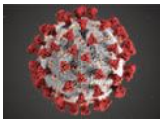
SOURCE: Clinical Microbiology Reviews, Oct. 2007, p. 660–694 Vol. 20, No. 4 0893-8512/07/$08.000 doi:10.1128/CMR.00023-07

Bill Gates TED Talk - April 2015
"The Next Outbreak? We're Not Ready"

If anything kills over 10 million people in the next few decades it is not likely to be a nuclear war but a highly infectious virus.

WATCH ON YOUTUBE: https://www.youtube.com/watch?v=6Af6b_wyiwI

MM



MSMA Recommends "Shelter-In-Place" to Missouri Governor to Curb COVID-19

Missouri State Medical Association

113 Madison Street ◆ P.O. Box 1028
Jefferson City, MO 65102-3015
800-869-6762 ◆ Fax 573-636-8552
www.msma.org

March 23, 2020

Dear Governor Parson:

On behalf of the physicians and surgeons practicing in Missouri, the Missouri State Medical Association requests the enactment of a "shelter-in-place" requirement by executive order.

We appreciate the previous actions you have taken regarding this crisis, and understand the interwoven policy issues at play during this critical time. However, we now believe that a statewide "shelter-in-place" order is the only way to curb the exponential spread of COVID-19 in Missouri.

If things progress as is, COVID-19 patients will deplete the state's available hospital beds, ventilators, and precious personal protection equipment. Any additional time without a "shelter-in-place" requirement wastes crucial healthcare resources, including manpower.

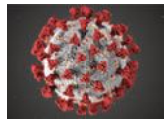
As physicians, we understand our role as the first line of defense against this virus. We accept the likelihood that a number of physicians will contract COVID-19 while treating the citizens of Missouri. Despite that known fact, we are prepared to carry out our responsibilities for as long as needed.

We ask for your assistance as we begin this difficult journey.

Regards,

James A. DiRenna, DO

James A. DiRenna, DO, FAAFP
President



MSMA Urges Congress Independent Physician Financial Stability in Economic COVID-19 Relief Legislation

Missouri State Medical Association

113 Madison Street ◆ P.O. Box 1028
Jefferson City, MO 65102-3015
800-869-6762 ◆ Fax 573-636-8552
www.msma.org

March 24, 2020

Dear Senator Blunt:

As physicians across the country voice their concerns about the various effects of the COVID-19 pandemic on the healthcare system, the physicians of the state of Missouri would like to add our voice to the effort.

You may have seen a letter from March 20 addressed to Senate and House leadership, signed by the American Medical Association and several other national physician organizations. In this letter, the groups outline a plea for financial assistance in federal stimulus legislation. Such assistance "should support and sustain physicians and their practices during this unprecedented national emergency through tax relief; no-interest loans; direct payments; payment for virtual visits, including phone calls; and other measures." The Missouri State Medical Association seconds this call to action.

While all physicians are facing unexpected and unfamiliar challenges as the pandemic progresses, independent physicians and practices are feeling an additional financial burden. Private practices across Missouri have been forced to cancel appointments as they desperately try to keep their patients safe by limiting exposure to this dangerous virus. This decrease in appointments reduces patients' risk of contracting COVID-19, but the lack of revenue has already pushed many independent practices to a financial breaking point.

In rural areas where hospitals are few and far between, independent practices play an essential role in local economies. Physicians generate $29.2 billion of economic activity in Missouri. Unfortunately, many practices must now weigh their financial options as they lose patients and income. Jobs are at stake as physicians and practice owners make difficult choices between maintaining their support staff's salaries, making payments for their facilities and supplies, repaying loans, and an array of other financial necessities.

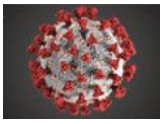
Physicians volunteer to put their patients' wellbeing before their own. As non-emergent appointments dwindle and offices necessarily instruct patients stay home and protect their health, our members are feeling the financial repercussions. Without assistance from Congress, many Missouri physicians fear they may be unable to keep their practices open to serve their patients and the communities they love.

Please consider independent physician financial stability during discussions involving economic relief legislation. We greatly appreciate your consideration and support during this difficult time for our nation.

Regards,

James A. DiRenna, DO

James A. DiRenna, DO, FAAFP
President



COVID-19 Teaches Hard Lessons

by Jin Wang, MD & Sharon Frey, MD

Crises teach societies hard lessons but from these challenges come ingenuity, growth, and a renewed sense of kindness towards each other.

Can the COVID-19 pandemic be controlled?

Since the government of China first announced the COVID-19 outbreak on December 31, 2019, the Severe Acute Respiratory Syndrome Coronavirus 2, SARS-CoV-2, has caused disease in 392,331 known cases in 169 countries with resultant 17,159 deaths according to the Johns Hopkins Center for Systems Science and Engineering's Covid-19 Global Cases map (https://coronavirus.jhu.edu/map.html).

By January 12, 2020, the genetic sequence of the virus was shared with the explicit plan to develop diagnostic kits. This is the third coronavirus known to cause outbreaks of severe respiratory diseases (SARS-CoV-1, MERS and SARS-CoV-2) in humans in recent years. These coronaviruses are thought to have originated in bats and have mutated sufficiently to be transmitted to intermediary animals and then humans.

Will there be more coronavirus outbreaks from newly mutated viruses in our future?

Most likely, but the outcome of future outbreaks will depend on what we learn from the current pandemic and how well we control the spread of virus.

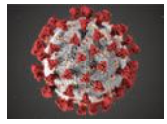
Testing for coronavirus in the U.S. had a slow start due to technical difficulties with the test kit which needed to be resolved to ensure the results are accurate. Despite the slow start, several commercial labs and health care networks are validating and using their own tests but are incapable of keeping up with the demand for testing due to insufficient availability of test reagents. As of March 23, 2020, the Centers for Disease Control (CDC) reported a total of 33,404 cases from 54 jurisdictions (50 states, District of Columbia, Puerto Rico, Guam, and U.S. Virgin Islands) and 400 deaths (https://www.cdc.gov/coronavirus/2019-nCoV/index.html). The hardest hit state is New York with 5,001 plus cases followed by seven states with 1,001 plus cases and counting.

Shortly after Missouri encountered the first confirmed case of COVID-19, local governments and health departments acted swiftly to close schools, and not long after many people were ordered to stay at home. Only essential businesses are allowed to remain open to the general public while those who are able will work from home.

Are we really prepared to contain the COVID-19 outbreak caused by a novel virus that is easily transmitted and for which there is no pre-existing immunity? What can we do to effectively stop transmission of the virus?

An important goal must be to decrease the lag time between the onset of symptoms and diagnosis which is prolonged by limited testing capability. Decreasing the lag time for testing would help to decrease transmission rates, decrease the burden of hospital isolation, reduce length of hospital stay and conserve resources which are in very short supply. To shorten the lag time, more convenient, accessible, safe and efficient test centers such as drive-through sites are being implemented in countries like South Korea and Germany and some states including Missouri. Additionally, test reagents must be made available.

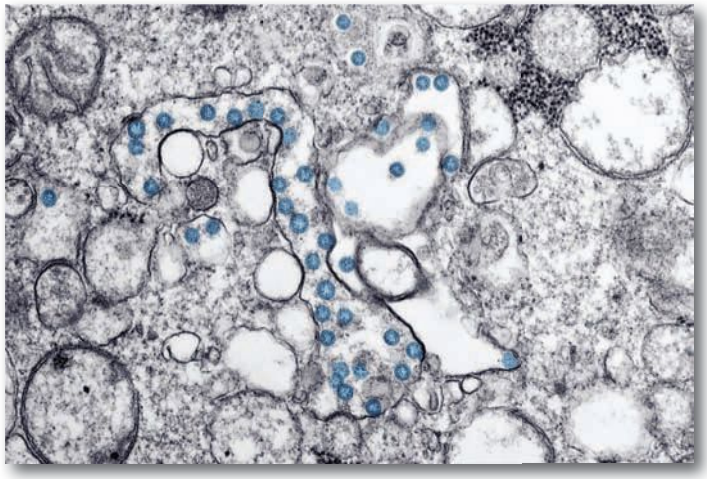
Another important goal to control COVID-19 is for our medical care system to adjust rapidly to the pandemic. Currently, primary care physician offices have limited personal protective equipment (PPE) and usually only one waiting area for all infected and noninfected patients. This can cause healthcare associated infections. Telemedicine is currently being used in multiple healthcare systems in the U.S., complemented by the wide use of electronic medical record (EMR) systems. Telemedicine can provide safe medical care without direct patient contact, effectively decreasing the risk of healthcare associated transmission while maintaining



a high quality of care and effective patient-physician communication. Now is the time to invest in telemedicine for primary care physicians and specialty consultants for care of most COVID-19 patients and to limit the office visits for stable patients with other health conditions.

What will happen when stay-at-home orders are lifted? When will they be lifted?

We can only try to predict the timelines but it will not be until the outbreak curve flattens and starts to decrease considerably. One infected person can transmit virus to many other persons. Once stay-at-home orders are lifted, we must have sufficient capabilities to quickly identify cases of COVID-19 and case contacts to impose limited quarantines on those at risk of infection as we work towards complete elimination of virus transmission. Careful follow-up and quarantine of all infected persons now will allow businesses and people to return to normal work and life as quickly as possible and save lives. In the meantime, governments need to find creative ways to support the poor and those who suddenly find themselves without incomes or with limited incomes and without insurance, as well as businesses to mitigate both foreseeable as well as unforeseeable hardships.



Transmission electron microscopic image of an isolate from the first U.S. case of COVID-19, formerly known as 2019-nCoV. The spherical viral particles, colorized blue, contain cross-section through the viral genome, seen as black dots.
Source: CDC Public Health Library

What do science, industry and community have to offer?

The Centers for Disease Control and industry have provided us with the capability to quickly develop testing kits and has shortened the time for a result from a few days to 45 minutes. The National Institutes of Health is funding and has initiated the first studies of drugs and vaccines to protect against SARS-CoV-2; more drugs and vaccines are soon to be tested. Previously designed vaccine platforms are being utilized to quickly develop new vaccines. Industries are shifting priorities to provide health care workers with much needed personal protection equipment and other medical equipment. Neighbors are sewing masks, checking on each other and shopping for the elderly. These are just a few examples from a multitude of efforts being made toward our collective efforts of containing the virus and minimizing bad health and economic outcomes.

What will we learn from this pandemic?

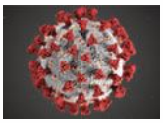
Crises teach societies hard lessons but from these challenges come ingenuity, growth, and a renewed sense of kindness towards each other. We will learn more efficient and less costly ways to provide health care; new innovations will occur with development of drugs, vaccines, and diagnostics. There will be innovations in education and changes in models for conducting business. Governments will enhance surveillance and response systems. We will have limited the death toll of COVID-19 which is currently estimated to have an average mortality rate between two to four percent. Hopefully, there will be a renewed appreciation of life with good will towards others and our shared home which we call Earth. **MM**

SAINT LOUIS UNIVERSITY.





Jin Wang, MD, (left), is an Infectious Diseases Fellow, and Sharon Frey, MD, (right), is Professor of Internal Medicine, both in the Division of Infectious Diseases, Allergy and Immunology at Saint Louis University School of Medicine, St. Louis, Missouri.
Contact: sharon.frey@health.slu.edu



COVID-19 REPORT

China's Coronavirus-Induced Paralysis Threatens U.S. Drug Supply Chain

by Henry I. Miller, MD & John J. Cohrssen, JD

The Wuhan coronavirus outbreak is a reminder that the production of vital medicines should not be compromised by reliance on a single, potentially unreliable source or country.

As the number of cases of infection with the Wuhan coronavirus (formally SARS-CoV-2, with the illness itself designated COVID-19) continues to mount, and China and other countries aggressively perform screening, isolation, treatment, and tracking of patients' contacts, demand for various essential medical items is unprecedented. Ironically, most of the world's supply of masks and respirators, along with other materials essential for health care, comes from manufacturers in China. For example, American medical practitioners and dentists who go through large numbers of surgical masks daily had begun to find their supply chain interrupted by early February.

This situation reveals a vulnerable link in the global supply chain that supports everyday health care in hospitals around the world, and it has elicited concerns at the highest levels of the Trump administration. Peter Navarro, the president's senior trade adviser, urged the government to adopt policies that will limit U.S. involvement in global supply chains that could leave the country vulnerable to shortages in a medical crisis. "This is a wake-up call for an issue that has been latent for many years but is critical to U.S. economic and national security," Mr. Navarro said.

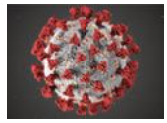
Even absent an aberration like the emergence of a new pandemic virus, drug shortages have plagued the practice of medicine in the United States. University of Chicago researchers in 2018 surveyed 719 pharmacists at large and small hospitals across the country and found that all of them reported experiencing at least one drug shortage in the past year, and 69 percent had experienced at least 50 shortages in that time.[1] The majority were generic injectable pharmaceuticals commonly used in hospitals, including analgesics, cancer drugs, anesthetics, antipsychotics for psychiatric emergencies, and electrolyte solutions needed for patients on IV supplementation.

The FDA maintains a current list of drugs that are currently in shortage.[2] As of March 11, 99 drugs were on it, and the list read like the contents of the pharmaceuticals cabinet of a hospital ICU or Emergency Room. As a result, hospitals are scrambling to assure adequate supplies of drugs that are in short supply, or to find substitutes for them. In the University of Chicago study, one-third of hospitals actually had to ration drugs at least once. That means that some patients got the second or third choice of a drug treatment, increasing the likelihood that the drug will be ineffective or only marginally effective, or have unwanted side effects.

Thus, the wake-up call that presidential adviser Mr. Navarro referred to is long overdue, and the pharmaceutical



Henry I. Miller, MD, a physician and molecular biologist, is a Senior Fellow at the Pacific Research Institute in San Francisco, California. He was the founding director of the FDA's Office of Biotechnology. John J. Cohrssen, an attorney and psychologist, served in senior positions at White House agencies, including the office of the vice president.
Contact: henryimiller@gmail.com



sector is particularly vulnerable: China has become the world's largest producer and exporter of the essential "active pharmaceutical ingredients" (APIs) used in the manufacture of drugs, not only in China but also in other countries, including the United States.

APIs in China are currently produced without sufficient quality control to ensure drug safety and efficacy, according to the findings of an important, recent report from the U.S.-China Economic Security Review Commission, which was established by Congress in 2000 when China was permitted to enter the World Trade Organization.[3]

The report's major points include:

- China is the world's largest producer of APIs, and the U.S. is heavily dependent on drugs that either come from China in finished form or from APIs sourced there.
- Because drug companies are not required to list the country of origin for APIs on drug labels, "U.S. consumers may be unknowingly accepting risks associated with drugs originating from China."
- The Chinese government promotes and protects the nation's pharmaceutical companies to the disadvantage of foreign competitors, as it does in other sectors, such as chemicals, electronics, and telecommunications.
- There are thousands of drug manufacturers in China, and the government's regulatory apparatus has insufficient resources to oversee them. Not surprisingly, it is ineffective, and failures of data integrity and drug safety scandals are common. In 2016, the China Food and Drug Administration investigated 1,622 drug clinical trial programs and rejected 80% of these applications after it found evidence of fraudulent data reporting or submissions of incomplete data, among other problems. (In the U.S. and Europe, the percentage would be in single digits.)
- The deficiencies in regulatory oversight of Chinese manufacturing also extend to the U.S. FDA. The report observed that the FDA deploys far too few inspectors to China for the large number of manufacturers there.

The report's conclusions are stunning:

1. "Because of U.S. dependency on China as a source of many critical drugs, banning certain imports due to contamination risks creating drug shortages in the United States." As discussed above, even in the absence of such bans, we are experiencing critical shortages of drugs, many of which are important and commonly used here. As a result, U.S. hospitals and EMTs must resort to second- or third-line medicines, because many drugs are produced only by a very limited number of foreign manufacturers.

2. "As a result of U.S. dependence on Chinese supply and the lack of effective health and safety regulation of Chinese producers, the American public, including its armed forces, are at risk of exposure to contaminated and dangerous medicines."

3. "Should Beijing opt to use U.S. dependence on China as an economic weapon and cut supplies of critical drugs, it would have a serious effect on the health of U.S. consumers." And, not only U.S. consumers: If China were to block or slow supplies of common, essential drugs, such as those to treat hypertension, high cholesterol, pain, stroke, cardiac disease, infections, pain and so on, morbidity and mortality would skyrocket worldwide – in effect, cause a policy-induced pandemic.

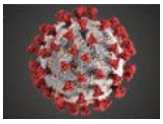
Complementing the findings of the Commission, a Government Accountability Office report released on Dec. 10, 2019, found that the FDA is not completing enough foreign drug inspections, cannot hire enough inspectors, and provides up to 12 weeks advance notice for some overseas inspections.[4] "We have long-standing concerns about FDA's ability to oversee the global supply chain, a High Risk Series issue for 10 years," it concluded.

In summary, quite apart from the threat of disruption caused by the coronavirus outbreak, this is a prescription for disaster. To address the threats it identified, the Commission's report made several recommendations, which focus on congressional actions, including:

1. Congress should hold hearings to assess: (1) the capacity of the U.S. pharmaceutical industry to meet domestic demands; and (2) the extent of the United States' dependence on Chinese pharmaceuticals and active pharmaceutical ingredients; and (3) the ability of the U.S. FDA to guarantee the safety of such imports from China.

2. Congress should direct the Government Accountability Office to prepare a report on the U.S. FDA's ability to conduct inspections of Chinese drug manufacturing facilities.

3. Congress should pass legislation that would require drug companies to "list active pharmaceutical



ingredients and their countries of origin on labels of imported and domestically produced finished drug products"; and that would create a "risk-based system making importers of active pharmaceutical ingredients (APIs) and finished products liable for any health risks incurred by consumers in the event the product is proven unsafe."

4. Congress should require Medicare, Medicaid, the U.S. Department of Veterans Affairs, the U.S. Department of Defense, and other federally funded health systems to buy pharmaceuticals only from domestic or foreign FDA-certified production facilities (unless the FDA finds that a specific drug is not available in sufficient quantities from such sources).

At least some members of Congress have gotten the message. Earlier this month, Senators Marco Rubio (R-Fla) and Chris Murphy (D-Conn) asked Dr. Stephen Hahn, the Commissioner of the Food and Drug Administration, whether the agency had the "necessary tools to ensure the safety and supply of pharmaceuticals, food and medical supplies" from China, worth $12.7 billion in 2018. We can now answer that question in the negative.

The supply chain disruptions from the COVID-19 outbreak are a reminder that the benefits of globalization of the production of vital medicines should not be compromised by reliance on a single, potentially unreliable source or country. The Commission's proposed sweeping changes are the minimum necessary to protect the health of Americans.

References

1. https://www.uchicagomedicine.org/forefront/research-and-discoveries-articles/drug-shortages-limited-warnings-followed-by-rationing-and-hoarding
2. https://www.fda.gov/
3. https://www.uscc.gov/sites/default/files/2019-11/Chapter%203%20Section%203%20-%20Growing%20U.S.%20Reliance%20on%20China's%20Biotech%20and%20Pharmaceutical%20Products.pdf
4. https://www.gao.gov/products/GAO-20-262T

MM



Today – Do more of what you love

At Mercy Clinic, we span across four states with a team of more than 2,100 Mercy primary care and specialty care physicians, 600 advanced practitioners. Mercy was named one of the top five largest U.S. Health Systems in 2017 by Truven, an IBM Watson Health Company and we serve millions annually. Mercy includes 44 acute care and specialty (heart, children's, orthopedic and rehab) hospitals, more than 700 physician practices and outpatient facilities, more than 40,000 co-workers and more than 2,000 Mercy Clinic physician in Arkansas, Kansas, Missouri and Oklahoma. Mercy also has outreach ministries in Arkansas, Louisiana, Mississippi, and Texas.

To find out about Physician and Advanced Practitioners openings across the Mercy System please contact:

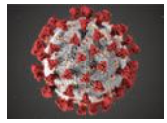
Tammy D. Hager, Director of Physician Recruitment
Tammy.Hager@mercy.net | 417-820-6650

Or go to **http://www.mercy.net/careers** to search for your specialty opportunities.

Mercy

List of Specialties:

- Anesthesiology
- Cardiology - Electrophysiology
- Cardiology - Interventional
- Cardiology - Non-Invasive
- Critical Care - Intensivist
- Dermatology
- Emergency Medicine
- Endocrinology
- Family Medicine
- Family Medicine - OB
- Gastroenterology
- General Surgery
- General Surgery - Breast Surgery
- Geriatric Medicine
- Gynecology - Urogynecology
- Hematology and Oncology
- Hospitalist
- Infectious Disease
- Internal Medicine
- Maternal-Fetal Medicine
- Med-Peds
- Neonatology
- Nephrology
- Neurological Surgery
- Neurology
- Neurology - Neuroimaging
- Obstetrics and Gynecology
- Obstetrics and Gynecology - OB Hospitalist
- Occupational Medicine
- Oncology - Gynecological
- Oncology - Surgical
- Ophthalmology
- Oral and Maxillofacial Surgery
- Orthopaedic Surgery
- Orthopaedic Surgery - Adult Reconstructive Surgery
- Orthopaedic Surgery - Hand Surgery
- Orthopaedic Surgery - Trauma
- Otolaryngology
- Pain Medicine
- Palliative Care
- Pediatrics
- Pediatrics - Emergency Medicine
- Pediatrics - Hospitalist
- Pediatrics - Ophthalmology
- Pediatrics - Surgery
- Pediatrics - Urgent Care
- Physical Medicine and Rehab
- Plastic Surgery
- Psychiatry
- Psychiatry - Child
- Pulmonary Disease
- Pulmonary Disease - Critical Care
- Radiation Oncology
- Radiology
- Rheumatology
- Sleep Medicine
- Telemedicine
- Trauma Surgery
- Urgent Care
- Urology
- Vascular Surgery



Imported Infections in Rural Mid-West United States - A Report from a Tertiary Care Center

by Amy Meyer, Hariharan Regunath, MD, Christian Rojas-Moreno, MD, William Salzer, MD† & Gordon Christensen, MD†

School of Medicine
University of Missouri Health

The current COVID-19 pandemic illustrates the importance of this type of education and data accumulation now and in the future.



Amy Meyer, is at the University of Missouri School of Medicine, Columbia, Missouri. Hariharan Regunath, MD, MSMA member since 2019, (above), is in the Department of Medicine, Division of Pulmonary, Critical Care and Environmental Medicine, and Division of Infectious Diseases, University of Missouri, Columbia, Missouri. Christian Rojas-Moreno, MD, William Salzer, MD,† and Gordon Christensen, MD,† is in the Department of Medicine, Division of Infectious Diseases, University of Missouri, Columbia, Missouri.
Contact: regunathh@health.missouri.edu
Preliminary data from this article was presented as a poster in IDWeek 2014. Completed data was presented as a poster in NIAID/IDSA 2019 Infectious Diseases Research Careers Meeting.

Abstract

Background

There is lack of specific data on imported infections in the mid-west United States (U.S.).

Methods

Retrospective data on demographic and geographic data of imported infections seen by the infectious diseases clinics and consultation service from 2001-2018 was collected.

Results

Of the 64 infections, tuberculosis(TB) was most common [20(31.3%); pulmonary(11,55%), lymphadenopathy(8,40%), gastrointestinal(4,20%), disseminated(2,10%), and 1(5%) each of genitourinary and vertebral spine infection, 4 Human immune-deficiency virus infection and 1 echinococcosis)] followed by malaria(11,17.2%). Other infections: Cysticercosis [7,10.9%], giardiasis (4,6.3%), 3 each (4.7%) Human T-lymphotrophic Virus infection and schistosomiasis, 2 each (3.1%) leprosy, strongyloidiasis, and typhoid fever, one each (1.6%) of ascariasis, brucellosis, Chagas disease, Chikungunya virus, hepatitis A virus, echinococcosis, Japanese encephalitis virus, loiasis, paratyphoid fever, Q fever, and unspecified parasitosis. Geographic origins: Africa(26,40.6%), Asia(16,25%), Central America(11,17.2%), Europe(2,3.1%), Oceania(2,3.1%), South America(2,3.1%), and Unknown(5). More cases were seen after 2015.

Conclusions

With increasing tourism, it is important to educate rural mid-west healthcare professionals on travel medicine. The current COVID-19 pandemic illustrates the importance of this type of education and data accumulation now and in the future.

Introduction

As of 2015, foreign born individuals constituted approximately 4% of the population in Missouri.[1] Among these individuals, 39.5% were from Asia, 31.1% from Latin America, 16.2% from Europe, 2.3% from North America and 0.9% from Oceania.[1] Despite a significant number of foreign-born individuals in Missouri and 33,864,417 year-to-date international arrivals to the United States (U.S.) as of June 2017, the variety and number of imported infections acquired by Midwest travelers and immigrants is not well-known.[2] As a consequence of inadequate data supporting the occurrence of imported infectious diseases in the region, Midwest physicians, particularly in rural settings, may not consider foreign,

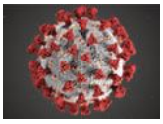


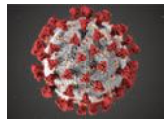
Table 1. Focused list of imported infectious diseases.

Focused Sub-List of GeoSentinel Diagnoses	
Respiratory	**Diarrheal/Gastrointestinal**
1. Pulmonary Anthrax	1. Amebiasis
2. Tropical Pulmonary eosinophilia	2. Cholera
3. *Mycobacterium tuberculosis* – Pulmonary, Extrapulmonary	3. Cryptosporidiosis
Febrile Illness	4. Cyclosporiasis
1. *Bartonella bacilliformis*	5. Giardiasis
2. *Bartonella henselae*	6. Isosporiasis
3. Acute brucellosis	7. Ascariasis
4. Chronic brucellosis	8. Clonorchiasis
5. Chagas disease	9. Echinococcosis
6. Dengue	10. Fascioliasis
7. Ebola Virus	11. Helminth
8. Acute hemorrhagic fever	12. Hepatitis A, E
9. Acute HIV infection	13. Hook worm
10. Lassa fever	14. Schistosomiasis (recurrent)
11.*Leptospira*	15. Strongyloidiasis
12. Malaria	16. Tapeworm (*D. latum, H. nana, T. saginata, T. solium)*
13. Measles	**Neurologic**
14. Melioidosis	1. Japanese encephalitis
15. Q fever	2. CNS Tuberculosis
16. Rickettsioses (*akari, felis, prowazeki, rickettsii, tsutsugamushi*)	3. Neurocysticercosis
17. Salmonellosis, *S. typhi*	**Tissue Parasite**
18. Yellow fever	1. Filariasis (Wuchereriasis, Loiasis, Onchocerciasis)
19. Bubonic and pneumonic plague	2. Visceral leishmaniasis
Genitourinary	3. Strongyloides hyperinfection syndrome
1. Schistosomiasis	4. Trichinellosis
Dermatologic	5. African Trypanosomiasis (*T. gambiense, T.rhodesiense*)
1. Cutaneous larva migrans	6. Visceral larva migrans
2. Cutaneous leishmaniasis	
3. Mucocutaneous leishmaniasis	
4. Leprosy	
5. Myiasis	
6. Rabies	
7. Tungiasis	
8. Yaws	

imported infections as the cause of illness among patients who were also travelers or immigrants.[3] We conducted a retrospective review of imported diseases seen at a referral center for the rural mid-west.

Methods

A sub-list (Table 1) was abstracted from the GeoSentinel diagnosis list of the International Society for Travel Medicine (ISTM) and the Centers for Disease Control and Prevention(CDC). This includes infections that were acquired outside of the continental U.S. that would raise concern for health care providers and public health officials in Missouri based on our prior experiences. Common infections such as influenza were excluded. GeoSentinel sites are specialized travel medicine clinics that conduct continuous clinician-based sentinel surveillance for travel-related illnesses in cooperation with the International Society for Travel Medicine and the Centers for Disease Control.[4-6] Using this abstracted sub-list, we first performed a retrospective chart review of all cases aged ≥18 years and had a diagnosis of an imported infection listed within our focused list of imported diseases seen within the Division of Infectious Diseases at the University of Missouri Hospital and Clinics from 2001-2014. Demographic, clinical, laboratory, and imaging data were gathered. These data were presented as a poster in the 2014 IDWeek (San Francisco, CA).[7] But, as we suspected that the number of cases were an underestimation, we continued to gather data for 2015-2018. We performed descriptive analysis using Microsoft ® Excel 2019. Data presented as number(N)/ percentages, mean/standard deviation or median/range. Travelers were classified as visiting family/relatives(VFR), business, mission/relief work, immigrants, refugees, schooling and vacationers.



Results

In total, 64 cases (57.8% male, mean age 38.54 ± 13.14 years) of imported infections were seen between 2001 and 2018. We identified relatively more cases during the shorter 2015-18 study period (18 cases) than the longer previous study period (46 cases from 2001- 2014).

Symptoms at presentation: In 55(85.94%) cases, the most common symptoms were fever(14.9%), chills(8.9%), abdominal pain(7.2%), diarrhea(7.2%), and headache(5.9%). The rest(each <5%) were cough, myalgia, nausea, vomiting, masses/swellings, night sweats, weakness, seizures, dermatologic symptoms, vision changes, decreased appetite, malaise, dizziness, infection diagnosis during blood donation, dyspnea, back pain, bloating, chest pain, fatigue, hematochezia, anemia, weight loss, urinary frequency, eye pain, hematuria, insomnia, dysuria, flatulence, decreased urination, and cramping.

Diagnoses associated with travel destinations: Tuberculosis (TB) was the most common infection seen in 20 patients (31.3%) with one or more of the following manifestations: pulmonary TB(11, 55%), lymphadenopathy (8, 40%), gastrointestinal TB (4, 20%), disseminated TB (2, 10%), and vertebral/spine TB (1, 5%). There were no specific geographical trends for TB acquisition: 6 each from Africa and Asia, 3 from Central America, 2 from Oceania, and 1 from Europe. Four patients with TB also had HIV and another had concomitant echinococcosis. Excluding TB, the remaining cases were diverse in diagnosis and geographic area of acquisition (Table 2). Of all cases of imported infections including TB, Africa was the most frequently documented geographic origin of infection, followed by Asia then Central America.

Diagnoses associated with reasons for travel: The reasons for travel among those whose destinations were outside the U.S. included visiting family or relatives (VFR), business, and mission/relief work. Travelers from elsewhere to the U.S. included immigrants, refugees, students studying within the United States, and vacationers. Reason for travel was documented in 51 of 64 cases of imported infection. Diagnoses and associated reasons for travel are represented as a sunburst diagram (Figure 1). Most cases of imported infections were in those immigrants to the U.S., followed by VFR. TB was the single most common infection among immigrants (70.6%), refugees (57.1%), and students (33.3%). Malaria was the most common diagnosis in those traveling for VFR(37.5%) and giardiasis was the most common diagnosis in those traveling for mission/relief purposes, there was no specific disease that was common for business travel. All vacationers to the U.S. were diagnosed with malaria. In 13 patients, reasons for travel were not known.

Travel period and time to medical attention: Duration of travel was not documented among immigrants and refugees to the U.S. and those who came to the U.S. for schooling. It was 203 days for business (N=1/6), 7 days (median, N=4/4, range 8-750 days) for mission/relief, 50 ± 17.3 days for VFR (N = 3/8) and 23 days (median, N=3/3, range 22-150 days) for vacation. Time to first medical attention following return from travel destinations was 1080 days (median, N=12/17, range 14 – 4015 days) for immigrants, 1460 days (median, N= 7/7, range 240 – 4680 days) for refugees, 730 days (median, N = 3/6, range 7-1440 days) for schooling and 51 days (median, N=4/8, range 30 – 720 days) for VFR travelers returning to the U.S.. This data was not documented for those who travelled for mission/relief and vacation. Among those diagnosed with TB, 8 immigrants presented at a median of 1080 days, whereas refugees presented with 1991.25±1865.34 days.

Discussion

According to the United Nations World Tourism Organization 2016 Report, international tourism has increased by approximately 4% annually since 2009, totaling 1.2 billion international tourist arrivals in 2016. The largest increases were seen in Africa, Asia, and Pacific regions, portending potential for transmission of imported infections.[8] The CDC reported that approximately 22-64% of travelers to developing countries experience health problems and up to 8% of travelers eventually seek healthcare attention.[6,8] At least a portion of the 8% of travelers do so in the rural mid-west. Similar to travelers and immigrants in coastal and urban U.S. settings, rural mid-west travelers and immigrants are also at risk of acquiring imported infections.

In our study 19 different imported infectious diseases from a wide variety of geographical origins, were seen. Most illnesses were acquired from Africa, Asia, and Central America. Our data suggests that the likelihood of acquiring is probably not a function of volume, but rather, specific to travel destination and/or demographics.[9-11] A thorough review of the travel itinerary is important to recognize destination-specific differences in epidemiology, differential diagnosis and empiric therapy as recommended by others.[4,12]

TB was the most common diagnosis among all (70.6% of immigrants, 57.14% of refugees, and 33.3% of those who came to the U.S. for schooling). They are mostly acquired from their native countries with a later re-activation or

Table 2. Geographic origin of disease acquisition for infections other than tuberculosis.

Continent	Imported infection	Region (Number of cases)
Africa	Malaria (5 *P. falciparum*, 3 unknown spp.)	Angola (1), Burundi (1), East Africa (1),Ghana (1) Ivory Coast (2), Malawi (1)
	Giardiasis	East Africa (1), Gambia(1) Unspecified (1)
	Neurocysticercosis	Congo(1)
		Nigeria(1)
	Schistosomiasis	Eritrea(1)
		Ethiopia(1)
	Leprosy	Burundi (1)
	Loiasis	Gabon (1)
	Paratyphoid fever	Sierra Leone (1)
	Typhoid fever	Ghana(1)
	Unspecified gastrointestinal parasitosis	West Africa(1)
Asia	Malaria (1 *P. vivax*, 1 unknown spp.)	India (1), Unknown (1)
	Strongyloidiasis	Cambodia (1), Malaysia (1)
	Hepatitis A Virus	Bangladesh (1)
	Japanese Encephalitis	Thailand (1)
	Leprosy	Sri Lanka (1)
	Q fever	Iraq (1)
	Typhoid fever	Nepal(1)
Central America	Neurocysticercosis	Mexico (3)
	Human T lymphocytic virus infection	Jamaica(1), Mexico (1)
	Ascariasis	Costa Rica
	Brucellosis	Mexico
	Chagas disease	El Salvador
South America	Chikungunya virus	Trinidad(1)
	Giardiasis	Ecuador(1)
Europe	Schistosomiasis	Unknown (1)
Unknown	Chickungunya virus	Unknown (1)
	Human T lymphocytic virus infection	Unknown (1)
	Malaria (*P. vivax*)	Unknown (1)
	Neurocysticercosis	Unknown (1)



Figure 1. Sunburst diagram for reasons (%) for travel and corresponding number/s of imported infections

incidental discovery of latent disease while in Missouri. Malaria was most common among VFR travelers mostly due to the perceived belief that prophylaxis is unnecessary for destinations native to the traveler.[13] They are more likely to stay in rural regions and are less likely to seek pre-travel health consultation or stay in urban hotels.[8,13] Giardiasis was most common among mission/relief travelers, reflecting rural destinations with poor water quality and inadequate preventative measures. Other infections with mission/relief travel were typhoid and Hepatitis A, both transmitted by fecal-oral route reflecting rural unhygienic conditions. Considering all diseases and their duration to presentation, the average time to presentation for both immigrants and refugees was approximately 48 months, whereas, it was only 24 months for those attending school in the U.S.. This is mostly from improved healthcare access through institutional student health programs.

The small number of cases seen for the study period (N=64 for 18 years) is an underestimation. We suspect that many cases were missed from lack of documentation, inability to extract or track/data from electronic records and also ignorance on imported diseases not prevalent in the rural mid-west U.S.. We saw more cases within the past 4 years than over the preceding 14 years, reflecting either an increase in international tourism and/or suggesting that a prospective study may accrue more data. In the future, we hope to create a database of imported infections to guide physicians regarding appropriate evaluation, diagnosis, and treatment. As international tourism steadily increases in all geographic locations, hospitals and clinics must be prepared to not only provide pre-travel prophylaxis, but also appropriately triage and manage travel-related diseases by making a timely diagnosis and treatment[14-16] The 2002-2003 severe acute respiratory syndrome coronavirus (SARS

CoV) spread within few days to a few countries and the 2009 H1N1 influenza pandemic spread to 30 countries within six weeks, similarly, the ongoing pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus -2 (SARS-CoV-2) spread to >28 countries within six weeks affecting >40,000 people.[17-19] This is primarily related to the vast increase in international travel in past couple of decades, partly from expanding economy and wealth among populations and travelers.[20] Institutional data such as our study will promote these goals by providing regional epidemiological data, educating local health care providers, fostering the development of travel medicine clinics and potentially serve as hubs for identifying emerging infections at and from foreign destinations. Travel clinics in Missouri are located in their major cities. Below you will find the links to a few of these clinics in Columbia, Springfield, Kansas City and St. Louis. When travelling to destinations requiring Yellow fever vaccination, travelers will need to seek a travel clinic specifically authorized for providing this vaccination. Useful Links to Travel Clinics in Missouri: https://www.muhealth.org/locations/travel-clinic, https://www.mercy.net/practice/mercy-clinic-travel-medicine-whiteside/, https://www.passporthealthusa.com/locations/mo/kansas-city/, https://www.passporthealthusa.com/st-louis.

Obvious limitations of our study include the use of an abstracted sub-list, retrospective data with incomplete documentation regarding illness severity, travel duration/itinerary, timing of illness in relation to travel, pre-travel consultation, adherence to chemoprophylaxis, and individual exposures while abroad.[8] But such limitations have also been observed by the International Society of Travel Medicine's (ISTM), who has been tracking traveler imported diseases at the point of entry for past 2 decades.[21,22] Travel and immigration are believed to be infrequent in the rural mid-west U.S., but through our study we demonstrate that a wide variety of imported diseases were seen and treated.

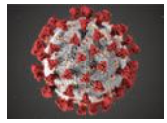
Conclusions

A wide variety of imported infections were diagnosed and/or treated in a referral center for the rural mid-west U.S. from 2001-2018. Infections were related to travel destinations and the reasons for travel. Pre-travel education is important for rural mid-west travelers. Presenting symptoms were non-specific in nature. Education of mid-west physicians on travel medicine is important to enable early diagnosis and treatment of imported infections among returning travelers. The current COVID-19 pandemic illustrates the importance of this type of education and data accumulation now and in the future.

References

1. Missouri State Demographics Data. 2015; https://www.migrationpolicy.org/data/state-profiles/state/demographics/MO, 2017.
2. 2017 Monthly Tourism Statistics. ITA Travel and Tourism Office;2017.
3. Gushulak BD, MacPherson DW. Globalization of infectious diseases: the impact of migration. Clin Infect Dis. 2004;38(12):1742-1748.
4. Freedman DO, Weld LH, Kozarsky PE, et al. Spectrum of disease and relation to place of exposure among ill returned travelers. The New England journal of medicine. 2006;354(2):119-130.
5. Freedman DO, Kozarsky PE, Weld LH, Cetron MS. GeoSentinel: the global emerging infections sentinel network of the International Society of Travel Medicine. J Travel Med. 1999;6(2):94-98.
6. Harvey K, Esposito DH, Han P, et al. Surveillance for Travel-Related Disease — GeoSentinel Surveillance
System, United States, 1997–2011. In. Morbidity and Mortality Weekly Report Surveillance Summaries. Vol 62. Centers for Disease Control and Prevention2013.
7. Regunath H, Salzer W, Halai UA, et al. 1663Imported Exotic Infectious Diseases in Columbia, Missouri. Open Forum Infectious Diseases. 2014;1(suppl_1):S444-S444.
8. Chiodini J. The CDC Yellow Book app 2018. Travel Med Infect Dis. 2017;19:75-77.
9. Tourism MDo. International Visa Vue 2015-2016. 2019; https://industry.visitmo.com/research.
10. Office INTaT. Fast Facts 2017. In. 2017 U.S. Travel and Tourism Statistics (Inbound)2017.
11. Bhutta ZA, Sommerfeld J, Lassi ZS, Salam RA, Das JK. Global burden, distribution, and interventions for infectious diseases of poverty. Infect Dis Poverty. 2014;3:21.
12. Fairley JK. General Approach to the Returned Traveler. 2017; https://wwwnc.cdc.gov/travel/yellowbook/2018/post-travel-evaluation/general-approach-to-the-returned-traveler#5013. Accessed 07/03/2019, 2019.
13. Hagmann SH, Han PV, Stauffer WM, et al. Travel-associated disease among U.S. residents visiting U.S. GeoSentinel clinics after return from international travel. Fam Pract. 2014;31(6):678-687.
14. Steffen R, Connor BA. Vaccines in travel health: from risk assessment to priorities. J Travel Med. 2005;12(1):26-35.
15. Steffen R, Behrens RH, Hill DR, Greenaway C, Leder K. Vaccine-preventable travel health risks: what is the evidence--what are the gaps? J Travel Med. 2015;22(1):1-12.
16. International Travel and Health. World Health Organization;2017.
17. Drexler M, Institute of M. In: What You Need to Know About Infectious Disease. Washington (DC): National Academies Press (U.S.)
Copyright (c) National Academy of Sciences.; 2010.
18. Knobler S. Learning from SARS: Preparing for the Next Disease Outbreak, Workshop Summary. National Academies Press; 2004.
19. Stein RA. The 2019 coronavirus: Learning curves, lessons, and the weakest link. 2020;74(4):e13488.
20. Daszak P, Olival KJ, Li H. A strategy to prevent future epidemics similar to the 2019-nCoV outbreak. Biosafety and Health. 2020.
21. Wilder-Smith A, Boggild AK. Sentinel Surveillance in Travel Medicine: 20 Years of GeoSentinel Publications (1999–2018). Journal of Travel Medicine. 2018;25(1).
22. Freedman DO, Chen LH, Kozarsky PE. Medical Considerations before International Travel. 2016;375(3):247-260.

MM



Washington University in St. Louis
School of Medicine

The Need for an Integrated Approach to Well-Being in Healthcare

by Lawrence M. Lewis, MD, Evan Schwarz, MD, Randall Jotte, MD & Colin P. West, MD

In addition to the COVID-19 stress of preparing for a potential tsunami of patients who are likely to require resources we will not have, and eventually having to make difficult triage decisions regarding who gets care, we currently do not even have enough personal protective equipment for our own protection, and are losing large numbers of our workforce to quarantine precautions even as the need for healthcare providers increases.

Physician "burnout" is not new, as suggested by a "Wellness for Emergency Physicians" handbook published by the American College of Emergency Physicians in 1995, and a highly cited editorial on the topic in the July 2001 Annals of Internal Medicine.[1,2] Burnout is defined by the presence of one or more of three cardinal symptoms: 1) emotional exhaustion, 2) depersonalization, or 3) a sense of reduced personal accomplishment.[3] Studies show physicians suffer more from burnout than the general U.S. working population and that this has gotten worse over the previous decade.[4,5] Although there appears to be some tapering of this trend, a 2019 national survey found that overall, 44% of physicians suffer from burnout. Burnout was particularly prevalent in front-line fields such as emergency medicine, internal medicine, and family medicine as well as certain other specialty practices such as urology, neurology, and physical medicine and rehabilitation.[6]

In 2017, the National Academy of Medicine (previously the Institute of Medicine) launched the Action Collaborative on Clinician Well-Being and Resilience, which resulted in more than 60 organizations, including the American Medical Association, the Association of American Medical Colleges, and the Accreditation Council for Graduate Medical Education, signing on to study and address this issue.[7] This culminated recently in the release of the National Academy of Medicine consensus report "Taking Action Against Clinician Burnout: A Systems Approach to Professional Well-Being (2019)".

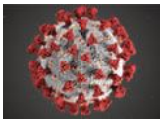
In recognition of these issues, over the past few years, several departments and divisions at Washington University School of Medicine hosted prominent guest lecturers to provide grand rounds in the area of physician wellness. These presentations were excellent, but resulted in almost no change in our approach to the problem. The solutions initially enacted were limited to mindfulness training and other activities to improve individual resiliency, suggesting that the individual was responsible for improving their own situation. Most faculty regard individual resiliency alone as insufficient to resolve burnout, as they view the problems as systemic and beyond individual coping mechanisms. In the fall of 2018, in an effort to address the issue of physician burnout in a more integrated way, we initiated interviews with several dozen stakeholders across a multitude of specialties to identify the major dis-satisfiers in our work environment.

These meetings culminated in an interdisciplinary symposium designed to highlight what we internally know about the problem, gain external insight, and set an agenda to address the issue across the entire medical center.[8]

What follows is a compilation of lessons learned from our experience and that of several healthcare organizations that pioneered efforts to improve well-being and restore joy in the practice of medicine. Much of the background data comes from the presentations at the symposium, particularly from our keynote speaker, Colin West, MD, Professor of Medicine, Medical Education, and Biostatistics at Mayo Clinic. Although the importance of the topic has become



Lawrence M. Lewis, MD, Professor of Emergency Medicine, MSMA member since 2017, (left); Evan Schwarz, MD, Associate Professor of Emergency Medicine, MSMA member since 2014; Randall Jotte, MD, Associate Professor of Emergency Medicine, MSMA member since 2016; Randall Jotte, MD, Associate Professor are at Washington University School of Medicine in St. Louis, Missouri. Colin P. West, MD, PhD, Professor of Medicine, Medical Education, and Biostatistics, is at the Mayo Clinic, Rochester, Minnesota.
Contact: lewisl@wustl.edu



self-evident to many physicians, we begin with an argument of why people both inside and outside medicine should care about this issue.

Why Should We Care? The Consequences of Physician Burnout

Physician burnout is associated with a doubling in the self-reported rate of medical errors,[9,10] as well as more than doubling the risk of reduced patient satisfaction scores.[10] Additionally, physician burnout is also associated with reduced hours in the workforce and earlier retirement.[11,12] This data not only has important consequences regarding patient safety and workplace reputation, it also suggests a financial cost through increased litigation in the former, and increased recruitment and training efforts in the latter. In fact, job turnover and reduced clinical effort from burnout are estimated to cost the healthcare system over 4.6 billion dollars a year, with total burnout-related costs rising much higher.[13]

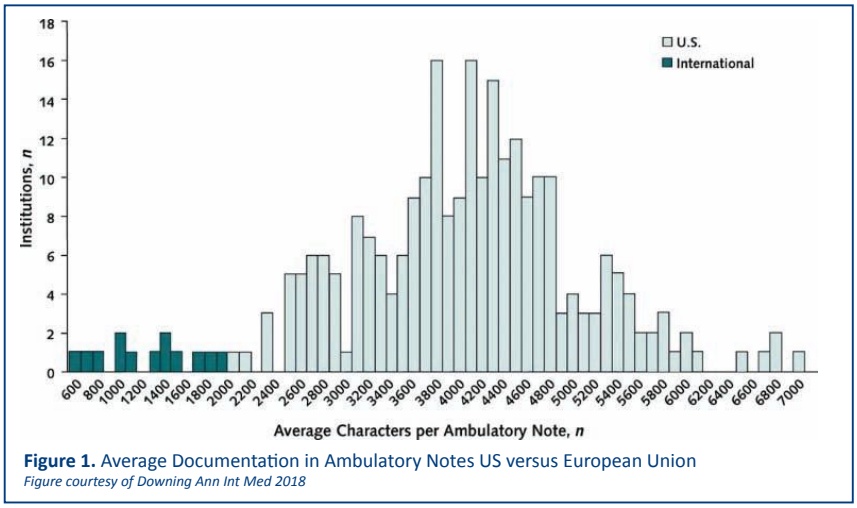


Figure 1. Average Documentation in Ambulatory Notes US versus European Union
Figure courtesy of Downing Ann Int Med 2018

Who is Most Affected?

Shanafelt et al. in a 2011 survey of over 7,000 physicians across 23 specialties found that the front-line specialties of emergency medicine, internal medicine, and family medicine, along with neurology had the highest rates of burnout.[14] Medscape has been reporting on U.S. physician burnout since 2013. Results differ year to year regarding the specialty with the highest reported percentage of physician burnout, but again front-line specialties consistently rank in the top five.[15] As demonstrated every year since the initial survey, women continue to have higher rates of burnout than men (50% vs 39%).[6] Age also appears to be a risk factor for physician burnout. Several studies suggest younger physicians are at higher risk of burnout,[16,17] although the aforementioned 2018 Medscape survey found that the percentage of physicians with burnout symptoms increased between the ages of 28 and 54, declining significantly in those older than 54 years.[15]

Where to Intervene: Leading Causes of Burnout Among Healthcare Providers

The 2017 and 2018 Medscape surveys also identified the four leading causes of burnout: 1) too many bureaucratic tasks; (2) spending too many hours at work; (3) lack of respect from administrators/employers, colleagues, or staff; and (4) the Electronic Health Record (EHR).[5,15] These findings are consistent with what we found in dozens of interviews within our medical center, and are supported by several independent reports. It is noteworthy that the European Union extensively used EHRs for many years, but the burden of documentation is considerably less in the EU countries than in the U.S. (Figure 1).[18]

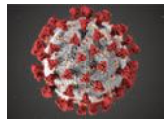
Based on several small surveys across multiple specialties at our medical center, we obtained nearly universal agreement on targeting three main areas: 1) Improving workplace efficiencies through re-design of processes and improved resourcing/training; 2) Improving communication between administration and faculty and between disciplines focusing on respect, collegiality, and shared decision-making; and 3) Improving transparency and incorporating shared decision-making in compensation and monetary decisions.

Initial Next Steps

The first step (number one below) was to form an interdisciplinary Wellness Task Force, which would identify and attempt to quantify the most problematic issues and recommend further analysis when needed, or partner with a wide variety of Washington University based resources to implement potential solutions.

1. Identify faculty in all clinical departments and divisions with an interest in improving well-being in the workplace and who were designated by their Chairs or Chiefs to sit on the newly-formed interdisciplinary Wellness Task Force.

2. Complete the purchase and implementation of a validated well-being survey (the Mayo Well-being Index) which all interested faculty members (of participating departments or divisions) can voluntarily and anonymously



complete with immediate personal feedback regarding their score and how their score compares with national averages. The survey was tailored to allow 3 institution-specific questions, which will better inform our efforts to address major dis-satisfiers in our workplace environment.

3. Reimplement a peer-to-peer program to help faculty cope with serious workplace issues affecting their well-being, in particular issues surrounding adverse outcomes and medical litigation.

4. Identify the major dis-satisfiers affecting well-being across disciplines through departmental and divisional representatives, and through the responses to the well-being survey.

5. Partner with the Washington University Clinical Assistance Team to identify and circumvent or improve the most cumbersome, time-consuming, and frustrating processes in our EHR.

6. Review current resources, and in some cases recruit additional resources and personnel to help manage serious mental health or life issues among faculty

7. Partner with Barnes-Jewish Hospital's Patient Satisfaction and Patient Safety initiatives in a multi-disciplinary committee to look at communication issues at all levels of interaction, including patients, nurses and support staff, and peer-to-peer consultative communications.

These efforts are just getting underway, as we attempt to identify resources both inside and outside our institution. We don't know what impact, if any, they will have on restoring satisfaction and joy in our work. Yet, colleagues within the Wellness Task Force collectively sense a recognized appreciation among peers simply in addressing the issue, dedicating resources to further insights as to the nature of the problem, and a willingness to promote solutions. Our colleagues seem grateful this issue is being addressed. Until recently, a lack of wellness was regarded as a private, personal issue, not a consequence of systemic dysfunction. Those attitudes are changing. There will need to be a sustained effort to view any changes in practice policies and procedures through the lens of physician wellness, with shared decision-making and transparency in the major decisions that affect our daily practice. As more medical centers across the country embark on wellness programs, we will need to see what interventions are most efficient and effective in helping to reduce the high burnout rate affecting so many physicians across the entire geographic and demographic spectrum, and share this information broadly.

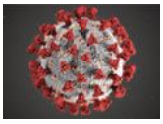
COVID-19: An Epilogue

As this comes to press, healthcare providers across this country are facing the frightening and daunting task of caring for large numbers of patients in what might become the worst pandemic in a century. In addition to the stress of preparing for a potential tsunami of patients who are likely to require resources we will not have, and eventually having to make difficult triage decisions regarding who gets care, we currently do not even have enough personal protective equipment for our own protection, and are losing large numbers of our workforce to quarantine precautions even as the need for healthcare providers increases. There is a real danger of overwhelming fatigue and an inability to provide the level of care we are accustomed to in this country if we do not develop a procedure to allow exposed but asymptomatic healthcare workers to return to work. Developing a uniform policy to support this effort while mitigating against potential spread may be the single most important thing any hospital or medical center can do; many physicians and nurses are already exhausted, and we are far from the peak.

On a positive note, this crisis may provide an opportunity to pilot programs and policies that may help restore the joy in practicing medicine once this crisis has resolved. The cooperation among various medical services is as high as many of us have ever seen it. There is a single focus that cuts across the various healthcare systems and multitude of specialty services which appears to have improved the satisfaction of many providers despite the enormous stress they are under. Appreciation, cooperation, streamlining unnecessary regulations and "red tape", and reducing unnecessary tasks, so that the care of patients and the health of our community is once again the principle focus of our work may be a partial antidote to the burnout we have been witnessing over the past several years.

A unique challenge is presented by this current pandemic. With the advent of social distancing, and the closure of most areas of entertainment, our usual methods of socializing and replenishing ourselves for the next onslaught have been severely curtailed. We and others are experimenting with virtual happy hours and sharing interesting tv shows, movies, or books, particularly for those of us furloughed or isolated at home. Probably limiting how much time you spend thinking about COVID out of work will be a necessary break.

The current COVID-19 crisis is likely to get much worse in this country before it gets better, but it has already shined a spotlight on the critical importance of healthcare provider well-being (both physically and psychologically) which we hope outlasts the pandemic and results in long-term proposals to address the problem of physician burnout.



Acknowledgment

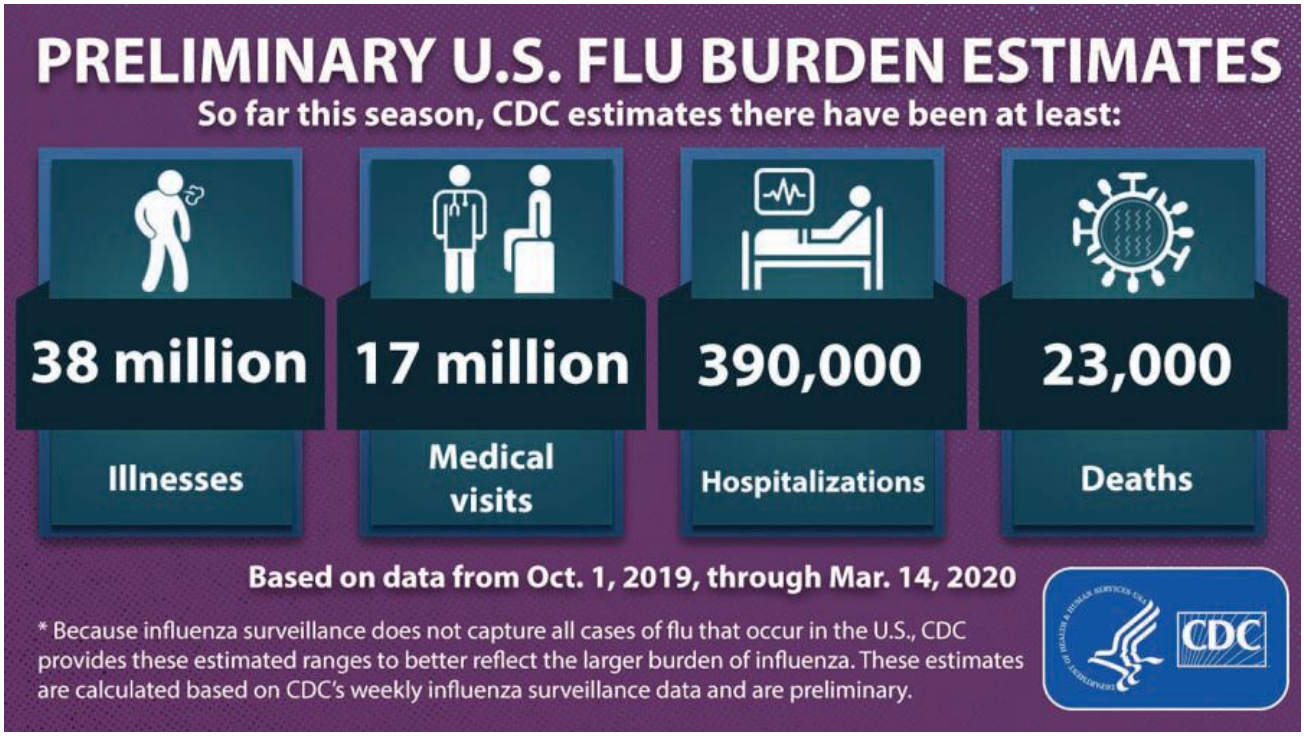
The authors would like to thank Christopher R. Carpenter, MD, Kamal Gursahani, MD, Kelly Estes, MD, Cindy Lefton, RN, PhD, Robert Mahoney, MD, and Dawn Pesti, BSN, MBA for their participation in developing the content for the Wellness symposium and their assistance in implementing many of the next steps.

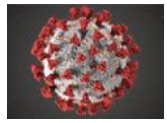
References

1. Wellness for Emergency Physicians. Eds. Andrew LB, Pollack ML. American College of Emergency Physicians, Dallas, Tx. 1995
2. Gundersen L. Current Clinical Issues: Physician Burnout. Ann Int Med 2001;135:145-148
3. Maslach C, Jackson SE, Leiter MP. Maslach burnout inventory manual, 3rd edn. Palo Alto: Consulting Psychologists Press, 1996.
4. Shanafelt TD, Hasan O, Dyrbye LN, Sinsky C, Satele D, et al. Changes in burnout and satisfaction with work-life balance in physicians and the general US working population between 2011-2014. Mayo Clin Proc. 2015;90:1600-1613
5. Medscape Lifestyle Report 2017. https://www.medscape.com › sites › public › lifestyle › 2017
6. Medscape National Physician Burnout, Depression, and Suicide Report 2019. https://www.medscape.com/slideshow/2019-lifestyle-burnout-depression-6011056
7. National Academy of Medicine Action Collaborative on Clinical Well-being and Resilience. nam.edu/clinicanwell-being
8. https://emergencymedicine.wustl.edu/events/lewis-health-policy-symposia/lewissymposium2019/
9. Tawfik DS, Profit J, Morgenthaler TI, Satele DV, Sinsky CA, et al. Physican burnout, well-being, and work unit safety grades in relationship to reported medical errors. Mayo Clin Proc. 2018;93:1571-1580
10. Panagioti M, Geraghty K, Johnson J, Zhou A, Panagopoulou E, et al. Association between physician burnout and patient safety, professionalism, and patient satisfaction: A systematic review and meta-analysis. JAMA Intern Med. 2018;178:1317-1330 (corrected see JAMA Intern Med. 2019 March 4; 179(4): 596)
11. Willard-Grace R, Knox M, Huang B, Hammer H, Kivlahan C, Grumbach K. Burnout and health care work force turnover. Ann Fam Med 2019;17:36-41
12. Shanafelt TD, Mungo M, Schmitgen J, Storz KA, Reeves D, et al. Longitudinal study evaluating the association between physician burnout and changes in professional work effort. Mayo Clin Proc. 2016:91:422-431
13. Han S, Shanafelt TD, Sinsky CA, Awad KM, Dyrbye LN, et al. Estimating the attributable cost of physician burnout in the United States. Ann Intern Med.2019;170:784-790. Doi:10.7326/M18-1422
14. Shanafelt TD, Boone S, Tan L, Dyrbye LN, Sotile W, et al. Burnout and satisfaction with work-life balance among US physicians relative to the general population. Arch Int Med 2012;172:1377-1385
15. Medscape National Physician Burnout and Depression Report 2018. https://www.medscape.com/slideshow/2018-lifestyle-burnout-depression
16. del Carmen MG, Herman J, Sandhya R, Hidrue MK, Ting D, et al. Trends and factors associated with physician burnout at a multispecialty academic faculty practice organization. JAMA Netw Open. 2019;2(3):e190554. doi:10.1001/jamanetworkopen.2019.0554
17. Shanafelt TD, West CP, Sinsky C, Trockel M, Tutty M, et al. Changes in burnout and satisfaction with work-life integration in physicians and the general US working population between 2011 and 2017. Mayo Clin Proc. 2019;94:1681-1694
18. Downing NL, Bates DW, Longhurst CA. Physician burnout in the electronic health record era: Are we ignoring the real cause. Ann Int Med. 2018;169:50-51.

MM

1 Picture = 1,000 Words





The Role of Alcohol, Drugs, and Deaths of Despair in the U.S.'s Falling Life Expectancy

by Mark S. Gold, MD

Recent anecdotal data suggests from suicide hotlines and suicide text services have increased dramatically as the COVID virus has spread.

After 2014, U.S. life expectancy fell for three straight years.[1] While this trend has stabilized in the most recent data,[2] this is a very disturbing finding, not associated with other wealthy countries in the world. Decreased life expectancy is most pronounced among males in the United States.[1] Declining life expectancy in the U.S. has been widely covered by newspapers around the globe and given rise to a cottage industry of speculation on causes, with varied social, cultural, and political actors making use of the findings for preferred narratives. Some of this speculation arose after Princeton economists Anne Case and Angus Deaton coined the term "deaths of despair,"[3] an easily misunderstood term. Case and Deaton used the term to refer to fatal drug overdoses, alcohol-related diseases, and suicides. "We think of all these deaths as suicides, by a very broad definition," these economists have written,[3] "and we attribute them to a broad deterioration in the lives of Americans without a college degree who entered adulthood after 1970."

In late 2019, a National Institute on Aging-supported review offered a comprehensive examination of falling U.S. life expectancy. This study[4] used data from the CDC, National Center for Health Statistics, and U.S. Mortality Database to trace life expectancy trends over a longer time frame and analyze mortality rates for particular age cohorts. It paints a complicated picture of poor U.S. mortality trends, which are not driven just by our polysubstance epidemics, and a decidedly unhappy one. The authors write, "According to one estimate, if the slow rate of increase in U.S. life expectancy persists, it will take the United States more than a century to reach the average life expectancy that other high-income countries had achieved by 2016."[4]



Mark S. Gold, MD, is Adjunct Professor in the Department of Psychiatry at Washington University and an internationally recognized and expert in addiction medicine.
Contact: msgold@ufl.edu

Results of Study on U.S. Life Expectancy

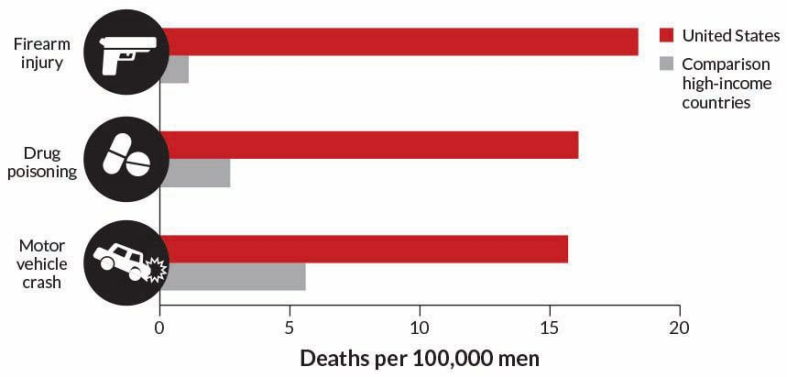
This study found that U.S. life expectancy, between 1959 and 2016, rose to 78.9 years from 69.9 years. But, following 2014, life expectancy began declining. "A major contributor," this study's authors write, "has been an increase in mortality from specific causes (e.g., drug overdoses, suicides, organ system diseases) among young and middle-aged adults of all racial groups, with an onset as early as the 1990s and with the largest relative increases occurring in the Ohio Valley and New England."

This study also finds that:

- Mortality increases are concentrated among Americans at "midlife", or those between 25-64 years of age. The all-cause mortality rate rose by six percent between 2010-2017 for Americans between these ages.
- Rising mortality between 2010-2017 led to 33,307 excess deaths.
- More than 32 percent of these deaths happened in Kentucky, Indiana, Ohio, and West Virginia—or the Ohio Valley states. The upper New England states also had some of the largest mortality increases, though they account for a lower share of the overall total.
- These rising mortality figures are found among all racial groups in the U.S.

These trends do not significantly reflect changes in violent crime or gun violence. The U.S. is much less violent than it used to be, and although it still has higher violent crime rates than other rich countries, things have gotten much better in the last 30 years. Other medical conditions, such as infectious diseases and cancers, were also not

Figure 1.
Three Causes of Death Among Men



behind these changes, as outcomes for certain medical problems actually improved.

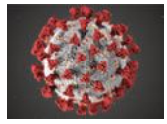
These researchers offer some answers. They first examine life expectancy from 1959 to trace when it started to change and, recognizing that fatal overdoses started to rise in the nineties, next look at cause-specific mortality between 1997-2017. They note that U.S. life expectancy first diverged from other wealthy countries in the '80s. Our rate of increase in life expectancy was not as fast as in other wealthy countries. In the '90s, cause-specific mortality rose for Americans in midlife. By 1998, the U.S. fell below the life expectancy average of other rich countries. Then U.S. life expectancy increases ended in 2010 and started falling in 2014. Fatal overdoses account for an important share of this increase — they rose by almost 387% between 1999-2017. Deaths from alcoholic liver disease rose by around 41 percent, and suicides by around 38 percent. But other causes were, or still are, at play, too. Hypertensive disease rates, for example, also rose — by about 79 percent. And obesity death rates were higher, rising by 114 percent. The authors observe that one study found that, for women, cardiovascular and respiratory conditions accounted for nearly as many deaths as fatal overdoses.

What's Going On?

It's a tough question. The authors write, "The largest relative increases in midlife mortality occurred among adults with less education and in rural areas or other settings with evidence of economic distress or diminished social capital." But these observations aren't necessarily explanatory factors in our life expectancy decline. This review considers different explanations and evidence in their favor. Isn't it really just our drug epidemics — the rising death toll from heroin in the '60s and '70s, cocaine in the '80s and then the three-stage opioid epidemic of prescriptions, heroin, and synthetics? Well, the authors say, this is a significant part of the story, but far from complete. Suicides and alcohol-related liver diseases have also contributed substantially and the timing is off because our life expectancy divergence started in the eighties, "and involved multiple diseases and nondrug injuries." They also point to two studies suggesting that only 15 percent of our life expectancy divergence can be explained by fatal overdoses. Washington University experts including Professor Ted Cicero were the first to alert us that the prescription opioid epidemic had morphed into an injection and heroin epidemic.[5] Sadly, things have only gotten worse with fentanyl being added to illicit heroin and now multiple fentanyl added to street drugs and the emergence of primary fentanyl use.[6]

What about smoking? Americans smoke less than we used to, but smoking more decades ago could still kill more people today. And, Americans are often more obese than their peer country counterparts, so could that account for the differences? This review points to research on other countries, like Australia, that resemble the U.S. in smoking and obesity but haven't followed our marked life expectancy divergence. Health care? The U.S. famously spends more to cover fewer people than its peers, and Americans also face higher costs of care, but the authors note that this wouldn't account for why we have more deaths from some diseases and not others, and from suicides or obesity-related deaths "which originate outside the clinic." Might the problem be "deaths of despair" after all, then, or a large increase in psychological distress? There's "inconclusive evidence" that depression and anxiety, which can also harm physical health, rose over the relevant time period, and, the authors say, it's also hard to figure out the link between conditions like depression and all the rising specific causes of death. But it is difficult to not conclude that overdose deaths, suicides, and accidents are not related. The Director of the National Institute on Drug Abuse and our own work[7] has supported this with data showing that many opioid overdoses are passive suicide attempts and others are death by opioids.

This review continues like this, carefully weighing the relative evidence about which factors make sense and under which conditions. For socioeconomic status, the authors say that the timing works, because the U.S. experienced



pronounced economic churn in the '80s and '90s, with the most economically impacted areas and people also experiencing the largest mortality rises. But then localized data on income and employment don't always align with the geographic and demographic trackers. What's the answer? It's likely that there isn't a particular cause, or at least one we can decisively identify right now. The authors say these various possible causes "are not independent and collectively shape mortality patterns." They call for the accumulation of more rigorous evidence, gathered from machine learning, migration research, and cohort studies, and interdisciplinary research, given how many different areas may contribute, and attempts to answer comparative questions about why some states and regions have worse life expectancy than others, and why other rich countries do better. These are sensibly modest conclusions but gravely important — they affect our view of the most important challenge we face.

This review does not consist of entirely dreary findings. Life expectancy has risen in some U.S. states, deaths from some causes, like violence, have declined, and black men's life expectancy has improved. Deaths from screenable prostate, breast, cervical, and colon cancer are down, as are cardiovascular diseases. Reports[8] say that the cancer death rate has dropped 29 percent, leading to about three million fewer deaths relative to a steady mortality rate. But supporting data has been stubbornly consistent. University of Pennsylvania researchers have found that outside of metropolitan areas following 1990, mortality increased even though it declined for many other demographic groups.[9] Overdoses and overdose deaths are projected by the Stanford artificial intelligence group to continue at this pace as opioid use disorders relapse and risk of overdose does not appear to diminish in these patients even after long term medication assisted therapy.[10]

Many death certificates show a different story. Looking at death certificates from 2017 nearly 75,000 people died in the U.S. in 2017 from liver disease and alcohol-related conditions, a steep rise from 1999, when 36,000 died from those causes. Women used to die at lower rates from these conditions, but that gap has closed.[11] As reported first by Case and Deaton and reiterated in their upcoming book,[12] rising morbidity and mortality among whites due to accidents, drug overdoses, alcoholism, liver disease, and suicides means reduced overall longevity. These deaths are alarming businesses, too, as there are more suicides in the workplace than in the past.[13] I expect that suicides, as well as overdose deaths, are undercounted.[14] This should not be surprising as suicide is generally more stigmatized than accidental overdose. The most recent Florida data suggests that 1 out of 3 opioid overdose deaths, and an even greater share of cocaine deaths, are not reported.[15] So, deaths of despair, may be occurring more frequently than we have thought.

Recent anecdotal data suggests from suicide hotlines and suicide text services have increased dramatically as COVID-19 has spread. Anxiety, by itself, can increase relapses in treated psychiatric illnesses including depression and also substance use disorders. Substance and Opioid Use Disorder relapses are often fatal. New SUDs can develop among people who had not had one beforehand. New drug use and users, can have more accidents and overdoses. Alcohol use may increase and the association between alcohol, depression, and suicide is direct. Chinese citizens[16] surveyed in February found that 42.6% of respondents experienced anxiety related to the coronavirus outbreak. Social distancing can cause loneliness and depression. Quarantine or extreme isolation can trigger PTSD as we found after the SARS outbreak.

References

1. https://www.ncbi.nlm.nih.gov/pubmed/31769830
2. https://www.cdc.gov/nchs/index.htm
3. https://www.princeton.edu/~accase/downloads/Case_and_Deaton_Comment_on_CJRuhm_Jan_2018.pdf
4. Woolf, S.H., Schoomaker, H. (2019). Life Expectancy and Mortality Rates in the United States, 1959-2017. JAMA 322(20), 1996-2016. doi: 10.1001/jama.2019.16932. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/31769830 several citations used in parentheses
5. https://www.nejm.org/doi/full/10.1056/NEJMc1505541
6. https://www.addictionpolicy.org/blog/tag/research-you-can-use/fentanyl-crisis-getting-worse
7. https://www.addictionpolicy.org/blog/tag/research-you-can-use/opioids-and-suicide
8. https://www.nytimes.com/2020/01/08/health/cancer-deaths-decline.html
9. Elo IT, Hendi AS, Ho JY, Vierboom YC, Preston SH. Trends in non-Hispanic white mortality in the United States by metropolitan-nonmetropolitan status and region, 1990–2016. Pop Dev Rev. 45(3), 549-583. doi: 10.1111/padr.12249. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/31588154
10. https://www.columbiapsychiatry.org/news/opioid-overdose-risk-high-after-medical-treatment-ends-study-finds
11. National Institute on Alcohol Abuse and Alcoholism (NIAAA). (2020). Alcohol-related deaths increasing in the United States [news release]. Retrieved from https://www.niaaa.nih.gov/news-events/news-releases/alcohol-related-deaths-increasing-united-states
12. Bureau of Labor Statistics. (2019). National Census of Fatal Occupational Injuries in 2018 [news release]. Retrieved from https://www.bls.gov/news.release/pdf/cfoi.pdf
13. https://www.amazon.com/Deaths-Despair-Future-Capitalism-Anne-ebook/dp/B082YJRH8D/ref=dp_kinw_strp_1
14. https://www.addictionpolicy.org/blog/tag/research-you-can-use/opioids-and-suicide
15. https://www.usf.edu/news/2020/federal-data-undercounts-fatal-overdose-deaths.aspx
16. https://www.reuters.com/article/us-china-health-mental/chinese-public-dial-in-for-support-as-coronavirus-takes-mental-toll-idUSKBN2070H2

MM



Physician Practice Cybersecurity Threats: Ransomware

by Christopher A. Budke & Peter J. Enko, JD

The exponential growth and use of computer networks and remote access devices has resulted in cybersecurity risk to every service sector, including healthcare. As more aspects of the healthcare delivery system depend on information technology, a particular cyber threat - ransomware - has evolved into a highly sophisticated and extremely damaging and costly crime that can cause days and weeks of downtime for critical networks. Unfortunately, healthcare providers appear especially vulnerable to it as cyber criminals have become keenly aware of the industry's reliance on IT and the crisis created by any inability to access necessary information. Accordingly, this article offers strategies to help healthcare professionals identify, avoid and respond to ransomware dangers.





Christopher Budke (left) is a special investigator and former FBI agent and Peter Enko, JD, (right) is a partner in the Kansas City office of Husch Blackwell. Mr. Budke leads a team of investigators as part of the firm's legal support team. Mr. Enko represents a full spectrum of health care providers on HIPAA compliance and other regulatory matters. 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 encouraged to consult their own attorney concerning their specific situation and specific legal questions.
Contact: peter.enko@huschblackwell.com

What is Ransomware?

Ransomware is a type of malicious software, which targets weaknesses in humans and technology and renders IT systems inaccessible. It is typically delivered through phishing emails and vulnerabilities in Remote Desktop Protocols. Once deployed, the malware may encrypt files on local drives, attached drives, backup drives, and other computers on the same network. Users are often unaware of the infection until they are unable to access their data or receive a message demanding a ransom payment in exchange for a decryption key. Because of the anonymity of virtual currency, payment generally must be made in bitcoin. If the demands are not met, the system or data remains locked down or, in extreme cases, may be wiped out.

Remarkably, the first recorded ransomware incident occurred in 1989, before the advent of internet itself. Joseph L. Popp, a Harvard-trained biologist carried out the attack by distributing 20,000 infected floppy disks at the World Health Organization's international AIDS conference. The malware embedded on those disks encrypted the user's computer files and required payment of $189 to regain access. While decryptions were quickly coded and the perpetrator was arrested and tried, a new business model was born. In the intervening years, it has been improved upon greatly and now ransomware variants are broadly and indiscriminately deployed through unsolicited emails and disreputable websites.

By the end of 2016, the cyber threat had grown to such an extent that Kaspersky Lab estimated a ransomware attack occurred every 40 seconds. Cybersecurity Ventures predicts that this time interval will shrink to one attack every 11 seconds by 2021. At that time, global ransomware costs will likely reach $20 billion, a number nearly fifty-seven times greater than that incurred in 2015.[1] Notwithstanding, it should be pointed out that ransomware remediation is rarely limited to the ransom payout and expenditures can quickly escalate when lost productivity, forensic examinations, regulatory compliance, reputational harm, and the need to restore data are factored in.

Underscoring the gravity of the situation, the FBI's Internet Crime Complaint Center (IC3) notes that ransomware attacks are gaining in specificity and sophistication. Most recently, cyber criminals have turned to sending spear fishing emails to lure key individuals in sensitive positions or exploiting unpatched software on end-user computers.[2] There is also little doubt that ransomware developers are rapidly adapting to IT security enhancements and improving the features of their malware in order penetrate systems. The McAfee Labs Threat Report for August 2019 indicated a 118% spike in network encrypting attacks with code innovations.

Who Does This Stuff?

Are ransomware attackers individual hackers, organized criminal gangs, or state-sponsored entities? The answer to that question is yes, yes and yes. And, interestingly, the nature of a ransomware attack offers insight into its source.

Amplifying this point, malicious code that makes ransomware work is readily available for purchase among individual hackers and hacker groups, who often randomly distribute their attacks. While one of their motivations may be financial gain, another is as simple as the bragging rights and community recognition that accompany a successful launch.

Organized criminal groups, on the other hand, are continually creating new code to maximize network destruction and target specific industries which are most likely to quickly pay a ransom request to regain access to their data. Such groups may deploy the malware themselves via a spear phishing email from an apparently trustworthy source or lease the ransomware to other criminal groups in exchange for a cut of the illicit profits. Either way, money is the motivating factor. Additionally, these organizations tend to operate out of Eastern Europe and have sophisticated infrastructures which include research and development departments, automated collection services, and customer (aka victim) support. The money they collect (which can run in the millions of dollars) is often reinvested in human capital in the form of highly skilled programmers and software engineers. Examples of their handiwork are found in the Dharma, Ryuk, and WYSIWYE (What You See Is What You Encrypt) ransomwares.

State-sponsored attacks typically originate in countries such as Iran, North Korea, and Russia (not Nigeria). While revenue generation can be a driving force behind the behavior, the desire to cause mayhem is equally attractive. One of the most high-profile state-sponsored (or at least state-sanctioned) cyberattacks was WannaCry, which was linked to North Korea and is renowned for the speed with which it spread. Just four days after it was discovered in 2017, there were more than 250,000 instances of the infection reported in 116 countries. Not to be outdone, Russia weighed in with its NotPetya ransomware, which is believed to have been initiated by the GRU, the Main Directorate of the General Staff of the Armed Forces of the Russian Federation. Because NotPetya had no functioning payment mechanism, it is speculated that it was launched purely for its disruptive effect.[3]

How Can I Lessen My Ransomware Risk?

While cyber criminals use a variety of techniques to penetrate systems and employ continuous quality improvement principles to their work, most ransomware attacks follow one of three formats:

1. Email phishing campaigns are by far the most prevalent source of ransomware infections and account for nearly 94% of all malware delivered.[4] In such campaigns, the bad actor distributes emails to which a malicious file is attached or linked. When the file is opened or the link clicked, the malware is downloaded and may be disseminated further by the victim's own email account.

2. Drive-by downloading occurs when a user unknowingly visits an infected website which has been spoofed or hacked and has code embedded on it.
3. Exploitation of security weaknesses in widely used software programs is another favorite criminal tactic used to push out ransomware.

To minimize threats, the Department of Homeland Security's Cybersecurity and Infrastructure Security Agency (CISA) suggests:

- Training users to review and verify emails from trusted sources before clicking on links or opening attachments. When an email is unexpected or an aspect of it appears unusual, the recipient should reach out by phone to confirm its authenticity.
- Updating software and operating systems with the latest patches and security upgrades.
- Following safe internet browsing practices.
- Restricting the ability of a user to install software applications on a computer or device.
- Allowing only approved programs to run on a network.
- Enabling strong spam filters to prevent phishing emails from reaching end users and authenticating inbound email to prevent email spoofing.
- Scanning all incoming and outgoing emails to detect threats and filter executable files from reaching end users.
- Configuring firewalls to block access to known malicious IP addresses.
- Immediately and regularly backing up all critical systems and data on separate devices and system.
- Developing and refining cyber incident response plans and making sure that they cover cyber insurance, business continuity, and risk analyses.
- Conducting annual penetration testing and vulnerability assessments.[5]

What Should I Do If I Am the Victim of an Attack?

When a ransomware attack occurs, legal counsel should be consulted to help coordinate business continuity, forensic investigation, law enforcement, liability and reputational issues. Additionally, for healthcare providers and their business associates, ransomware triggers significant HIPAA compliance concerns as its presence on computer systems is considered a security incident which must be resolved by:

- Analyzing the malicious software
- Containing the impact and propagation of the ransomware
- Eradicating the malware and remediating the vulnerabilities that enabled the attack
- Recovering or restoring impacted data
- Conducting post-incident reviews to determine whether any regulatory or contractual obligations result from the incident including reporting a data breach.[6]

Moreover, unless it can be demonstrated that the ransomware has not caused greater than a low probability of compromise to any protected health information, a breach is presumed to have occurred and the entity must comply with applicable HIPAA breach notification requirements.[7]

Should I Pay the Ransom?

Most law enforcement officers, including the FBI, do not recommend paying ransom as it does not guarantee that access to systems or data will be regained. There have been numerous cases wherein a victim has not been provided a decryption key or a flaw in the decryption algorithm has prevented recovery of some or all of the affected data. Additionally, paying ransom may enhance the profit motive and encourage bad actors to target others. That said, a ransom payment does not violate federal or state law and ultimately may come down to an assessment of the impact of the attack on the organization's healthcare and business operations. Once a decision to pay has been made, however, it should be noted that the likelihood of future cyberattacks increases dramatically.

What Are My Takeaways

As information technology plays an ever-increasing role in healthcare delivery, ransomware attacks are becoming more frequent and sophisticated due to the life and death situations they create and the payment decisions they drive. Accordingly, it is vitally important for healthcare providers to be proactive when it comes to implementing best practices in data security so that cyber criminals are unable to profit from system vulnerabilities.

References

1. See https://cybersecurityventures.com/global-ransomware-damage-costs-predicted-to-reach-20-billion-usd-by-2021.
2. See High-Impact Ransomware Attacks Threaten U.S. Businesses and Organization, Internet Crime Complaint Center Alert Number I-100219-PSA, published October 2, 2019.
3. See https://blog.chainalysis.com/reports/decoding-ransomware-attacks.
4. See 2019 Verizon Data Breach Investigations Report.
5. See https://www.us-cert.gov/Ransomware.
6. See 45 CFR 164.304 and 164.308(a)(6). See also NIST SP 800-61Rev.2, Computer Security Incident Handling Guide.
7. See 45 C.F.R. 164.400-414.

MM

The Curse of Time

by Charles W. Van Way, III, MD



In short, Daylight Savings Time is harmful to our collective health.

No, this isn't bad fiction about a rogue archeologist triggering an ancient curse in a forgotten tomb. It concerns a modern curse that's with us today. It's called (shudder) Daylight Savings Time (DST). It gives us jet lag twice a year with none of the benefits of travel. It's useless and unpopular. Farmers hate it. Nobody really likes it. It doesn't save money. It doesn't save energy. It certainly doesn't create more daylight. Yet, we still do it.

Origins of the Curse

How did it all get started? Some people say that Ben Franklin suggested it to the French in 1774. Old Ben had a lot of good ideas, but he also had some really bad ones. He was enthusiastic about rising early and going to bed early, anyway. "Oblige a man to rise at four in the morning, and it is probable he will go willingly to bed at eight in the evening." The French ignored him.

Others blame Kaiser Wilhelm the Second. They are correct. Yes, Germany started it in 1916, with the idea of increasing war production. Factories could work later in the evening. Of course, electric lights had been invented by then, but the Kaiser probably thought they had no future. As it turned out, they did, and he didn't. But his opponents, France and Britain, thought this was such a great idea that they immediately adopted it. And then, so did we. Everyone gave it up after the war, although some were reluctant. In the U.S., Woodrow Wilson wanted to keep it. Congress abolished it over his veto.[1] Some states never did give it up. Then, the Federal government started it up again in the 1940s. The excuse then was to increase war production. Yes, we had lots of electric lights in factories. And, war production was often around the clock. But never mind all that.

The government was so happy with the results that we simply kept DST after the war. But it was pretty much state by state, until 1966, when Congress passed a uniform law. Of course, Congress kept tinkering with it. They expanded it from five months to 10 months in 1974, during the oil crisis. Then they reduced it to eight months in 1975, and again to seven months in 1986. Since then, it's averaged seven months of the year. European countries pretty much adopted DST after the war, with different times of starting and stopping in different countries, until the European Union was formed. The European Union (EU) is a great fan of DST. It advocates it as a way to save energy, and helping to save the planet. We're really fighting climate change! It affects everyone, and makes them feel good.



Charles W. Van Way, III, MD, FACS, FCCP, FCCM, MSMA member since 1989, Missouri/AMA Delegate, and *Missouri Medicine* Contributing Editor, is Emeritus Professor of Surgery, University of Missouri - Kansas City.
Contact: cvanway@kc.rr.com

Effects of the Curse

Paradoxically, it doesn't make people feel good. In the EU, several countries are trying to get it reversed. Norway, for one. Could there be anything more pointless than DST when days during the summer average 20 hours of daylight? People make jokes about it. In England, people hate it. Across Europe, farmers lobby against it. People hate it in the U.S. Poll after poll agree. Nobody wants it.

Moreover, it's harmful. A number of studies show a variety of adverse effects, from auto accidents to heart attacks. For example, a study by Jiddou, et al. from Michigan, showed the incidence of myocardial infarction to be significantly higher during the week following the time shift, with a peak incidence on the Sunday following the spring shift.[2] A study from 2001 by Varughese et al. showed an increase in traffic deaths on the Monday following the spring shift, and the Sunday following the fall shift.[3] A New Zealand study showed traffic accidents increased on the first two days following the start of DST in the spring.[4] A study from Spain indicated that traffic deaths increased on the day following both the spring and fall transitions, with a greater effect in the spring. The authors estimated that the use of DST costs Spain as a whole five to seven lives per year in excess traffic deaths.[5] Then, there are effects on sleep disorders, seasonal affective disorder, mental health, and workplace accidents.[6] In short, DST is harmful to our collective health.

Robbing Peter to Pay Paul

Finally, it doesn't save energy. Consider. It's March. The sun has finally begun to rise about the time you wake up. You don't need to turn on the lights. But then DST comes along. For another six weeks, you have to turn on the lights in the morning. Where's the energy savings? Oh, yes. You don't need to turn on the lights for another hour in the evening. But that's not a net savings, that's time shifting. Energy use for air conditioning may actually increase, because the hottest part of the day is shifted later in the afternoon and into the evening, when people are at home.[1] All of this amounts to robbing the morning to pay for the evening. The only people this appeals to are politicians. Since they live by robbing Peter to pay Paul, they see no problem.

Echoes of the Pharaoh

Truly, that may be the real reason for DST. It's simply our government, doing what it does best. Passing laws. Regulating. Proving that it is more powerful than we are. DST in the U.S. currently starts three to four weeks before taxes are due, just while most people are working on their tax returns. A coincidence? I think not.

I understand this may be difficult to accept. But there is historical evidence for it. Consider Germany in 1916. The Great War was dragging on. Casualty lists were horrendous. Food was expensive, and hard to obtain. People were very unhappy. So, the Germans moved to what they would come to call War Socialism. The government, during 1916, assumed much of the control of the economy. What better way to make that obvious to all than by moving the clock around?

Then there is North Korea. North Korea is directly north of South Korea, same longitude, same times of sunrise and sunset. Yet, in 2015, North Korea told its citizens that they would observe a time which was half an hour earlier than South Korea. In 2018, they reversed the change. It made the point that the government controls everything.

What of the U.S.? Well, DST was adopted by the Progressive movement which also increased the role of government by giving us income taxes and Prohibition. It was re-started during the presidency of Franklin Delano Roosevelt, who increased the power and scope of government beyond anything previously thought possible. It was extended in 1974, during the Imperial Presidency of Richard Nixon.

Right on time, I rest my case.

References

1. The History of Daylight Savings Time. www.cecilbuffington.com
2. Jiddou MR, Pica M, Boura J, Qu L, Franklin BA. Incidence of Myocardial Infarction With Shifts to and From Daylight Savings Time. Am Jour Cardiol 2013; 111:631-35.
3. Varughese J, Allen RP. Fatal accidents following changes in daylight savings time: the American experience. Sleep Med 2001; 2:31-36.
4. Robb D, Barnes T. Accident rates and the impact of daylight saving time transitions. Accid Anal Prev. 2018 111:193-201.
5. Prats-Uribe A, Tobias A, Prieto-Alhambra D. Excess Risk of Fatal Road Traffic Accidents on the Day of Daylight Saving Time Change. Epidemiology 2018, 29(5) e44-e45.
6. Miller, Z. 10 Reasons Why Daylight Savings is the Worst. Insider.com, March 6, 2019. https://www.insider.com/daylight-savings-negative-effects-2018-3

MM

Life Happens During Training

It's Time to Change the Narrative for Childbearing Residents

by Lauren Umstattd, MD

Life happens during residency. We learn, grow, and change – this happens on a professional and personal level. We become better diagnosticians, troubleshooters, critical thinkers, and proceduralists. Many of us meet our life partners, get married, and think about starting a family.

Whereas men are often praised for becoming fathers and growing their families, women are looked at differently. Stigma surrounding mothers in medicine still exists. It is especially apparent if you're in training. Will she still work as hard? Are her priorities going to shift? Is she going to stay committed?

For women, our prime reproductive years fall during the years of medical school and residency. If you take the traditional path towards becoming a physician, you obtain a four-year undergraduate degree, complete four years of medical school, work as a resident for three to seven years, and possibly end with a fellowship, lasting anywhere from one to three years. On average, that lands you in your early to mid-thirties. Compared to the general public, studies have shown higher rates of infertility, miscarriage, and elective abortions among female physicians. This has been attributed to stress, more demanding work hours, and advanced maternal age.[1-3]



Lauren Umstattd, MD, MSMA member since 2011, is Chief Resident, Otolaryngology-Head & Neck Surgery, University of Missouri School of Medicine, Columbia, Missouri.
Contact: umstattdla@health.missouri.edu

Last year, I had a child. I worked eighty-hour weeks up until my due date, took my three weeks of vacation for "maternity leave," and gave up breastfeeding early because of the perceived lack of support. I felt alone, depressed, and relatively unsupported by my team.

Fast forward a few months and things improved. Time does tend to heal wounds. I'm happier now more than ever. And I think I'm a better physician – more productive, efficient, and compassionate towards patients. As I reflect on my own experience of having a child during my fourth year of a surgical residency, I think it is time to start advocating for change.

The Accreditation Council for Graduate Medical Education (ACMGE) currently has no recommended minimal standards for duration of parental leave for trainees. This leaves individual institutions and training programs to set their own leave policies.

As one of the leading advocates for maternal-child health, the American Academy of Pediatrics (AAP) states, "regardless of gender, residents should be guaranteed a minimum of six to eight weeks of parental leave."[4] The American College of Obstetricians and Gynecologists (ACOG) has a similar policy, recommending, "Medical schools, residency and fellowship training programs, medical specialty boards, the ACGME, and medical practices should incorporate paid parental leave policies as part of the physician's' standard benefit package." They go on to advocate for a "minimum of six weeks leave" and encourage training programs to develop mechanisms enabling residents to still be board eligible if they take greater than six weeks of parental leave.[5]

A recent comparative study of family leave policies showed the majority of residency training programs, both medical and surgical, allow for a maximum of four to six weeks.[4]

So why have we not adopted the recommendations of AAP and ACOG? Maybe it's because we don't think about it. Maybe it's because "that's how it's always been." Maybe it's because hospitals rely on the resident workforce and are apprehensive to allow for extended time away. Maybe it's because programs are worried about residents not meeting their case minimums. Maybe it's because peers may perceive a deficit in time-away equity between trainees. Or maybe it's because medical boards set arbitrary thresholds for the amount of time trainees can be gone and are reticent to adopt competency-based education.

Medical training is at a crossroads. Lifestyle issues now affect recruitment and retention. The rising number of females going into medicine and the increased number of women beginning families during training demands departmental leaders and program directors to address the challenges faced by childbearing trainees.

Doctors are meant to care for people. Healthcare is meant to promote the wellbeing of individuals – our patients and each other. Somehow, we've forgotten to care for each other. There's benefit in allowing a mother's body to heal, affording her the bonding time with her newborn, and providing her the opportunity to establish a breastfeeding regimen before returning to work.

In a nationwide survey of childbearing general surgery residents, three risk factors were associated with professional dissatisfaction: (1) altering fellowship plans owing to difficulty balancing childbearing, (2) lack of formal maternity leave policies, and (3) perception of stigma associated with pregnancy. In the same study, 39% of respondents strongly considered leaving surgical residency and 30% would discourage female medical students from a surgical career because of lack of support and inadequate duration of parental leave allowed during training.[6]

Unless women and their allies demand and drive necessary changes, they will never happen. Solutions begin with acknowledging failures and identifying opportunities for improvement.

And failure is the perfect word to describe what we've done so far for childbearing residents and new parents. We, as a medical profession, have contributed to the collective failure in supporting childbearing during residency. We haven't yet dedicated the emotional intelligence towards solving this "problem" and generating creative solutions to encourage our trainees to have children during training. Let us start the discussion – is there a better model?

Interventions at the program, hospital, state, and national levels should identify obstacles to maternity leave policies, design approaches to implementation of flexible training tracks, and examine methods to reduce maternal discrimination.

When a trainee approaches you with an announcement she's pregnant, ask not "what have we done in the past," but rather, "what should we be doing?" Stop waiting for top-down mandates and instead, challenge the archaic system by implementing your own policy change. Be the catalyst within your department and advocate for the mothers around you.

Gone are the days when we as physicians need to sacrifice our own needs for our patients. Healthier, more fulfilled physicians make better doctors. And we owe it to our patients to be the best we can be, both at work and at home. Often, this means procreating with our partners. And this procreation should be supported, dare I say even celebrated, during training.

References

1. Stentz NC, Griffith KA, Perkins E, Jones RD, Jagsi R. Fertility and Childbearing Among American Female Physicians. J Womens Health. 2016 Oct;25(10):1059-1065. Epub 2016 Jun 27.
2. Scully R, Melnitchouk N, Davids JS. Fertility and Pregnancy Outcomes in Female Physicians in Procedural Specialties: A Large National Survey. Am J Surg. October 2016 Volume 223, Issue 4, Supplement 1.
3. Marshall AL, Arora VM, Salles A. Physician Fertility: A Call to Action. Acad Med. 2019 Nov 12. doi: 10.1097/ACM.0000000000003079.
4. Lumpkin ST, Klein MK, Battarbee AN, Strassle PD, Scarlet S, Duke MC. Fellowship or Family? A Comparison of Residency Leave Policies with the Family and Medical Leave Act. J Surg Res. 2019 Sep;241:302-307. doi: 10.1016/j.jss.2019.03.004. Epub 2019 Apr 29.
5. American College of Obstretricians and Gynecology. College Statement of Policy: Parental Leave. https://www.acog.org/-/media/Statements-of-Policy/Public/92ParentalLeaveJuly19.pdf?dmc=1&ts=20200210T2133315009. Approved 2016. Amended and reaffirmed 2019.
6. Rangel EL, Lyu H, Haider AH, Castillo-Angeles M, Doherty GM, Smink DS. Factors Associated with Residency and Career Dissatisfaction in Childbearing Surgical Residents. JAMA Surg. 2018 Nov 1;153(11):1004-1011. doi: 10.1001/jamasurg.2018.2571.

MM

When helping your patients see clearly, **make each moment matter.**

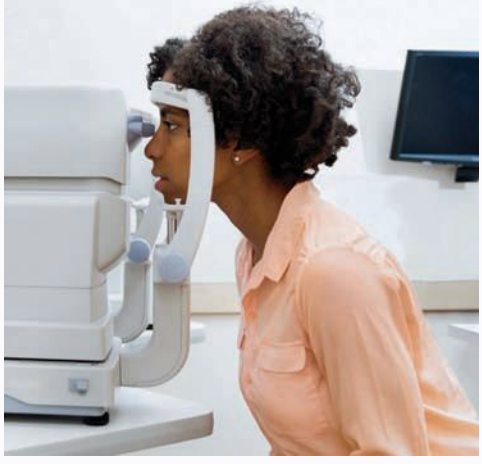
—

PNC can help.











We're making business banking easier.

At PNC, our team of dedicated Healthcare Business Bankers understands your business challenges and the important role that cash flow plays in your success. That's why we offer a range of solutions to help optimize management of your practice's revenue cycle and payables, so your business can run with less complexity and payments can be received promptly.

Learn more at pnc.com/hcprofessionals or by calling 877-566-1355

PNC BANK
Make today the day.®

©2020 The PNC Financial Services Group, Inc. All rights reserved. PNC Bank, National Association. **Member FDIC**

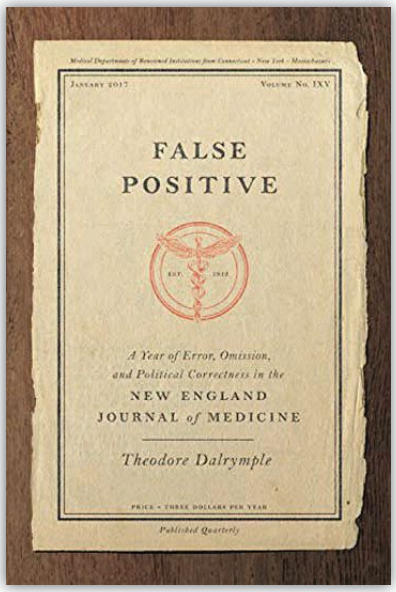
False Positive: A Year of Error, Omission, and Political Correctness in the *New England Journal of Medicine*

by Theodore Dalrymple

Reviewed by Arthur Gale, MD

Encounter Publishing
ASIN: B07FZB7Y56

Theodore Dalrymple is the pen name of a retired British psychiatrist and writer. He has written a book highly critical of the *New England Journal of Medicine* (NEJM). Instead of just writing an overall critique of the journal, Dalrymple uses the clever literary device of analyzing several articles from each issue of the NEJM published in the year 2017. He then demonstrates how flawed and biased these articles are.



Dalrymple writes, "The causes of error in the NEJM are multitudinous and range from carelessness to dishonesty, from wishful thinking to outright corruption, with everything in between." He writes "medical research relies on ever-more complex statistics to conclude anything at all, and common sense is often the first victim of medical sophistication."

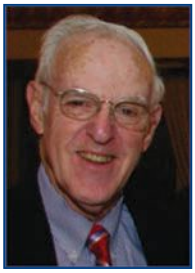
The author formerly considered the NEJM (along with *Lancet*) "the most important and influential general medical journal in the world." He states that his object in writing the book is to alert readers "to the sickly self righteousness" of the NEJM and "to attune readers to the ambiguities of medical research that are so often taken to provide unequivocal answers even to questions that are inescapably ethical in nature."

Dalrymple writes in a dry witty style of understated irony. The book cannot be read quickly. Each article that he reviews raises questions that require considerable thought and attention on the part of the reader. Some brief samples of his criticisms follow.

Conflicts of Interest

"Authors are now asked to declare their possible pecuniary interests and paid work for drug companies on the assumption that if they do so they will not bend their results at the behest of their paymasters." Dalrymple then cites an author of an article who admits receiving consulting fees from 30 different companies and grant support from 13 companies. Dalrymple concludes "It might have saved space to list those companies that had not paid him consulting fees and for whom he had never lectured. He adds, "Before one says, oh well, that's America for you, I note that the author was English, working in England."

One egregious but not uncommon example of conflict of interest is an article about a new breast cancer drug. The trial was designed in collaboration between the principal investigator and the pharmaceutical company which "was responsible for overseeing the collection, analysis and interpretation of the data"… "The manuscript was written with medical-writing support, which was funded by the pharmaceutical company."



Arthur H. Gale, MD, MSMA member since 1976, is a *Missouri Medicine* Contributing Editor. He is a retired Internist in St. Louis.
Contact: agalemd@yahoo.com

Although the drug showed little benefit, it was not how it was described in the abstract of the article. And, Dalrymple notes, "probably the great majority of doctors" only read the abstracts.

Administrative Dictates of "Medico Bureaucrats"

Dalrymple loathes "medico-bureaucrats" who develop programs like the Hospital Readmissions Reduction Program (HRRP) in the U.S. which penalize hospitals if they have higher than average readmission rates. He cites the experience of Britain where similar penalties are levied for not reaching certain targets according to protocol. It results in practicing medicine in a way that what the doctor does for patients "is not what he thinks best for them, but what the government has, in effect bribed him to do." Such mass prescription can result in "falsification of records and lying. The scale of the falsification is unknown." In the U.S. we have seen how hospitals use observation status as one way of getting around HRRP penalties. This practice often results in higher patient out of pocket payments.

As the late economist Uve Reinhardt pointed out in his book *Priced Out,* methods like the HRRP will never significantly lower the cost of hospital care. It is only through lowering the excessively high prices charged by hospitals and the other major players in the medical industrial complex that health care costs can be controlled.

Misuse of Statistics

In another section of the book Dalrymple describes misleading statistics often used in studies sponsored by drug companies, screenings or other interventions. The results of a study may show that the relative risk reduction of a drug, screening procedure or intervention, may look significant when actually the absolute risk reduction is miniscule. The author points out that even if a study shows statistical significance it may have no clinical significance and is often meaningless.

One of the few articles in the NEJM that the Dalrymple wholeheartedly agrees with is titled "Medical Education in the Era of Alternative Facts." The author of the article writes, "Critical review (of scientific literature) is such an essential skill that I believe it should be taught, practiced, and honed throughout all four years of medical school and even formally in postgraduate education."

Misleading Rankings of Health Care Systems

A Commonwealth Fund study ranking health care systems of the major industrialized democracies that comprise the Organization of Economic Cooperation and Development (OECD) ranks the United Kingdom first and the United States last. The study measures outcomes and other factors such as administrative efficiency, equity and access. Dalrymple states that a look at the table in the article "should make people laugh" because the United Kingdom is next to last in outcomes. Only the U.S. is worse according to the study. Dalrymple concludes, "In other words the United Kingdom equitably and efficiently administers very nearly the worst healthcare outcomes of those measured." He then writes that the average citizen would not understand "that administrative process is more important than outcome."

The author believes that such rankings defy common sense. Departing from his usual aloof dispassionate style of writing he angrily condemns his own British health care system by writing "I have never heard any Western European speak of Britain's health service with anything other than fear or disgust."

Conclusion

This book has seriously undermined the credibility of the NEJM and by implication other leading medical journals. If as Dalrymple writes, the "most influential medical journal in the world is careless, dishonest and corrupt, it would be reasonable to conclude that most lesser clinical medical journals in circulation today are likewise careless, dishonest, and corrupt."

When leading journals such as the NEJM publish studies that are not independent and objective, when the authors of such studies receive compensation and writing assistance from drug and device companies, practicing physicians and the public alike will no longer trust them. These once respected journals will then lose their influence, be ignored and will be regarded as just another throwaway. **MM**

Robert (Bob) Bondurant: A Remembrance

by Nancy Morton
MPHP Hospital Services Coordinator & Editor of The Physician Lifeline

Robert (Bob) Bondurant, RN, LCSW, Executive Director of the Missouri Physicians Health Program (MPHP) for 26 years passed on February 20, 2020 at the age of 74. He lost a very difficult battle with Non-Hodgkin's Lymphoma, leaving us too soon.



His intention was to remain in his position until he was 80 years old as he was passionate in his dedication to providing quality recovery that led to restored lives, families and careers. Bob was always available to meet or talk with a physician in need. He impacted the lives of thousands of people over his many years of service. Bob was tireless in traveling across the state to spread the word of our available resource and desiring most of all to warn medical students and residents about the pitfalls they could succumb to. He always preferred to speak extemporaneously with his educational presentations which allowed him to read the audience and keep them engaged. He understood that physicians were inundated with PowerPoint presentations, and were often relieved with his style of presentation. Following a presentation, Bob would sometimes hear from one of the attendees who was relieved to know of the MPHP and that he could talk confidentially about some problem that was plaguing them.

At times a physician was told by their hospital or the Board of Healing Arts that they must join our program. At that point, the physician often was resentful, however, later as they matured into their recovery, they sometimes would send notes saying that they realized they had been rude and unappreciative at first, but now were extremely grateful for their career and life that was saved.

Bob had a unique and diverse background that served him well in leading the MPHP. After an honorable discharge from the U.S. Army, having completed his tour of duty in Vietnam, he earned his Master's Degree in Social Work. Bob worked in the corrections arena, performing casework as well as acting as Superintendent of the St. Louis County Jail. He then had a private practice as a social worker where he provided counseling and performed interventions for families of alcoholics and drug addicts. Bob went on to several nursing positions having worked for Barnes Jewish Hospital, St. Anthony's Psychiatric Center, and Alexian Brothers Hospital.

In 1994, he began his career with the MPHP. When he was hired, he only had one part-time assistant. Under his leadership, he developed the reach of the MPHP across the state, stimulated donations from hospital administrations and medical staffs, as well as built an effective team around him to accomplish the overall mission of the program. Each staff member feels his loss profoundly. He truly was the heart of the MPHP. While taking his responsibilities seriously, he kept us energized and at times laughing at his clever wit and humor.

One of the traits of his leadership style was that he would sit down with each staff member almost daily, as the demands on his time allowed. He kept us informed on important developments, and inquired about our work. He made each of us feel like a valued team member.

Bob was an influential member of the national organization, Federation of State Physician State Programs, having served on its board, as well as a number of committees. He was respected for his ideas, as well as for developing the MPHP to the point of being considered a model program which other state programs could emulate. Bob was steadfast in wanting the program to remain independent in order to be able to advocate honestly for a physician when he was called to do so by the Board of Healing Arts. His reputation was such that he was invited to speak at a national meeting of the AMA in Hawaii about physician health.

One of his constant concerns was the lack of compassion on the part of many physicians. Many would express their appreciation for our services, but were reluctant to provide financial donations to help maintain the program. Very few program alums made donations after they had "graduated" and were again working and getting on with their lives. As a 501(c) 3 organization that is dependent on donations for more than 50% of its operating budget, that had always been distressing.

Bob leaves behind a wife, Marley Ann Herzog, two sons, David O. Bondurant and Stephen R. Bondurant, two daughters, Melissa A. Wright, and Nicole M. Bondurant, as well as grandchildren Brayden Bondurant, Elizabeth ("Ellie") Bondurant, and Colin Wright.

Bob was equally passionate about his family life. I remember on occasion his receiving a phone call from his daughter anxious for him to return home to help her with some difficulty. He never refused her. Bob was so proud of his daughter, Nicole, for becoming a nurse. While she was in nursing school, he often worked with her in the evenings to help her prepare for an exam or class.

Since his passing, the staff have received cards and donations dedicated to Bob's memory. Some have written comments on the website, dignitymemorial.com about his impact on their lives that you may enjoy reading. If you would like to make a donation in Bob's honor, please send a check to the MPHP, 1023 Executive Parkway, Suite 16, St. Louis, MO 63141.

On February 20, Physicians Lost One of Our Greatest Heroes

by Anonymous

As Missouri physicians combat the COVID-19 pandemic, we are faced with longer work hours, increased patient mortality, fear, rationing, and burnout. While most of us are armed with the coping mechanisms to combat these issues; there are those of us that likely have or will use a substance to cope. All too often, these behaviors metastasize hijacking our day-today lives and ultimately result in addiction. I know because this happened to me.

As a young physician I lost a patient on the table and started to struggle with severe anxiety. I eventually was overwhelmed by my emotions and ultimately, I chose to self-medicate. Eventually this "self-treatment" lead to addiction. I was referred to the Missouri Physicians Health Program (MPHP) for guidance. This was my first interaction with Bob Bondurant. I was truly terrified. Expecting a heavy-handed approach, I was met with benevolence and understanding.

Bob Bondurant quickly moved his team into action, referred me to a treatment facility, and played defense for my career. After 90 days of treatment I returned home, unemployed, broke, and without direction. Bob called in favor after favor with recruiters, department chairs, and hospital executives to help me find work. He would call me weekly to check-in and offer encouragement to stay-the-course. I eventually secured employment; however, my largest task was still in front of me.

I was summoned to the Board of Healing Arts. I entered the conference room and sat with my attorney to my left and Bob to my right. After many lines of questioning by the Board, the Board Chairman asked Bob his opinion. He offered a simple response: "Dr. X is the posterchild for recovery and is deserving of a second chance." A second chance? THIS IS THE BOARD OF HEALING ARTS! They won't give me a second chance.

Six weeks later I received a letter… the Board was willing to give me a second chance. I was in disbelief. It was in that moment that I realized that it was not only my respect that Bob commanded, but also that of the medical community at large.

Frankly, I would not be a practicing physician today without Bob Bondurant. He led me through some of the darkest times of my life, as he has with countless others. To borrow from the "Divine Comedy", Bob was my Virgil; leading me, and at times carrying me though darkness. On February 20, we physicians lost one of our greatest heroes. I was blessed to know him and will be forever grateful.

MM

Correspondence

Cannabis-Related Illness in Missouri Emergency Rooms

Following passage of medical marijuana in Colorado, there was an increased incidence of cannabis related illnesses seen in Colorado emergency departments. (ED) This increased even more dramatically when Colorado made recreational high THC cannabis legal.[1,2] Recreational marijuana also brings with it numerous social, educational, law-enforcement, vehicle accidents/DUI and other health problems including homelessness.[2] With the legalization of medical marijuana in Missouri, we have personally observed an increased incidence of ED initial and repeat visits and hospitalizations for marijuana complications especially cannabis hyperemesis. If this is typical of Missouri EDs, as we think it is from discussion with other physicians, it will strain hospital and ED physician resources to provide care for Missourians with non-marijuana related accidents and illnesses. To document the adverse effects of medical marijuana,[2] we hope that medical researchers will study the increase of marijuana related ER visits and hospitalizations in 2020 versus three to five years ago when access to marijuana was more restricted.

References

1. Randall K, Hayward K. Emergent medical illnesses related to cannabis use. Missouri Medicine 2019;116:239-241
2. Rocky Mountain High Intensity Drug Trafficking Area Program. The legalization of marijuana in Colorado: The Impact Volume 6 September 2019. Executive Summary Missouri Medicine 2019;116:450

Lancer G. Gates, DO, Hospitalist
North Kansas City, Missouri
MSMA Member since 2003
Shelley H. Bridgford, MD, Emergency Medicine
North Kansas City, Missouri

Editor's Note

This correspondence was received prior to the COVID 19 Pandemic crisis. Reports received by the Editor from Colorado ERs indicate that the increased ER burden from medical/recreational marijuana users[1] has disproportionally increased; that chronic marijuana users may be more suspectable to the COVID 19 virus; and this marijuana user burden is interfering with the ability to treat non-marijuana users. (emails Finn Marijuana Study Group March, 2020)

Warning the Medical Community and Public on the Dangers of Medical Marijuana

After reading the January/February 2020 *Missouri Medicine* editorial on the legal marijuana issue, I'm proud to have known you since our Mexico, Missouri, high school days. I'm extremely thankful of your lifelong devotion to providing thoughtful, detailed, and researched information to the medical community and general public on the dangers of various substances disguised as "medicine." More is needed; so many remain under informed or misinformed especially among the media. Your editorial will also provide solace to those whose lives or the lives of family members have been permanently affected in drastic, dramatic, and deleterious ways. You and your colleagues of like mind and devotion are doing God's work on earth. Keep it up!

Michael J. Pohlmeyer
Former Mayor, Redding California

Court Releases Physician Imprisoned For His Medical Opinions/Diagnoses

HB: 4836-1455-1735.1

In the November/December 2019 issue of *Missouri Medicine*, I wrote an article concerning potential criminal and civil liability based on a physician's medical opinion. In my article, I discussed the case of *U.S. v. Paulus*, 894 F.3d 267 (6th Cir. 2018). The *Paulus* case involved a cardiologist convicted by a jury of healthcare fraud for performing unnecessary stenting procedures when angiograms showed only minimal blockage. In that case, the question before the Sixth Circuit Court of Appeals was whether a medical opinion could ever be false (the lower court had determined they could not). The Sixth Circuit concluded that a medical opinion could be false if there was evidence that the doctor repeatedly and systematically saw one thing on an angiogram but consciously wrote down another.

In *Paulus's* case, testimony from three expert witnesses called by the prosecution supported a conclusion that he had repeatedly and systematically overestimated arterial blockage. One expert had reviewed 250-300 procedures and concluded that 62 of them (or 20.6%-24.8%) were unnecessary. The other two experts each reviewed less than 20 procedures. One of those experts concluded that 100% of the procedures he reviewed were unnecessary, and the other determined that 50% of the procedures he reviewed were unnecessary.

After the case was remanded by the Sixth Circuit for further proceedings, *Paulus* discovered that the prosecution

had withheld certain evidence that could have aided his defense. More particularly, *Paulus* learned that the health system where he worked, King's Daughters Medical Center (KDMC), had retained an independent consultant to review *Paulus's* procedures. While the government had previously disclosed to *Paulus* that KDMC's independent consultant determined 75 procedures were unnecessary, the government failed to disclose that the consultant had determined another 974 of his procedures were non-problematic. In other words, the independent review showed only 7% of *Paulus's* procedures were unnecessary. *Paulus* filed another appeal with the Sixth Circuit arguing that the failure to disclose this information violated his Fifth Amendment due process rights under the case of *Brady v. Maryland*, 373 U.S. 83 (1963) (a case in which the Supreme Court held that a criminal defendant's due process rights are violated if material evidence favorable to the accused is suppressed by the prosecution).

The Sixth Circuit issued a decision in this second case on March 5, 2020, vacating *Paulus's* conviction.[1] The Court easily determined that the evidence withheld from *Paulus* was material and favorable to his defense because the much smaller percentage of misdiagnoses found by KDMC's independent consultant "tend[ed] to refute the government's evidence that *Paulus* systematically misdiagnosed the amount of blockage in his patients' arteries" and instead supported an argument that *Paulus* made occasional mistakes or had occasional differences of opinions. The evidence could have also been used by *Paulus* to show that the government's sample was too small, and that the government cherry-picked its sample (the 75 procedures found by KDMC's consultant to be unnecessary were intentionally included in the sample reviewed by one of the government's experts).[2]

The Sixth Circuit noted that whether *Paulus* had the necessary fraudulent intent to support a guilty verdict was a close issue in his trial. The jury took four days to deliberate and deadlocked twice.[3] Since *Paulus's* intent was such a close issue, the Court concluded that withholding information concerning KDMC's independent review was prejudicial. The Sixth Circuit vacated *Paulus's* conviction and remanded the case for a new trial.

It is important to note that *Paulus* could still be convicted despite having this new evidence. It is also important to note that the government continues to pursue these cases despite the decisions recently rendered against it. Moving forward, I anticipate that the government will work around these cases by having their experts reframe their testimony.

Reference

1. U.S. v. Paulus, --- F.3d ---, 2020 WL 1057394 (6th Cir. Mar. 5, 2020).
2. Although one of the government's experts reviewed the same 75 procedures that KDMC had determined were unnecessary, the government's expert concluded only 62 of the procedures he reviewed were problematic. This shows how experts can disagree with one another concerning the extent of arterial blockage, further supporting an argument that Paulus did not have fraudulent intent.
3. And, even after his conviction, the district court found the government had failed to prove Paulus had fraudulent intent.

Emily Park, JD
Associate Attorney, Husch Blackwell
Jefferson City, Missouri

MM



Letters to the Editor

Submissions reflect readers' opinions and may be edited for length.

Email: drjhagan3@gmail.com
Mail: Missouri Medicine
P.O. Box 1028
Jefferson City, MO 65102

TRI-STATE OCCUPATIONAL MEDICINE

Physicians Needed for Outpatient Exams/ No Treatments

Tri-State Occupational Medicine, Inc. (TSOM) is looking for physicians to perform disability evaluations in their MO offices. Part-time opportunities. No treatment is recommended or performed. No insurance forms. No follow up. No call, no weekends and no emergencies. Preferred specialties – rehab med, emergency med, internal med or family med. Training and all administrative needs including scheduling, transcription, assisting, and billing are provided. Must have a current MO medical license.

Contact: Susan Gladys
susang@tsom.com
866-929-8766 / 866-712-5202 (fax).

Alliance Members Lobby, Fundraise

by Gill Waltman

This will be my last article for *Missouri Medicine* in my role as the MSMA Alliance president as I come to the end of my second term. Despite many achievements, this year has not run as smoothly as last, with first bad weather and now the global crisis from the coronavirus outbreak interfering with MSMA and Alliance activities, as well as the far-reaching effects on our personal lives with disruptions to work, travel, and home routines.

Annual Meeting Cancellation

With the necessary cancellation of the MSMA Annual Convention, I am saddened not to be able to give the customary annual Alliance report to the House of Delegates, that the James Bond-themed fundraiser will not take place after all the preparation by Alliance Foundation Chair Kathy Weigand and her committee, but especially that George Hruza, MD, Diana Corzine, and their respective officers will not be installed and celebrated in the style they deserve, and to which we have all become accustomed.

Winter Board Meeting and White Coat Day

Traditionally, the Alliance Winter Board Meeting and Day at the Legislature is held around the third week of February and is independent of any specific MSMA events. This year the dates were changed so that the Alliance activities coincided with the MSMA White Coat Day. Vice President for Legislation Kirk Doan took on the responsibility of organizing this change, with the help of the MSMA staff. Kirk, who is a partner in a busy law practice in Kansas City, is a business lawyer specializing in health care. He currently has over 600 physicians as clients, so he is well informed about their issues and concerns. Kirk also knows Rep. Dan Stacy [R] from Blue Springs and arranged with him for the Alliance to be recognized and introduced in the House.

The Winter Board Meeting took place on Monday afternoon March 2 at the new Holiday Inn & Suites, Jefferson City. This hotel has recently been built on the site of the old Ramada Inn. Cheerleaders, the Pub and Grill attached to the hotel, provided menu service in the room to board members on arrival. Despite delightful weather for a change, only a baker's dozen attended the board meeting with others joining the discussion by conference call.

The numbers swelled when we arrived at Madison's Café that evening as we were joined by MSMA President James DiRenna, MD, accompanied by Cheryl Douglas, who is a new Alliance member. MSMA Immediate Past President Joe Corrado, MD, joined us and JoEllyn Ryall, MD, came with a colleague. JoEllyn is not only an MSMA member and former Councilor but also an Alliance member.

We were lucky to catch MSMA Executive Director Patrick Mills, and MSMA lobbyists Jeff Howell and Heidi Geisbuhler before they headed out for more meetings. Those guys work hard for the practice of medicine! Patrick talked about the role of the Alliance and thanked us for our service. He also announced that he will be retiring this year – a big surprise. Jeff spoke about the bills to be discussed the next day. The topic raising its ugly head that week was the Medical Marijuana bill [HB 1896.] MSMA added an amendment to require physician certifications for medical marijuana patients to be conducted in a face-to face visit, not over the phone. Liz Fleenor showed us all how to sign up for the Phone2Action App, a collaboration with MSMA for members to connect with lawmakers for grassroots advocacy responses. Visit www.msma.org/action to sign up!

After dinner we persuaded Dr. DiRenna to talk about his year so far as MSMA president. He said that he has always been a strong supporter of the Alliance. He shared some of his insights from visiting medical societies in many other states. He has been a tough advocate for controlling vaping in Missouri.



Gillian Waltman is the 2019-2020 MSMA Alliance President and Professor, Ophthalmology, Saint Louis University, St. Louis, Missouri.
Contact: gillian.waltman@gmail.com

On Tuesday morning Alliance members met in the Rotunda, joining MSMA physicians from all over Missouri. Rep. Jon Patterson, MD [R] from Lees Summit spoke eloquently on the current bills we needed to discuss with our legislators. The MSMA still needs support for the Prescription Drug Monitoring Program [HB 1693; SB 677] and Scope of Practice issues, the most alarming being non-physicians wanting to perform surgery without a medical license. MSMA is working with physicians to produce a definition of surgery – not an easy task. Sen. Bill White was supposed to address us, but his flight was delayed. Jeff Howell talked again about the issues to bring up to the lawmakers.



Above, Alliance members at the Capitol for White Coat Day, and below, Alliance members sign up for Phone2 Action.



A few quick visits to legislators were possible before we headed to the House for the Alliance to be recognized and introduced by Rep. Dan Stacy [R]. We split up after the introductions and dispersed to disseminate MSMA materials and make a few more contact visits with the legislators. Before heading off home to various parts of the state, MSMA hosted a delicious box lunch for all who supported the White Coat Day.

The MSMA Alliance Annual Meeting that is usually held in conjunction with the MSMA Annual Convention has, of course, been cancelled too. President-elect Diana Corzine and I have worked together, with the help of Allene Wright, to combine a belated annual business meeting with our Alliance Executive Board meeting in Columbia. This is usually held in May. With great optimism, we chose Tuesday May 5 for an all-day condensed meeting. The Installation and Awards luncheons will be combined. I will still be the presiding officer for the morning session; Diana and her officers will be installed and awards presented, followed by her executive board meeting. We will plan a COVID-rain date for the end of May. If it is still not safe to congregate and that also gets cancelled, we will either postpone to a later date, or conduct business by conference call.

For those who are interested, the in-person Cabi Fashion Show (another small fundraiser) scheduled to be held at the convention has been cancelled but plans are underway to hold a virtual show by Zoom in the near future. Contact me if you would like to be kept informed about this. Proceeds from the event will benefit MSMF.

Match Day Events

All Match Day events planned across the state for the week of March 16-20 were cancelled due to the virus. Some will be conducted virtually but exclude any outside guests. Many thanks to Millie Bever and Angela Zylka for organizing these thwarted events and for the local Alliance members who planned to participate in Columbia, Kansas City and St. Louis. Millie is looking into some form of ceremony or recognition for the students at the time of their graduations, assuming those even take place.

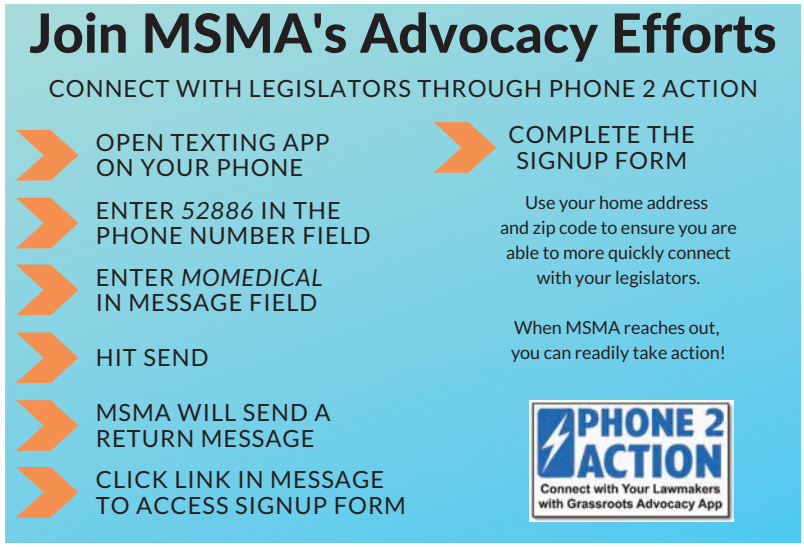
Current Alliance Activities

The Alliance has vice presidents for four focus areas in its efforts to support the family of medicine and its

physicians in Missouri; Health, Membership, Legislation and Foundation.

Health

Health Vice President Kelly O'Leary has taken our *Drugs are Not for Me* program around the state to different counties during the year. In addition to the opioid crisis, the presentation now includes the dangers of electronic cigarettes. We had hoped to piggy-back onto the presentation on vaping by Donald Bohnenkamp, MD, at the MSMA Convention to learn the latest updates, but it was cancelled. The topic will be included in our community health programs going forward.



Membership

Membership continues to decline in most counties, mostly by attrition and the difficulty in recruiting new members. Although Cape Girardeau has an active local alliance membership, VP Jennifer Gast has not had much success re-recruiting her Cape Girardeau fellow members to participate at the state level. We are delighted that Mary Catherine Heimburger, with the help of Donna Corrado and the support of Boone County Medical Association, have formed a new alliance combining three former counties. It will be known as Central Missouri Medical Alliance and it is already attracting members. This is our fastest growing alliance.

Legislation

Legislation Vice President Kirk Doan organized our Day at the Legislature at the Capitol to coincide with the MSMA White Coat Day on March 3. (See above.)

Foundation

Foundation Vice President Kathy Weigand was denied her chance to fulfil the exciting Friday night James Bond event at convention as that was also cancelled. Although the expected funds to be raised at the event will not materialize, the results of the Alliance efforts to fundraise for MSMF looks unusually successful this year. In addition to the $3220.00 raised from the Holiday Sharing Card, arrangements were made at the end of July to turn over the former Alliance Scholarship monies to MSMF. This amounted to $74,084.81 and will now be managed and disbursed to medical schools by MSMF. We had hoped to present this amount to Dr. David Chalk, the incoming MSMF Chair, during the HOD speech, in the form of a large cardboard check. This is a fortuitous donation in these troubled times.

Upcoming Events

We are hoping that the AMA and AMA Alliance annual meeting will still take place in Chicago in June, particularly because Sue Ann Greco is being installed as AMA Alliance President. Our Social Media Chair Jana Wolfe keeps everyone informed by posts on Facebook as more details emerge.

Gratitude

We would like to thank the MSMA Council members and MSMA staff for their support during the year, particularly our tireless Alliance liaison Liz Fleenor. We will miss Patrick Mills, and Stephen Foutes as they move on, and thank them for their involvement with us during their time at MSMA. We would also like to remember the many contributions made to Missouri physicians and their families by Bob Bondurant at MPHP. The Alliance is sending a donation in his memory to MPHP.

The Alliance wishes everyone a safe passage through the next few unpredictable months, especially those of you on the front lines. We are living in unprecedented times and it is hard to make any future plans! Hopefully, by the summer we can begin another productive year working with MSMA. **MM**

Gluten Free Diets – A Challenge for the Practicing Physician

by Richard Hellman, MD

Americans spend more than $30 billion dollars annually on health foods, herbal preparations, anti-aging potions of various sources and a wide variety of diets, of which low-gluten diets are just one option.

Introduction

In recent years, gluten free diets have become commonplace. Nearly one-third of all Americans report that they have either tried to reduce the amount of gluten in their diet or tried to eliminate it altogether.[1] In 2016, the sales on gluten free products sold in the U.S. were over $15.5 billion.[2] The proportion or prevalence of people attempting to follow a gluten free diet is highest in Latin America. The Middle East is second highest, and the United States has the third highest prevalence.[3] Fueled by a confluence of testimonials by celebrities and other well-known public figures and relentless marketing, many people are of the opinion that a gluten-free diet is useful for better health, is more nutritious, will help in a variety of non-gastrointestinal illnesses, and will aid in weight loss and in improved athletic performance. However, these claims, for the most part, are without any scientific basis.

There are abundant data that prove that gluten free diets are life-saving for those with celiac disease and are a lifelong necessity. Yet, less than 1% of the population has celiac disease (CG), and only about 6% of the population carry the diagnosis of gluten sensitivity but not celiac disease (non-celiac gluten sensitivity - NCGS). However, when tested rigorously with a double-blind study, only 16-30% of the NCGS population show signs that it is the gluten to which they are sensitive.[2] IgE mediated allergy to gluten is quite rare, less than 0.4-0.9% of the population, and usually found in young children. Yet, the percentage of those in the U.S. who are on a gluten free diet has risen steadily in recent years. A 2014 CDC report showed that 72% of persons on a gluten free diet had neither gluten sensitivity nor celiac disease, an increase from 2009, when it was 44%.[2,4]

So why should a practicing physician care that people are wasting their money buying gluten free products that will not add to their health or longevity? Surely we should be spending our valuable time spent with our patients on other more pressing and less contentious matters. After all, when a patient tells us that since they started on a gluten free diet they sleep better at night, have lost 10 pounds, and have a better tennis game, should we not just acquiesce and move on to another topic? Yet, the more well-informed we are regarding the benefits and hazards of these diets, the more compelling is the case that we should at the very least inform the patients that these diets have some very real long term hazards for most patients, and for some patients, warn them that their choice to begin on a largely gluten free diet may put them at very high risk for a bad outcome.

Risks of a Gluten-Free Diet – Undiagnosed Celiac Disease

So, what are the facts? What are the serious risks the patients may be inadvertently taking? Probably the most common severe risk comes with patients who are at high risk for celiac disease and do not know it. Celiac disease is a severe autoimmune disease which can destroy the small intestinal lining and cause a multitude of problems, some related to the intestinal malabsorption and inflammation and others that are extraintestinal in nature. A sizeable number of patients may have no symptoms and there is a small, but not insignificant, risk of intestinal lymphoma, or even adenocarcinoma of the small intestine in the



Richard Hellman, MD, FACP, FACE, MSMA member since 1976, is an Endocrinologist at Hellman & Rosen Endocrine Associates, North Kansas City, Missouri.
Contact: RHellman@nkcendo.com

long term. The keys to diagnosis of celiac disease are the presence of a specific genetic genotype (HLA-DQ2 and/or HLA-DQ8 genes) and the presences of highly specific autoantibodies, the IgA tissue transglutaminase antibodies (IgAt), antiendomysial antibodies (IgA EMA), and/or deamidated gliadin peptide (IgG) antibodies. Usually the IgAt antibody is used for screening, and confirmation is by the IgA EMA antibody. The disease is triggered by exposure to the environmental antigen, gluten.[5] Gluten is a protein found in wheat, barley, rye, and spelt, and contains a mixture of prolamins and glutenins. These proteins are rich in prolines and glutamines and are incompletely digestible by intestinal enzymes. These indigestible proteins are potentially immunogenic and in patients with the genetic predisposition of the HLA antigens DQ2 or DQ8, a cascade of immunomodulated events are triggered that begin with disruption of the epithelial barrier of the small intestine, an immediate transient increase in gut permeability, followed by a cascading sequence of recruitment of multiple components of the immune system, and eventually causing the destruction of the intestinal villae. This sequence is accompanied by rising titers of both IgAt antibodies and IgA EMA antibodies.

Malabsorption of food may follow, leading to failure to thrive in children, widespread vitamin and protein deficiencies, pain and disability. The key to early diagnosis and avoidance of the pathological immunological cascade is early detection of the specific serum antibodies, particularly the IgAt. It is important to also recognize that this sequence is triggered by exposure to gluten and, in some patients, the amount of gluten required can be very small. Unfortunately, if the patient is already on a strictly gluten free diet, the titer of the antibody, which is at least two times higher than the upper limit of normal, begins decreasing and may become undetectable, delaying the diagnosis. If either avoidance of gluten is incomplete or the patient is very sensitive to very small amounts of gluten, long-term damage and risk of other extraintestinal complications may ensue.

Unfortunately, a strict gluten free diet in a patient with established celiac disease does not guarantee that healing will result, and medical evaluation and follow-up by a gastroenterologist is needed. There is a consensus among experts in celiac disease that if your patient is desirous to be on a gluten free diet, if there is any risk at all that they have a form of celiac disease, it is wise to ask them to first undergo a challenge with gluten and obtain the antibody titer after the challenge in order to rule out missed celiac disease. Unfortunately, if a person with undiagnosed celiac disease chooses to be on a gluten free diet before they are diagnosed, a gluten challenge of at least three months or more may be needed in adults before elevated levels of antibodies occur. There are reports that in children it may take up to a year for them to redevelop diagnostic antibody levels. If that person with celiac disease becomes symptomatic with a rechallenge of gluten after only a day or two, since the duodenal biopsy may not be diagnostic after being on a gluten free diet, it creates a dilemma for the patient and the physician, as to how to prove whether they have underlying celiac disease or not.

One option, albeit an imperfect one, is to do genetic testing, for if the patient does not have genes for the HLA-DQ2/DQ8, it would be improbable that their symptoms are due to celiac disease. Unfortunately, these genes are common in the general population, in some ethnic groups as high as 40%, and while a negative test for HLA DQ2/DQ8 genes makes celiac disease very unlikely, if the test is positive it does not prove they have celiac disease, since most people with the HLA DQ2/DQ8 genes do not have celiac disease. If IgA deficiency is present, since IgA antibody titers are no longer useful, IgG deamidated gliadin peptide antibodies may be used to screen for celiac disease. If the antibody titer is now elevated, the next step is a duodenal biopsy, which is considered to be the gold standard for the diagnosis of celiac disease. However, there are European guidelines which recommend that in children a biopsy can be avoided, (but not in adults), if the patient has an IgAt antibody titer greater than 10x the upper limit of normal of the assay, and the presence of the HLA DQ2/DQ8 genes, and a positive IgA EMA obtained at a time that is different from the time of the screening IgAt antibody test, and a family history that suggests high risk. The IgA EMA measurement is primarily used only as a confirmatory test. Although in clinical practice testing for HLA-DQ2/DQ8 genes is less often performed, when biopsy results and antibodies are discordant, checking for the HLA DQ2/DQ8 genes is indicated, because only very rarely can a patient have celiac disease without the presence of the genes.

It is important to check the family history carefully, since there is a very high concordance of celiac disease in families, particularly in first order relatives, and highest in monozygomatic twins (75-80%).[6] Also, there are numerous disorders with an autoimmune basis that are much more likely to be found in patients with celiac disease, such as Addison's disease, type 1 diabetes, Hashimoto's thyroiditis, Graves' disease, dermatitis herpetiformis, autoimmune hepatitis, primary sclerosing cholangitis, rheumatoid arthritis, Sjogrens syndrome, systemic lupus, as well as

other disorders such as IgA deficiency, idiopathic dilated cardiomyopathy, cerebellar ataxia, and chromosomal diseases such as Downs syndrome, Turner syndrome, and Williams syndrome. The presence of one of these conditions should also trigger a search for celiac disease.

Cost and Social Issues with Gluten Free Diets:

One of the many challenges patients with celiac disease face is that a lifelong pattern of being on a strict gluten free diet is difficult, socially isolating, extremely expensive, and the diet itself increases the risk for nutritional deficiencies. The public is largely unaware of the expense of the diet. A recently reported study by Lee et al. shows that in the U.S., the cost of a well-balanced gluten free diet is about 240% or more than a comparable well-balanced diet. Certain types of gluten-free foods are often over 300% higher in cost, and the prices vary considerably in different parts of the U.S.[7]

Gluten Free Diets May be Nutritionally Inferior

Because of the physical and chemical characteristics of gluten – it is viscoelastic, rich in nutrition, and can easily be made into bread and baked – it is difficult to substitute for, and many of the commonly used substitutes are not fortified with the nutrients commonly found in gluten containing products. Numerous studies have shown that diets that are gluten free tend to be deficient in protein, folate, iron, niacin, riboflavin, thiamin, B12, zinc, selenium, and fiber. In addition, they are more apt to have higher levels of nickel, which is highly allergenic to some patients.[1,2] These diets may also contain higher levels of arsenic, mercury, cadmium, lead, and higher levels of fat, saturated fats, and cholesterol.[8] It can be quite challenging to obtain the correct nutritional balance with a strict gluten free diet, and the list of foods to avoid when eating out is sufficiently daunting that it tends to encourage patients to avoid restaurants and become obsessive about their food choices.

Social Costs

Several researchers have carefully evaluated the degree to which a gluten free diet has a negative social impact on patients who do not have celiac disease but are choosing a gluten free diet in hope of other benefits. In one study, 11% of respondents reported that following a gluten free diet led to high levels of interference with social leisure activities.[2] The respondents noted that they spent more money on the diet, spent more time on the food preparation, and wound up eating more at home, and enjoying their time eating much less than if they had not been following this diet. There are even reports of some patients developing an obsessive disorder, which is termed orthorexia nervosa,



Source: Sprint Science

and obsession about healthy eating which can become very destructive.[2]

Long-Term Cardiovascular Risks of Gluten Free Diets

Other documented problems that persons on a gluten free diet face is weight gain. In general, unless the diet is constructed by a skilled professional, gluten free diets tend to have increases in the fat content of the foods. Although weight gain in an underweight patient with celiac disease is often welcome initially, in patients who do not have an indication for a gluten free diet, weight gain is often an unwelcome surprise and it may be accompanied by abnormal lipids and a higher risk for coronary heart disease. Hyperglycemia and an increase in insulin resistance and obesity has been reported as well.[2] These diets are also not recommended for a pregnant woman.

Non-Celiac Gluten Sensitivity (NCGS)

Patients who have been tested and do not have either celiac disease or IgE mediated wheat allergy, but have demonstrated sensitivity to gluten are initially considered to have non-celiac gluten sensitivity (NCGS). As many as 6% of the population in the United States may have this condition. These patients often experience intestinal or extraintestinal symptoms related to the ingestion of

gluten. The intestinal symptoms may include diarrhea, constipation, bloating, and abdominal pain, and the extraintestinal symptoms include fatigue, anxiety, fibromyalgia, headaches, and mental "fogginess". These patients have negative serologic markers for celiac disease and no evidence of duodenal villous atrophy.

In controlled, randomized, blinded studies, patients without celiac disease, but with a HLA DQ2 or DQ8 haplotype tended to be more likely to be sensitive to gluten. However, careful testing on many patients who tested negative for celiac disease and were negative for HLA DQ2/DQ8 genes, but who had been on a gluten free diet and considered themselves to have gluten sensitivity, did well on a low FODMAP diet. FODMAP diets are diets that contain low levels of fermentable oligosaccharides, di-and monosaccharides, and polyols that are poorly absorbed in the small intestine. While in the gut, these saccharides are often fermented by intestinal bacteria, leading to production of short chain fatty acids which are very active metabolically, and also increase bowel osmolality, increasing gut motility and gas formation.[9] When gluten was then reintroduced to the diet of these patients, there was no specific effect, suggesting that although a gluten free diet shares some features with low FODMAP diets, it is the low FODMAP diet that is therapeutic.[10] Other items may also masquerade as gluten sensitivity, such as amylase trypsin inhibitors, commonly found in wheat. Also, fructans, which are common among the FODMAPS that are common in diets,[11] nickel allergy, small intestinal bacterial overgrowth, or lactose intolerance may also be confused with NCGS.[12]

One effort to establish objective criteria for the diagnosis of NCGS, which does not have any unique diagnostic feature, is the Salerno Expert's Criteria (2015), a consensus strategy of an initial six-week observation period of a gluten free diet, followed by a reintroduction of gluten.[13] This should be blinded, ideally double blinded, but in a clinical practice a single blinded method is used. Most authorities recommend the blinded studies should not use gluten capsules added to a gluten free diet, but instead prefer foods that are very similar, but one group of meals contains gluten, and the others do not. This is not easy to do, as the texture of non-gluten foods is often quite different. Clearly this testing procedure has several shortcomings. Nevertheless, for the patient who firmly believes they have NCGS, a blinded trial may be an appropriate choice before committing a patient to a lifetime of a regiment of a gluten free diet.

Overlap of Symptoms of NCGS or CD with IBS

Many patients who have symptoms of irritable bowel syndrome (IBS) will try a gluten free diet and some patients report that they have improved on a gluten free diet. Yet, a number of medical societies, in their guidelines and systematic reviews, are very careful to recommend against using a gluten free diet in the treatment of IBS.[14,15] The reasoning behind these recommendations is relevant to our discussion, as the study of patients who are categorized as having IBS illustrates some of the complexities that we face when we counsel patents regarding gluten free diets.

Many clinicians consider diet to be a key factor in the treatment of the heterogeneous group of patients who initially may present as possibly having an IBS. Perhaps the first order of business is to be sure that the diagnosis is correct, for many different GI conditions may have features of IBS. Each of these patients should also be checked for IgAt antibodies, and, if they are IgA deficient, deamidated IgG gliadin antibodies would be an alternative. After other diseases, such as inflammatory bowel disease, small intestinal bacterial overgrowth, etc., have been ruled out, and the diagnosis of IBS has been established, treatment of IBS can begin. Some of the research regarding treatment of IBS discusses FODMAP diets. Gluten free diets also tend to be somewhat lower in FODMAPS, but when patients without celiac disease but with symptoms that are compatible with IBS are put on low FODMAP diets, may of these patients have a reduction in symptoms, and are surprised when reintroduction of gluten later does not cause symptoms. Because the evidence supporting gluten free diets in IBS is lacking, both the Canadian Association of Gastroenterology guideline and the Italian Pediatric Gastroenterological Association systematic reviews, in their dietary treatment recommendations, include a trial on FODMAPS, but not on a gluten free diet.[14,15] It is important to note that the FODMAP diet is considered to be a temporary diet, as it is widely recognized that long-term the FODMAP diet, as is the gluten free diet, is not usually nutritionally sound and long-term use is to be avoided if possible.[14] Many patients who have had IBS-like symptoms and have chosen to start a gluten free diet would be better served to be evaluated first for celiac disease and a number of other causes of IBS-like symptoms and then, after a careful workup, if a dietary change is suggested, to first consider FODMAP diets as part of a careful evaluation. It is important to reemphasize that neither a low FODMAP diet nor a gluten free diet are prescribed for healthy patients, but are reserved for those who have a diagnosis that indicates that such a diet will have a benefit that outweighs the risks.

Conclusion

Americans spend more than $30 billion dollars annually on health foods, herbal preparations, anti-aging potions of various sources and a wide variety of diets, of which low-gluten diets are just one option. It is unlikely that physicians, even armed with the facts, are likely to prevail in all discussions with patients about which diets should not be used. Food is so central to most people that by the time they reach adult age, they often have many strong opinions about how best to eat. However, the gluten free diets are more frequently used as a choice for diets today throughout much of the world. Those persons who do so without a clear medical indication often have very limited knowledge about the risks and benefits of gluten free diets, and often are quite grateful when a physician provides evidence-based advice,[16] allowing them to decide whether this popular diet is right for them, or rather a mistake that should be corrected.

References

1. Taetzsch A, Das SK, Brown C, Krauss A, Silver RE, Roberts SB. Are Gluten-Free Diets More Nutritious? An Evaluation of Self-Selected and Recommended Gluten-Free and Gluten-Containing Dietary Patterns. Nutrients. 2018;10(12):1881.
2. Niland B, Cash BD. Health Benefits and Adverse Effects of a Gluten-Free Diet in Non-Celiac Disease Patients. Gastroenterol Hepatol (N Y). 2018;14(2):82–91.
3. Dieterich W, Zopf Y. Gluten and FORDMAPS-Sense of a Restriction/When is Restriction Necessary? Nutrients. 2019 Aug 20;11(8).
4. Kim H, Patel KG, Orosz E, Kothari N, Demyen MF, Pyrsopoulos N, Ahlawat SK. Time Trends in the Prevalence of Celiac Disease and Gluten-Free Diet in the US Population: Results From the National Health and Nutrition Examination Surveys 2009-2014. JAMA Intern Med. 2016;176(11):1716-1718.
5. Leonard MM, Sapone A, Catassi C, Fasano A. Celiac Disease and Nonceliac Gluten Sensitivity. JAMA. 2017;318(7):647-656
6. Caio G, Volta U, Sapone A, et al. Celiac disease: a comprehensive current review. BMC Med. 2019;17(1):142.
7. Lee AR, Wolf RL, Lebwohl B, Ciaccio EJ, Green PHR. Persistent Economic Burden of the Gluten Free Diet. Nutrients. 2019;11(2):399.
8. Diez-Sampedro A, Olenick M, Maltseva T, Flowers M. A Gluten-Free Diet, Not an Appropriate Choice without a Medical Diagnosis. J Nutr Metab. 2019;2019:2438934.
9. Werlang ME, Palmer WC, Lacy BE. Irritable Bowel Syndrome and Dietary Interventions. Gastroenterol Hepatol (N Y). 2019;15(1):16–26.
10. Krigel A, Lebwohl B. Nonceliac Gluten Sensitivity. Adv Nutr. 2016;7(6):1105–1110.
11. Llanos-Chea A, Fasano A. Gluten and Functional Abdominal Pain Disorders in Children. Nutrients. 2018;10(10):1491.
12. Borghini R, Donato G, Alvaro D, Picarelli A. New insights in IBS-like disorders: Pandora's box has been opened; a review. Gastroenterol Hepatol Bed Bench. 2017;10(2)79-89.
13. Roszkowska A, Pawlicka M, Mroczek A, Bałabuszek K, Nieradko-Iwanicka B. Non-Celiac Gluten Sensitivity: A Review. Medicina (Kaunas). 2019;55(6):222.
14. Moayyedi P, Andrews CN, MacQueen G, et al. Canadian Association of Gastroenterology Clinical Practice Guideline for the Management of Irritable Bowel Syndrome (IBS). J Can Assoc Gastroenterol. 2019;2(1):6–29.
15. Scarpato E, Auricchio R, Penagini F, Campanozzi A, Zuccotti GV, Troncone R. Efficacy of the gluten free diet in the management of functional gastrointestinal disorders: a systematic review on behalf of the Italian Society of Paediatrics. Italian Journal of Paediatrics. 2019;45(9).
16. Miller D. Maybe It's Not the Gluten. JAMA Intern Med. 2016;176(11):1717-1718.

MM



Together Credit Union

Our specialized **Doctor's Loan Programs** allow for 100% financing with no mortgage insurance requirement.

In addition, if you mention that you saw this ad in *Missouri Medicine*, you will receive a **$500 closing cost credit!**

Please inquire about our **Doctor's Loan Refinancing Programs** as well.

Michele Piperides | Mortgage Loan Officer
Together Credit Union
NMLS#500381
423 Lynch Street | St. Louis, MO 63118
Direct: 314-324-8482 | Email: mpiperides@togethercu.org

Forbes 2019 BEST-IN-STATE CREDIT UNIONS Powered by STATISTA
TOP WORK PLACES 2019



Children's
HOSPITAL & MEDICAL CENTER
OMAHA

When one number connects you to the region's best pediatric specialists, **Anything can be.**

1.855.850.KIDS (5437) is your 24-hour link to pediatric specialists for physician-to-physician consults, referrals, admissions and transport.

Education • Research • Advocacy • Care

Saint Louis University School of Medicine and Vaccine Center Mobilize for COVID-19 Pandemic

by Robert W. Wilmott, MD

The role of medicine is continuously evolving and changing in our world, and for those we serve. Medicine, once a reactionary practice, is becoming a preventative practice. We have developed vaccines, screenings, and prophylactic measures to help us live longer, healthier, and happier lives. Throughout history, medicine and medical professionals have been challenged, and we have turned reactionary responses into preventative practices. In times of trial and times of prosper, medicine continues to move forward, impacting our communities one patient at a time.

We are currently navigating through a critical time with the rapid spread of COVID-19. The medical community is being challenged, stretched thin, and forced to solve problems in new ways for an outbreak we never expected. The team at Saint Louis University Vaccine Center, led by Daniel Hoft, MD, is working diligently to develop antiviral agents. We anticipate that soon, Sarah George, Associate Professor, Infectious Diseases, Allergy, and Immunology, will be starting a COVID-19 therapy trial with a new antiviral agent. Our Saint Louis University Vaccine Center is one of nine federally-funded vaccine centers in the country, with an in-house clinical trial unit.

We look forward to utilizing our clinical trials unit for a potential COVID-19 vaccine trial.

Like all medical schools across the country, we are pivoting daily to keep our faculty, staff, students, trainees, and our community at top of mind during this outbreak. We are experiencing a time of trial, but it's also a time to work together to evolve and adapt to what is going on around us and to take medicine to the next level. We recognize it is time for challenge and growth, and we welcome the opportunity. In just a short time, our teams on campus have come together to solve problems and prepare for an emergency we've never experienced.

Our students have organized babysitting services for our healthcare workers who need childcare to report to work. They are volunteering in our call centers and the telehealth process. They are taking on documenting faculty and staff who are in quarantine, or otherwise unable to work, so we can keep track of our workforce to avoid a critical workforce shortage. They are volunteering with our Employee Health program to administer virtual COVID-19 phone screenings. They are volunteering at the VA, making spreadsheets of test results, and tracking data. Our students have been a shining example of the mission of Saint Louis University and its Jesuit tradition. Our campus community has adjusted its lives quickly and efficiently to keep our campus and our community safe. Residents are splitting into shifts. The staff is working from home. Physicians are mobilizing and leading teams to cover vulnerable service lines. Despite the challenges, we will learn some lessons, implement some changes, and emerge as better medical professionals on the other side.

Although we face challenges, we are continuing to prosper in many areas. We have many shining moments on the horizon, and I am proud to showcase the Department of Surgery, headed by Sameer Siddiqui, MD, Associate Professor and Interim Chair of Surgery. He is also the director of robotic surgery at Saint Louis University. You will read about what his team is doing with immunotherapy in urologic cancer; breast cancer screenings to detect a malignancy at its earliest stage; the exploration in 3D printing technology to benefit our tiniest patients with craniofacial anomalies; the advancement of robotic technology; and advancement in the development of lymphatic surgery. They are taking their craft to a new level and developing new approaches.

The new SSM Saint Louis University Hospital is still on schedule, and the 316-bed, 802,000 square-foot hospital will open in September 2020. Our patients will experience all-private patient rooms; we will have larger intensive care units, an expanded emergency department, and a new outpatient care center. Additional clinic space will be available for SLUCare physician practices. And finally, the hospital has been designed to provide excellent educational spaces for training. We are excited to have the facilities to educate the caregivers of tomorrow and provide our patients with the technology they deserve.

We are excited about the future and what the ever-changing landscape of medicine will bring us. Evolution in medicine and technique demand up-to-date facilities to serve our patients, advance our doctors, and propel medicine forward; so in the future, when we experience yet another need to grow, we will be ready. **MM**



Robert W. Wilmott, MD, and IMMUNO Professor, MSMA member since 2007, is a pediatric pulmonologist, Professor, Dean, and Vice President for Medical Affairs, Saint Louis University School of Medicine, St. Louis, Missouri.
Contact: robert.wilmott@health.slu.edu

Punctuated Equilibrium: Surgical Innovation and an Evolutionary Theory

by Sameer Siddiqui, MD

SAINT LOUIS UNIVERSITY

Our future includes automation, simulation training, artificial intelligence, smaller incisions, fewer incisions, and probably less surgery.



Sameer Siddiqui, MD, FACS, is Chief of Urology and Interim Chair, Department of Surgery, Saint Louis University, St. Louis, Missouri.
Contact: sameer.siddiqui@health.slu.edu

When I was in college, I read a book called *Bully for Brontosaurus* by Stephen Jay Gould. He was an evolutionary biologist best known for developing the evolutionary theory of punctuated equilibrium. The theory proposed that evolution took place in punctuated, sudden spurts of speciation followed by periods of quiescence. Like evolution, I think of the history of medicine in a similar fashion: periods of quiet mixed with bursts of innovation. In the 19th century, the discovery of ether as an anesthetic and the use of carbolic acid for antisepsis fundamentally transformed the world of surgery into how we operate today.

In my own world of urology, we had been performing large, morbid flank incisions for ureteral stones for over 100 years. Suddenly, seemingly out of the blue, the world was introduced to shockwave lithotripsy and ureteroscopy, and flank incisions for ureteral stones disappeared within five years. Kidney stone treatment today is in its quiescent phase. Fast forward to the 2000s, the world of chemotherapy for solid organ cancers was in a state of stagnation. Cancers were (and still are) being treated with drugs introduced over 50 years ago. In prostate cancer, we had one drug. In kidney cancers, two drugs. All were ineffective. Fast forward to 2019, there are more than ten FDA approved agents for each of these malignancies, principally a new class of immunotherapy agents called checkpoint inhibitors.

What we are witnessing today is a major transformation in the world of surgery. The last transformation took place in the 1990s with the introduction of laparoscopy.

The articles in the current issue of *Missouri Medicine* highlight the punctuated surgical innovation taking place today. Resident physician Allison May, MD, and our lead urologic oncologist, Zachary Hamilton, MD, detail the amazing proliferation of immunotherapy in urologic cancer. Our breast cancer team of Drs. Kaitlin Farrell, Debbie Bennett, and Theresa Schwartz provide an update on breast cancer screening. Plastic surgery resident, Lauren Yarholar, MD, and our Chief of Pediatric Plastic Surgery, Alexander Lin, MD, detail their amazing work with 3D printing technology and craniofacial anomalies in children. I am also very excited to introduce plastic surgeon, Kyle Xu, MD, and resident physician Aurora Kareh, MD, who describe the development of lymphatic surgery, and advances in lymphovenous bypass and vascularized lymph node transfer. Grace Montenegro, MD, our colorectal surgeon, with resident surgeon Claire Wunker, MD, outline the use of robotic technology in rectal cancer and complicated diverticulitis.

It is hard to predict when the next growth spurt in medicine will take place. The papers presented in this issue suggest that surgery will not undergo a quiescent phase any time soon. Our future includes automation, simulation training, artificial intelligence, smaller incisions, fewer incisions, and probably less surgery. For the deep thinkers, nerds, and innovators, it is a great time to be a surgeon. **MM**

The Role of Immunotherapy in Urologic Cancers

by Allison May, MD, Loren Roustio, BS & Zachary A Hamilton MD

Future studies regarding immunotherapy for these cancers will focus on treatment in the non-metastatic setting.



Allison May, MD, Loren Roustio, BS, and Zachary A Hamilton, MD, (above), are in the Division of Urology, Department of Surgery, Saint Louis University School of Medicine, St. Louis, Missouri.
Contact: zachary.hamilton@health.slu.edu

Abstract

In recent decades, there has been significant growth in the understanding of the immune system and its role in cancer. The recent introduction of checkpoint inhibitors has drastically changed the treatment landscape of cancer as a whole. In this review, we discuss the major clinical developments of immunotherapy in urologic specific cancers, as well as address future directions in this field.

Introduction

The immune system plays a vital role in cancer prevention and defense. Over the past several decades, immunotherapy has emerged as a treatment option in various urologic malignancies. Recent advances in immunotherapy promise to change the field of urologic oncology substantially. In this review, we aim to summarize the use of immunotherapies for treatment of urothelial, kidney, and prostate cancer.

The roots of immunotherapy in urologic cancers began with the introduction of Bacillus Calmette-Gueren (BCG) for superficial bladder cancer by Morales and colleagues in 1976.[1] This was followed in the 1990s by the introduction of cytokines, such as interferon and IL-2, for metastatic renal cell carcinoma (RCC). The treatment of prostate cancer joined the field of immunotherapy in 2010 with the approval of the autologous cancer vaccine, sipuleucel-T. In more recent years, checkpoint inhibitors have been introduced with dramatic results for urology specific malignancies.

It is helpful to briefly summarize the relationship between the immune system and cancer cells. The immune system constantly scans the body to detect sites of infection and potential cancer cells. In order to prevent erroneous attack on normal cells, the immune system utilizes a series of cellular interactions. T-cell activation requires the engagement of the T-cell receptor (TCR) with the major histocompatibility complex (MHC) on the antigen presenting cell or tumor cell. Activation also requires co-stimulatory signals, namely binding of CD28 on the T-cell with a B7 protein on the antigen presenting cell. At the same time, there are multiple co-inhibitory signals that may take place. Two of the most studied include the cytotoxic T-lymphocyte associated antigen-4 (CTLA-4) and programmed death 1 (PD-1) pathways, also known as "checkpoints". CTLA-4 is a protein on T-cells that can take the place of CD28 and bind B7, thus resulting in T-cell inhibition. PD-1 is a protein on the T-cell which can bind with programmed death ligand 1 (PD-L1) on tumor or normal cells, leading to down regulation of the T-cell

Table 1. Comparison of results of trials for checkpoint inhibitors in metastatic UCC following platinum based chemotherapy.

Trial	Immunotherapy	ORR
NCT01375842	atezolizumab	11-43%*
IMvigor210	atezolizumab	15%
IMvigor211	atezolizumab	62%
JAVELIN	avelumab	16%
NCT01693562	darvalumab	17%
CheckMate 032	nivolumab	24%
CheckMate 275	nivolumab	16 – 28% *
KEYNOTE-012	pembrolizumab	26%
KEYNOTE-045	pembrolizumab	21%

*range based on range of PD-L1 expression

response. These co-inhibitory signals serve as checkpoints to prevent immune attack on normal cells. Cancers avoid attack by taking advantage of these cellular interactions to essentially mask themselves and remain undetected. Checkpoint inhibitors work by preventing these regulatory cellular interactions, thus unmasking the cancer cells.

Urothelial Cancer

Of all urologic malignancies, urothelial cell carcinoma (UCC) of the bladder and upper tracts has arguably been the most impacted by immunotherapy. The development of BCG for bladder cancer in the 1970s remains a standard of care for treatment of high risk, non-invasive disease in the modern era.[2] In the past several years, checkpoint inhibitors have found notable success in metastatic UCC. Several checkpoint inhibitors are now approved for two main areas of use: in metastatic UCC following standard platinum based chemotherapy, and in metastatic UCC for those deemed 'unfit' for traditional chemotherapy.

Checkpoint Inhibitors in Metastatic Urothelial Cancer Following Platinum-Based Chemotherapy

Five drugs are currently FDA approved for use in patients with metastatic UCC and progression following platinum based chemotherapy. These include the PD-L1 inhibitors, atezolizumab, avelumab, and durvalumab as well as PD-1 inhibitors nivolumab, and pembrolizumab (Table 1).

Atezolizumab, a PD-L1 inhibitor, was the first checkpoint inhibitor approved in bladder cancer. A phase I trial of 68 patients with previously treated advanced bladder cancer demonstrated an objective response rate (ORR) for atezolizumab of 11% to 43%.[3] Response was highest in patients with high PD-L1 expression (≥5% PD-L1 expression). These results lead to the phase II IMvigor210 trial in which 316 patients with metastatic UCC who had progressed after chemotherapy were treated with atezolizumab.[4] The ORR was 15% overall, compared to 10% in historical controls of alternative chemotherapy regimens, and better response was noted with increasing PD-L1 expression. This led to FDA approval and was later followed by the IMvigor211 phase III study which looked at a similar population of patients with metastatic UCC, including both bladder and upper tract, that had failed traditional platinum based chemotherapy.[5] Patients were randomized to treatment with atezolizumab versus treatment with physician's choice of alternative chemotherapy (paclitaxel, docetaxel, or vinflunine). Overall survival (OS), ORR, and progression free survival (PFS) were not significantly different between the groups, however atezolizumab had an improved safety profile compared to chemotherapy.

Two other PD-L1 inhibitors, avelumab and darvalumab, are FDA approved. Approval for avelumab was based on the UCC cohort of the single-arm, open-label JAVELIN Solid Tumor trial.[6] ORR was 13.3% among 226 patients that were followed for at least 13 weeks and 16.1% for 161 patients that were followed for at least six months. This included an impressive 5.6% complete response rate in the six-month follow up cohort. Traditionally, the ORR rate was poor for alternative chemotherapy regimens and alternative chemotherapy was given for palliation alone, thus a complete response for this patient population garnered considerable excitement amongst clinicians. Interestingly, there was no association found between PD-L1 expression and response. In a similar fashion, darvalumab was approved based on the single-arm phase I/II study 1108.[7] 182 patients were included with an ORR of 17%. Higher PD-L1 expression was associated with better ORR (27.6% in PD-L1 high patients and 5.1% in PD-L1 low or negative).

Table 2. Comparison of results of trials for checkpoint inhibitors in metastatic UCC prior to platinum based chemotherapy.

Trial	Immunotherapy	ORR
IMvigor210	atezolizumab	23%
KEYNOTE-052	pembrolizumab	24%

Table 3. Comparison of results of trials for checkpoint inhibitors in advanced or metastatic RCC

Trial	Immunotherapy	ORR
CheckMate 025	nivolumab	25%
CheckMate 214	nivolumab + ipilimumab	42%
KEYNOTE-426	Pembrolizumab + axitinib	55.2%
JAVELIN Renal 101	Avelumab + axitinib	30 – 68%*

*range based on range of PD-L1 expression

The PD-1 antibody, nivolumab, was approved following the CheckMate 032 and 275 trials for use as second line therapy in metastatic UCC following progression on platinum based therapy. CheckMate 032 was a phase I/II single-arm study which showed an ORR of 24.4% in this patient population.[8] Response rate was not associated with PD-L1 expression, however median OS was higher in patients with high PD-L1 expression. CheckMate 275 was a phase II single-arm study evaluating nivolumab in a similar population and found an ORR of 19%.[9] Furthermore, when stratified by PD-L1 expression the ORR was 28.4% with PD-L1 expression of ≥5%, 23.8% with expression of ≥1%, and 16.1% when expression was <1%.

Another PD-1 antibody, pembrolizumab, achieved FDA approval following the KEYNOTE-012 and KEYNOTE-045 studies. KEYNOTE-012 was a phase Ib study including only patients with ≥1% PD-L1 expression.[10] ORR was 26% in this study. KEYNOTE-045 was a phase III trial comparing pembrolizumab with physician's choice chemotherapy.[11] Improved OS of 10.3 months was found for pembrolizumab compared to 7.4 months for chemotherapy, and the ORR was 21% for pembrolizumab group compared to 11% for chemotherapy. OS was higher for patients with higher PD-L1 expression.

In summary, the use of checkpoint inhibitors for metastatic UCC that has failed traditional platinum based chemotherapy has shown exciting responses when targeting the PD-L/PD-L1 pathway. Most of the five approved therapies show an ORR of ~20% and correlate response with degree of PD-L1 staining. Historically, there was no standard therapy for patients that failed platinum based chemotherapy; however, checkpoint inhibitors are quickly becoming the standard of care in this setting.

Checkpoint Inhibitors in Metastatic Urothelial Cancer Prior to Platinum-Based Chemotherapy

Checkpoint inhibitors have also been investigated with metastatic UCC that has not received traditional platinum based treatment (Table 2). Atezolizumab was studied in a cohort of the IMvigor210 trial, including patients with metastatic UCC who were ineligible for platinum therapy, with an ORR was 23%.[12] IMVigor130 is an ongoing phase III trial studying treatment naïve patients, including platinum eligible patients. Initial results revealed worsened OS for patients with low PD-L1 expression (<5%) treated with atezolizumab as compared to platinum based therapy.[13] Thus, the FDA has limited use of checkpoint inhibitors as first line therapy only to patients who are ineligible for cisplatin with PD-L1 expression ≥5% or those who are ineligible for any platinum therapy.

Pembrolizumab was studied in the KEYNOTE-052 trial as first line therapy in platinum ineligible patients.[14] ORR was 24% and was higher in those with increased PD-L1 expression. Additionally, the KEYNOTE-361 trial is evaluating pembrolizumab versus pembrolizumab in combination with platinum based chemotherapy versus chemotherapy alone. Similar to atezolizumab, OS was worse compared to chemotherapy for patients with low PD-L1 expression and thus pembrolizumab is only approved for platinum ineligible patients or cisplatin ineligible with higher PD-L1 staining.

Future Directions in Urothelial Cancer

While bladder cancer has been one of the most responsive tumors to checkpoint inhibitors, only 20-25% of patients treated respond overall in this advanced stage of disease. Thus, trials are underway to investigate use of multiple immunotherapies in combination or combined with chemotherapy in hopes of increasing response rates. Studies are also underway to investigate checkpoint inhibitor use in the non-metastatic setting after primary surgical treatment. In addition, while higher PD-L1 expression tends to favor a response to therapy, patients with minimal PD-L1 expression may still respond. Further research in this area remains ongoing.

Table 4. Comparison of results of trials for checkpoint inhibitors in metastatic prostate cancer.

Trial	Immunotherapy	OS (months)
IMPACT	Sipuleucel-T	4.1
KEYNOTE-028	pembrolizumab	8.0
CA184-043	ipilimumab	6.5 – 22.7 *
CA184-095	ipilimumab	28.7
CheckMate 650	Nivolumab + ipilimumab	*Accumulating*

*range based on high to low risk factors

Kidney Cancer

Most kidney tumors are resistant to traditional chemotherapy,[15] thus, investigation into alternate therapies for advanced tumors has been well studied in renal cell carcinoma (RCC). The first drug approved for treatment of metastatic RCC (mRCC) was the cytokine interleukin-2. This immunotherapy achieved complete response in a small number of very well-selected patients with minimal comorbidity and limited metastatic burden,[16] however due to its low overall efficacy and severe side effect profile, it has been mostly abandoned. Anti-angiogenic drugs have been developed and widely used, including tyrosine kinase inhibitors such as sunitinib. These targeted agents improve survival, but they have not achieved the complete responses that were historically seen with cytokines. In the past decade, interest towards immunotherapy has surged for RCC, and several checkpoint inhibitors have been approved for advanced or metastatic disease (Table 3).

Checkpoint Inhibitors in Renal Cell Carcinoma

Nivolumab was the first checkpoint inhibitor approved in kidney cancer. The CheckMate 025 phase III trial compared nivolumab to everolimus in 821 patients with locally advanced or mRCC who had progressed on other therapy.[17] Median OS for nivolumab was 25 months compared to 19.6 months. Interestingly, the improvement in OS was seen regardless of PD-L1 expression in staining. ORR was also higher for nivolumab at 25% versus 5%. Subsequent quality of life assessments noted a change from baseline improved in the nivolumab group which suggested an improvement in quality of life with treatment. This study led to the FDA approval of nivolumab in November 2015 for use in patients with RCC who had previously progressed on one or two regimens of antiangiogenic therapy.

Combination therapies have also been investigated. The IMmotion 150 trial is a phase II trial of 305 patients with advanced or mRCC, randomized to atezolizumab, atezolizumab with bevacizumab, or sunitinib.[18] Patients treated with the combination had improved PFS of 6.1 months compared to either agent alone. This study highlighted the promise of combination immunotherapy in the mRCC setting.

The CheckMate 214 trial assessed the combination use of two checkpoint inhibitors, nivolumab and ipilimumab, as compared to sunitinib.[19] This phase III trial included 1096 patients with advanced or mRCC. Just under half of these patients had poor or intermediate risk disease and all patients had no prior treatment. OS was not reached in the treatment group compared to 28 months for sunitinib and ORR was 42% versus 27% respectively. Those with >1% PD-L1 expression had improved PFS in the treatment arm of 22.8 months versus 5.9 months, as well as improved ORR of 58% versus 22%. Of note, when analysis was done looking at the favorable risk group alone, outcomes were better in the sunitinib group, suggesting the immunotherapy modulated response for mRCC was most significant with more advanced disease. The FDA has now approved nivolumab with ipilimumab in previously untreated advanced RCC with poor or intermediate risk disease.

Additional combination trials have shown benefit for mRCC. The KEYNOTE-426 trial randomized 861 patients with previously untreated advanced RCC to pembrolizumab with axitinib versus sunitinib alone.[20] OS was improved in the pembrolizumab/axitinib arm with 12 month OS of 90% compared to 78%. Median PFS was also improved at 15.1 months versus 11.1 months. This led to FDA approval of pembrolizumab in combination with axitinib in advanced, previously untreated RCC. Similarly, the JAVELIN Renal 101 trial randomized 886 patients with untreated advanced RCC to avelumab with axitinib or sunitinib alone.[21] Improved PFS was noted in the avelumab group of 13.8 months compared to 8.4 months. This led to FDA approval of avelumab with axitinib in advanced untreated RCC.

Future Directions in Kidney Cancer

Due to the success of checkpoint inhibition for mRCC, particularly with combination therapy, future developments are focused on neoadjuvant treatment for locally advanced disease. The phase III PROSPER trial is underway in which investigators are looking at the use of nivolumab for patients with localized renal masses, who

will be randomized to standard of care surgical therapy versus nivolumab prior to surgery and then continued adjuvantly. All in all, the use of immunotherapy has led to significant advancements for mRCC with promising use of combination therapy.

Prostate Cancer

The main area of study for immunotherapy in prostate malignancy is with metastatic castrate resistant prostate cancer (mCRPC). Men who develop metastatic disease will eventually progress to castrate resistant disease and fail traditional therapies. At this stage, their disease often becomes lethal with a median OS of 12 months from the time of castrate resistance.[22] Newer therapies have improved survival to an extent, but immunotherapy offers the potential for novel targets in this patient population (Table 4).

Sipuleucel-T was the first, and still the only, immunotherapy approved for prostate cancer and is marketed as a personalized vaccine against prostate cancer. A patient's blood is collected and transferred to an outside facility where antigen presenting cells are harvested from the sample and incubated with sipuleucel-T. The sipuleucel-T is thought to stimulate a T-cell modulated response against prostatic acid phosphatase. The sample can then be infused back into the patient for treatment response.[23] In men with asymptomatic or minimally symptomatic mCRPC, an improvement in OS of 4.1 months was shown in the IMPACT trial.[24] However, due in part to high costs and logistics of infusions, the use remains limited. Additionally, there was a lack of associated PSA response to treatment, making it difficult to determine patient response to therapy. Ongoing trials are examining the use of sipuleucel-T with other immunomodulating agents in a combination fashion, as well as introducing this immunotherapy to men on active surveillance for low risk non-metastatic disease.[25, 26]

PD-1 checkpoint inhibitors have been investigated in prostate cancer, however results to date have not been particularly impressive. A multicenter phase I trial looked at safety and efficacy of Nivolumab in multiple cancers, including advanced prostate cancer.[27] Seventeen men with mCRPR were enrolled and no survival benefit was seen. When tumors from these patients were stained for PD-L1, all were negative. In fact, PD-L1 staining in prostate tumors in general has been shown to be low.[27, 28] The phase Ib KEYNOTE-028 trial evaluated 245 men with mCRPC and included only the 35 who had positive PD-L1 staining ($\geq$ 1%).[29] Twenty-three of these men were treated with pembrolizumab. The ORR was 17% (four patients) and there were no complete responses. Stable disease was achieved in 35%. Median OS for the whole group was eight months and for the patients that responded to therapy was 13 months. Due to the low level of PD-L1 staining and minimal objective response, PD-L checkpoint inhibitors have not yet found a role for prostate cancer.

Two phase III studies investigated the treatment of prostate cancer with ipilimumab, a checkpoint inhibitor of the CTLA-4 pathway. The CA184-043 trial randomized 799 men who had progressed after docetaxel therapy and had undergone bone directed radiotherapy to ipilimumab or placebo.[30] There was no difference in OS. Subset analysis demonstrated lower OS in the ipilimumab group for patients with poor prognostic factors including presence of visceral disease, older age, anemia, elevated alkaline phosphatase and elevated LDH. The CA184-095 trial randomized 598 patients with chemotherapy naïve metastatic prostate cancer with low disease burden to ipilimumab or placebo.[31] Ipilimumab demonstrated no survival benefit.

In an effort to amplify the small benefits seen with prostate cancer utilizing the PD-L1 and CTLA-4 pathways, the CheckMate 650 phase II trial was created for men with mCRPC evaluating the use of nivolumab combined with ipilimumab.[32] An ORR of 26% was achieved in the cohort of patients with no prior chemotherapy and 10% in the cohort with prior chemotherapy. PSA response rates were 18% and 10% respectively. An exploratory biomarker analysis showed a correlation of higher ORR in those with higher tumor mutational burden. Final data is still accumulating for this combination therapy.

In summary, checkpoint inhibitors have shown limited benefit in patients with metastatic prostate cancer, and the responses have not yet outperformed other novel therapies directed at androgen deprivation or androgen signaling pathways. More research is needed to develop genetic and biochemical markers that may identify which patients will respond to immunotherapy. Furthermore, the use of immunotherapy for non-metastatic disease remains unknown.

Conclusions

Historically, immunotherapy has played an important role in the treatment of urologic malignancies, while in the modern era the development of checkpoint inhibitors has been critical to urology. The introduction of checkpoint

inhibitors has changed the paradigm for treatment of urothelial and kidney cancer. Multiple checkpoint inhibitors are now approved for use in metastatic urothelial cancer following treatment with platinum based chemotherapy, or as frontline in patients not eligible for standard chemotherapy. Additionally, several checkpoint inhibitors are approved for treatment of advanced RCC and show impressive response when used in combination. On the contrary, prostate cancer has found some limited success in the immunotherapy realm with sipuleucel-T; yet, checkpoint inhibition has not yet found a defined treatment role. Future studies regarding immunotherapy for these cancers will focus on treatment in the non-metastatic setting.

References

1. Morales A, Eidinger D, Bruce AW. Intracavitary Bacillus Calmette-Guerin in the treatment of superficial bladder tumors. J Urol. 1976;116(2):180-183.
2. Gandhi N, Morales A, Lamm D. Bacillus Calmette-Guerin immunotherapy for genitourinary cancer. BJU Int. 2013;112(3):288–297.
3. Powles T, Eder JP, Fine GD, et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature. 2014;515:558-62.
4. Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: A single-arm, multicentre, phase 2 trial. Lancet 2016;387(10031):1909-1920.
5. Powles T, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2018;391:748-757.
6. Patel MR, et al. Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): pooled results from two expansion cohorts of an open-label, phase 1 trial. Lancet Oncol. 2018;19(1):51–64.
7. Powles T, O'Donnell PH, Massard C, et al. Efficacy and safety of durvalumab in locally advanced or metastatic urothelial carcinoma: updated results from a phase 1/2 open-label study. JAMA Oncol. 2017;3:e172411.
8. Sharma P, Callahan MK, Bono P, et al. Nivolumab monotherapy in recurrent metastatic urothelial carcinoma (CheckMate 032): a multicentre, open-label, two-stage, multi-arm, phase 1/2 trial. Lancet Oncol. 2016;17:1590-8.
9. Sharma P, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicenter, single-arm, phase 2 trial. Lancet Oncol. 2017 Mar;18(3):312-322.
10. Plimack ER, Bellmunt J, Gupta S, et al. Safety and activity of pembrolizumab in patients with locally advanced or metastatic urothelial cancer (KEYNOTE-012): a non-randomised, open-label, phase 1b study. Lancet Oncol. 2017;18:212-20.
11. Fradet Y, et al. Randomized phase III KEYNOTE-045 trial of pembrolizumab versus paclitaxel, docetaxel, or vinflunine in recurrent advanced urothelial cancer: results of >2 years of follow up. Ann Oncol. 2019 May.
12. Balar AV, Galsky MD, Rosenberg JE, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet. 2017;389:67-76.
13. E Grande, et al. IMvigor130: Efficacy and safety from a phase III study of atezolizumab (atezo) as monotherapy or combined with platinum-based chemotherapy (PBC) vs placebo + PBC in previously untreated locally advanced or metastatic urothelial carcinoma (mUC), Ann of Onc, 2019: 30;5
14. Balar AV, Castellano D, O'Donnell PH, et al. First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. Lancet Oncol. 2017;18:1483-92.
15. Rini BI, Campbell SC, Escudier B. Renal cell carcinoma. Lancet. 2009;373:1119–32.
16. Fyfe G, Fisher RI, Rosenberg SA, et al. Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. J Clin Oncol 1995; 13:688-696.
17. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015; 373:1803-1813.
18. McDermott DF, et al. Clinical activity and molecular correlates of response to atezolizumab alone or in combination with bevacizumab versus sunitinib in renal cell carcinoma. Nat Med. 2018 Jun;24(6):749-757.
19. Escudier B, Tannir NM, McDermott D, et al. CheckMate 214: efficacy and safety of nivolumab. ipilimumab (N.I) v sunitinib (S) for treatment-nai[Combining Diaeresis]ve advanced or metastatic renal cell carcinoma (mRCC), including IMDC risk and PD-L1 expression subgroups, Ann Oncol 2017; 28(Suppl 5):LBA5.
20. Rini B, et al. Pembrolizumbab plus axitinib versus sunitinib for advanced renal cell carcinoma. N Engl J Med 2019;380:1116-1127.
21. Motzer R, et al. Avelumab plus axitinib versus sunitinib for advanced renal cell carcinoma. N Engl J Med 2019;380:1103-1115.
22. National Institute for Health and Clinical Excellence. Docetaxel for the treatment of hormone-refractory metastatic prostate cancer. NICE, London, UK (2009).
23. Anassi E, Ndefo UA. Sipuleucel-T. (provenge) injection: the first immunotherapy agent. (vaccine) for hormone-refractory prostate cancer. P T. (2011) 36:197–202.
24. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411-22.
25. Scholz M, Yep S, Chancey M, Kelly C, Chau K, Turner J, et al. Phase I clinical trial of sipuleucel-T combined with escalating doses of ipilimumab in progressive metastatic castrate-resistant prostate cancer. ImmunoTargets Ther. 2017;6:11–16.
26. ClinicalTrials.gov. National Library of Medicine (U.S.). (Sep 2018 -) Open label trial of sipuleucel-T administered to active surveillance patients for newly diagnosed prostate cancer (ProVent). NCT03686683.
27. S.L. Topalian, F.S. Hodi, J.R. Brahmer, et al.Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med, 366 (2012), pp. 2443-2454
28. K.S. Sfanos, T.C. Bruno, A.K. Meeker, A.M. De Marzo, W.B. Isaacs, C.G. DrakeHuman prostate-infiltrating CD8+ T lymphocytes are oligoclonal and PD-1+. Prostate, 69 (2009), pp. 1694-1703
29. Alley E, et al. Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028): preliminary results from a non-randomized, open-label, phase 1b trial. Lancet Oncol. 2017:18(5):623-630.
30. Kwon ED, Drake CG, Scher HI, et al. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): A multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol. 2014;15(7):700-712.
31. Beer TM, Kwon ED, Drake CG, et al. Randomized, double-blind, phase III trial of ipilimumab versus placebo in asymptomatic or minimally symptomatic patients with metastatic chemotherapy-naïve castration-resistant prostate cancer. J Clin Oncol. 2017;35:40-47.
32. Sharma P, Pachynski R, Narayan V, et al. Initial results from a phase II study of nivolumab (NIVO) plus ipilimumab (IPI) for the treatment of metastatic castration-resistant prostate cancer (mCRPC; CheckMate 650) [ASCO GU abstract 142]. J Clin Oncol. 2019;37(suppl 7S).

Disclosure

None reported.

MM

Screening for Breast Cancer: What You Need to Know

by Kaitlin Farrell, MD, Debbie Lee Bennett, MD & Theresa L. Schwartz, MD

Breast cancer risk assessment offers health care providers the opportunity to identify healthy women who are at a higher than average risk of breast cancer development and individualize their screening regimen accordingly.



Kaitlin Farrell, MD, is Assistant Professor of Surgery, Debbie Lee Bennett, MD, is Associate Professor of Radiology, and Theresa L. Schwartz, MD, MS, FACS, (above), is Associate Professor of Surgery, all at the Saint Louis University School of Medicine, St. Louis, Missouri.
Contact: theresa.schwartz@health.slu.edu

Abstract

Significant controversy surrounds current recommendations for breast cancer screening. This has resulted in wide variation among national organizations in breast cancer screening guidelines. With the expanding field of breast imaging techniques, risk assessment and genetic testing, it has become clear that the recommendations for breast cancer screening need to be individualized in order to maximize the benefit and minimize harms of screening.

Introduction

The purpose of breast cancer screening is to detect a malignancy at its earliest stage with the intent to decrease disease-related mortality. Randomized breast cancer screening trials have demonstrated a 15% reduction in breast cancer mortality with the routine use of screening mammography in women aged 40 to 74 years,[1] with the same 15% reduction expected from screening in women aged 39 to 69 years described by the U.S. Preventive Services Task Force in both 2009 and 2016.[2-4] A meta-analysis of 8 randomized controlled trials showed screening mammography to have a 24% mortality reduction.[5] Due to the well documented risks of screening mammography, including false positives, false negatives, and over-diagnosis, both the age at which to start screening and the interval in which imaging should be performed has been questioned. At the same time, supplemental screening modalities have been introduced to improve breast cancer detection, without clear guidelines on which patients should be screened with these additional tests. This has led to a tremendous variation in recommendations, leaving patients, primary care providers (PCP) and ob/gyn specialists in a state of confusion.

Risk Assessment

In order to have an informed discussion with our patients regarding appropriate breast cancer screening, it is essential to assess their lifetime risk of breast cancer development. Known risk factors for breast cancer include a family history of breast cancer, a personal history of mantle irradiation between the ages of 10 and 30,[6-7] personal history of atypical hyperplasia or locular carcinoma *in situ*, early menarche (<12), late menopause (>55), nulliparity or age at first childbirth >30, hormone replacement therapy with combination estrogen and progesterone, high alcohol intake (>1 drink/day), obesity,[8-9] and dense breast tissue on mammography.[10]

Ideally, a risk assessment should be performed on every woman starting between the ages of 25 and 30 years by a health care professional. In otherwise healthy women, this would generally be done during a yearly physical with her PCP or well-woman exam with her gynecologist. As there can be changes to family history as well as personal

health information from year to year, this risk assessment and subsequent screening recommendations should be updated annually. The general population risk of breast cancer development is estimated to be 12%. If a patient's lifetime risk of breast cancer is calculated to be >20%, she would be considered at high risk.

Multiple computer-based models are readily available to assess risk of breast cancer development based on many of the above factors. While there are other similar validated risk assessment programs, there is prospective data suggesting that the current Tyrer-Cuzick model is the most consistently accurate.[11-12] It includes personal patient information (BMI, age at menarche, age at menopause, parity, history of previous breast biopsies, breast density) in addition to family history of malignancies and family history of genetic predispositions to malignancy. It can be downloaded at http://www.ems-trials.org/riskevaluator/. It should be noted that all risk assessment models have significant limitations in all minority populations.

In patients with a significant family history of malignancy or a family history of a genetic predisposition to malignancy, her eligibility for genetic testing should be considered. The criteria for genetic testing have expanded greatly and can be found at https://www2.tri-kobe.org/nccn/guideline/gynecological/english/genetic_familial.pdf. A genetic predisposition is identified in up to 10% of breast cancers diagnosed in the United States,[11] and 50% of these will be either BRCA1 or BRCA2.[12] These two mutations confer the highest lifetime risk of breast cancer development, at 50-85% and 45% respectively.

Breast Density

Breast density refers to the amount of glandular tissue that is seen on mammography. Breast density is divided into 4 categories: almost entirely fatty, scattered fibroglandular densities, heterogeneously dense and extremely dense. Having increased breast density (heterogeneously or extremely dense) is an independent risk factor for breast cancer development and decreases the sensitivity of screening mammograms.[13] Reporting the category of breast density is now a required component of mammography reports in most states. While nearly 50% of women over age 40 are found to have dense breast tissue on mammogram, this notification of level of breast density should be taken as an opportunity to open a line of communication between the patient and her PCP regarding breast awareness. Combining breast density found on mammogram with the patient's other personal risk factors and family history will allow an appropriate risk assessment to be performed and subsequent screening recommendations established.

Breast Imaging Modalities for Screening

Digital mammography is considered the gold standard for breast cancer screening. This has an estimated sensitivity of 78% and specificity of 99%.[16] The sensitivity and specificity decreases, however, with increasing breast density to 70% and 91%, respectively, in women with heterogeneously dense or extremely dense breasts.[17] Digital breast tomosynthesis (DBT), more commonly known as 3-D mammography, permits individual planes of the breast to be visualized while simultaneously reducing the impact of overlapping or superimposed tissue.[18] The addition of DBT has been shown to increase cancer detection rates in women with breast density described as scattered fibroglandular densities or heterogeneously dense, but not in women with almost entirely fatty breasts or extremely dense breasts. DBT was found to decrease recall rates in women in all breast density categories.[19] While there was initially concern over the amount of radiation exposure associated with DBT, the most current units have begun reconstructing synthetic 2D images from the tomosynthesis image dataset to reduce the radiation dose by 50%, ultimately matching the dose delivered by standard 2D digital mammography alone.[20]

Breast MRI, as a screening tool in higher risk women, has a higher sensitivity than either mammography or ultrasound.[21] Although its specificity is quite variable, its implementation in high risk patients increases the cancer detection rate significantly and more patients are diagnosed with smaller tumors than with mammography or ultrasound.[22]

Whole breast ultrasound has been shown to increase the incremental cancer detection rates in women at higher risk. Prospective data has demonstrated an additional 4.2 detected cancers per 1,000 women deemed to be at a higher than average risk for breast cancer who underwent supplemental physician-performed screening. Screening with automated whole breast ultrasound in women of all risk categories results in an additional 1.9 cancers detected per 1,000 women.[23] While breast MRI is more sensitive than either mammography or ultrasound in women at higher risk, whole breast ultrasound could be used in those settings where breast MRI can not be performed (i.e. cost prohibitive, anxiety/claustrophobia, pregnancy, renal failure, gadolinium allergy).

Women at Average Risk of Breast Cancer

While there are multiple competing guidelines for breast cancer screening, updated reports from the Cancer Intervention and Surveillance Modeling Network (CISNET) models comparing the differing recommendations have demonstrated the greatest mortality reduction is achieved

with annual screening mammograms starting at age 40.[24] For this reason, the American College of Radiology, the Society of Breast Imaging, the American Society of Breast Surgeons and the National Comprehensive Cancer Network agree that women with an average risk of breast cancer should begin yearly screening mammograms at age 40 and continue annual imaging until life expectancy is less than 10 years.

Women at Intermediate (15-19%) Risk of Breast Cancer

Women at an intermediate risk of breast cancer development who are found to have heterogeneously dense or extremely dense breast tissue on mammogram may also benefit from supplemental screening with yearly whole breast ultrasound. Supplemental ultrasound screening has been demonstrated to lead to incremental cancer detection increases of 3-4 per 1,000 women. However, adding ultrasound after a negative mammogram was shown to increase the false-positive rate and benign biopsies, resulting in a decreased screening positive predictive value.[25] An informed discussion regarding the expected benefit (increased cancer detection rate) as well as the potential risks (higher false positive rate) of ultrasound should be held between the patient and her PCP or other health care provider prior to initiation of supplemental imaging.

Women at Higher-than-Average Risk of Breast Cancer

Women with a greater than 20% lifetime risk of breast cancer are deemed to be at higher-than-average risk. As outlined above, this risk can be estimated either based on a genetic predisposition to malignancy, a history of chest irradiation between ages 10 and 30 and/or computer models according to personal and family history. According to the NCCN guidelines,[26] recommendations from the American College of Radiology[27] and the American Society of Breast Surgeons Position Statement[28] released in April 2019, women deemed to be at higher risk should begin yearly mammography (3D modality preferred) no sooner than age 30 and also consider supplemental screening with yearly breast MRI no sooner than age 25.

Final Thoughts

There are risks and benefits to breast cancer screening, just as there are with any other screening modality or intervention. In order to determine the appropriate imaging strategy, including both the type of imaging to perform as well as the interval in which to have it performed, each patient should undergo a risk assessment. Breast cancer risk assessment offers health care providers the opportunity to identify healthy women who are at a higher than average risk of breast cancer development and individualize their screening regimen accordingly. This is also an excellent platform to encourage lifestyle changes to decrease their risk of breast cancer and improve their overall health.

References

1. Berry DA et al. Cancer interventions and surveillance modeling network (CISNET) Collaborators. Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med. 2005;353(17):1784-92.
2. U.S. Preventive Services Task Force. Screening for breast cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med. 2009;151:716-26.
3. Nelson HD et al. Screening for breast cancer: an update for the U.S. Preventive Services Task Force. Ann Intern Med. 2009;151:738-47.
4. Nelson HD et al. Effectiveness of breast cancer screening: systematic review and meta-analysis to update the 2009 U.S. Preventive Services Task Force Recommendation. Ann Intern Med. 2016;164:244-55.
5. Duffy SW et al. The mammographic screening trials: commentary on the recent work by Olsen and Gotzsche. Cancer J Clin. 2002;52(2):68-71.
6. Bhatia S et al. High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkins Disease: report from the late effects study group. JCO. 2003;21(23):4386-94.
7. Kenney LB et al. Breast cancer after childhood cancer: a report from the childhood cancer survivor study. Ann Intern Med. 2004;141(8):590-7.
8. Singletary SE. Rating the risk factors for breast cancer. Ann Surg. 2003;237(4):474-82.
9. McDonald JA et al. Alcohol intake and breast cancer risk: weighing the overall evidence. Curr Breast Cancer Rep. 2013;5(3). doi: 10.1007/s12609-013-0114-z.
10. Boyd NF et al. Mammographic density and the risk and detection of breast cancer. N Engl J Med. 2007;356:227-36.
11. Amir E et al. Evaluation of breast cancer risk assessment packages in the family history evaluation and screening programme. J Med Genet. 2003;40(11):807-14.
12. Terry MB et al. 10-year performance of four models of breast cancer risk: a validation study. Lancet Oncol. 2019;20(4):504-27.
13. The Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. Nature. 2012;490:61-70.
14. Castera L et al. Next-generation sequencing for the diagnosis of hereditary breast and ovarian cancer using genomic capture targeting multiple candidate genes. Eur J Hum Genetc.2014;22:1305-13.
15. Boyd NF et al. Mammographic density and breast cancer risk: current understanding and future prospects. Breast Cancer Res. 2011;13(6):223.
16. Kolb TM et al. Comparison of the performance of screening mammography, physical examination and breast us and evaluation of factors that influence them: an analysis of 27,825 patient evaluations. Radiology. 2002;225(1):165-75.
17. Pisano ED et al. Diagnostic performance of digital versus film mammography for breast-cancer screening. N Engl J Med. 2005;353:1773-83.
18. Niklason LT et al. Digital tomosynthesis in breast imaging. Radiology. 1997;205(2):399-406.
19. Rafferty EA et al. Breast cancer screening using tomosynthesis and digital mammography in dense and nondense breasts. JAMA. 2016;315(16):1784-86.
20. Simon K et al. Accuracy of synthetic 2D mammography compared with conventional 2D digital mammography obtained with 3D tomosynthesis. AJR. 2019;212(6):1406-11.
21. Kuhl CK et al. Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer. J Clin Oncol. 2005;23(33):8469-76.
22. Saadatmand S et al. MRI versus mammography for breast cancer screening in women with familial risk (FaMRIsc): a multicentre, randomised, controlled trial. Lancet Oncol. 2019;20(8):1136-47.
23. Brem RF et al. Assessing improvement in detection of breast cancer with three-dimensional automated breast ultrasound in women with dense breast tissue: the SomoInsight study. Radiology. 2014;17
24. Arleo EK et al. Comparison of recommendations for screening mammography using CISNET models. Cancer. 2017;123(19):3673-80.
25. Berg WA et al. Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. JAMA. 2008;299(18):2151-63.
26. National Comprehensive Cancer Network. Breast Cancer Screening and Diagnosis. Version 1.2019. https://www.nccn.org/professionals/physician_gls/pdf/breast-screening.pdf
27. Monticciolo DL et al. Breast cancer screening in women at higher-than-average risk: recommendations from the ACR. J Am Coll Radiol. 2018;15(3 Pt A):408-14.
28 American Society of Breast Surgeons Position Statement on Screening Mammography. April 2019. https://www.breastsurgeons.org/docs/statements/Position-Statement-on-Screening-Mammography.pdf.

Disclosure

None reported. **MM**

Plastic Surgery Innovation with 3D Printing for Craniomaxillofacial Operations

by Alexander Y. Lin, MD & Lauren M. Yarholar, MD

Our experience so far with patient-specific three-dimensional printing for surgery is that it can make surgeries faster, more accurate, and less invasive with smaller scars.



Alexander Y. Lin, MD, (above), and Lauren M. Yarholar, MD are in the Division of Plastic Surgery, Department of Surgery, Saint Louis University School of Medicine, St. Louis, Missouri and at SSM Health Cardinal Glennon Children's Hospital, St. Louis, Missouri.
Contact: Alexander.Lin@Health.SLU.edu

Abstract

Plastic Surgery restores unique human qualities such as appearance, speech (palate), hands, to improve interaction with others and quality of life. Three-dimensional printing technology can be applied to Plastic Surgery craniomaxillofacial operations to change the bony skeleton of the skull, face, and jaws. Three-dimensional printing for patient-specific applications have four types: Type I contour models, Type II guides, Type III splints, Type IV implants. Plastic Surgery innovation in 3D printing clinical applications are described here and https://www.slucare.edu/newsroom/kmov-science-of-healing-faces-of-childhood.php.

Plastic Surgery and 3D Printing

The word "plastic" is derived from the Greek word for "shape", and consequently Plastic Surgery is "shape surgery" that improves quality of life. A principal example is in craniofacial anomalies, as one of the main functions of the face is to appear normal, so that an individual can interact with others. Similarly, although speech is not vital, in a patient with a cleft palate, speech can sound hypernasal and abnormal, which is stigmatizing and jeopardizes normal social interactions. Plastic Surgery can be understood as the field that deals with the functions that make us human: how we look, how we speak (cleft palate), and how we use our hands – these are the very features that allow us to communicate, a unique human function.[2] This is even more critical in Pediatric Plastic Surgery which deals with these unique human functions in children, as they are still developing socially and therefore the ability to communicate is essential. Plastic Surgery craniofacial surgery includes both the soft tissues of the ears, eyelids, nose, tongue, lips, and face – and also the bones of the craniomaxillofacial skeleton: skull, forehead, orbits, cheeks, maxilla, and mandible. These craniomaxillofacial operations are frequently practiced in the pediatric population, whose compact surgical anatomy can have higher risks that can benefit from the precision of medical three-dimensional printing. Plastic Surgery is an ideal surgical specialty to help define the role of 3D printing in surgery.

Three-dimensional printing (3DP) has increasing medical applications in education and planning, but its specific role in surgery has remained challenging to define. Our group recently published a systematic review in the journal *Plastic and Reconstructive Surgery*, which helps solve this problem through a taxonomic analysis of patient-specific 3D printed models that were used in craniomaxillofacial procedures.[1] This systematic review

Table 1. Applications for Patient-Specific 3DP in Craniomaxillofacial Operations

Type I. Contour model	Type II. Guides	Type III. Splints	Type IV. Implants
Cranial vault reconstruction	Craniosynostosis surgery	Nasal reconstruction	Jaw (orthognathic) surgery
Frontal sinus reconstruction	Midface osteotomies	Cleft lip-nose-palate	Intermaxillary Fixation: Arch bars, hybrid system, screws
Orbit reconstruction	Mandible resection and reconstruction	Dental occlusion	Prosthetics
Hypertelorism correction	Bilateral sagittal split osteotomy of mandible		Cranial defects
Midface reconstruction	Bilateral intraoral vertical ramus osteotomy		Orbital fracture repair
Mandible reconstruction	Hardware placement: plates and screws		Condylar head reconstruction
Fracture visualization	Cranioplasty		Mandibular reconstruction
	Dental implant placement		Facial fractures
	Ear reconstruction		Nasoalveolar Molding
			Prosthetic teeth base

analysis was unique in that it only included relevant patient-specific intraoperative applications of 3D-printed parts. Therefore, the results have clear translatable clinical applications to patient-specific surgeries.

The insights from this new classification of 3DP objects for surgery, have broad implications in all surgical and procedural methodologies involving 3DP, or additive manufacturing. This paper focuses on understanding the identified four types of 3D-printed objects that can be translated for surgical use, with an emphasis on Plastic Surgery craniofacial and maxillofacial operations, and its high clinical relevance to all potential procedures utilizing 3DP assistance.

Systematic Analysis Revealing Four 3DP Types

The investigation titled "A New Classification of Three-Dimensional Printing Technologies: Systematic Review of Three-Dimensional Printing for Patient-Specific Craniomaxillofacial Surgery"[1] systematically analyzed the current state of research by methodically identifying and extracting data from peer-reviewed journal articles for patient-specific 3DP intraoperative use, resulting in 314 unique papers. To keep the search exclusively focused on clinically relevant direct patient care applications of 3DP in surgery, we used strict inclusion and exclusion criteria that specifically required a physical patient-specific 3D-printed object that was actually used for direct surgical application. Generic models not specific to a patient's anatomy, or not used for surgery, were excluded.

We then concentrated on the specific clinical applications of craniomaxillofacial surgeries, resulting in 335 patients who had 3D-printed patient-specific data that was actually translated for use in surgery, with operations including those in Table 1. We analyzed these craniomaxillofacial operations to find patterns in the usage of 3DP for direct patient-specific surgical application, and discovered four main categories of utilizing 3DP for patient-specific craniomaxillofacial surgeries which they classified into four types:[1]

Our new classification of 3DP objects utilized in surgery proceeds logically, as each type is more complex than the previous type:

Type I Contour models are the most straightforward application of medical 3DP, printing out patient-specific anatomy available on a patient's imaging data, such as a computed tomography (CT) scan. Although fairly straightforward to 3D print, creative application elevates this simple engineering to versatile and useful applications intraoperatively.[3-12]

Type II Guides require more complex computer processing, as the negative space needs to be mathematically characterized so that a 3D-printed guide can conform to a surface such as a bony surface.[13-17] This requires precision of both the image processing, and the 3D printer itself.

Type III Splints require significantly more computing and engineering to be able to accurately perform virtual surgery to virtually cut the anatomy and move the pieces to the final position.[19-23]

Type IV Implants require the most computing, and materials science engineering, to be able to create biocompatible implants that are placed in the body usually indefinitely polyethylene.[7, 10, 17, 25] There are also regulatory hurdles for implantable materials in the human body.

Table 1 demonstrates the applications of 3DP in craniomaxillofacial surgery and with representative procedures applied in each of the four categories.

Benefits of the Four Types of 3DP Surgical Applications

The benefits of the four types of 3DP objects for surgical applications are increasing in scope. In Plastic Surgery, craniomaxillofacial operations have their foundations in bone reconstructive surgery that changes the overlying soft tissues, so they are an ideal application for surgical 3DP as current 3DP technology still most often uses solid printing material that simulates hard tissues very accurately. Therefore, craniomaxillofacial operations involve bone surgery (osteotomies, recontouring, plating), provide an excellent opportunity to detect and employ emerging 3DP technologies. Another significant benefit is that craniomaxillofacial surgeries usually require significant symmetry and functionality, both of which can be simulated and virtually modeled with advanced image processing and computer software. Plastic Surgery craniomaxillofacial surgeries frequently involves children with cleft-craniofacial-maxillofacial birth defects and therefore have an even greater stringent requirement of precision in the small pediatric anatomy.

One of the keys for the most benefit for all these types is to understand the concept of mirroring, to find normal tissue to mimic, in order to design the most accurate replica specific to the patient. This involves analyzing the contralateral side that is normal, and using computer software to take its mirror image, thus creating something close to what the ipsilateral anomaly should look like. The contralateral body is therefore being mirrored and then used as a template. This new mirrored piece can be 3D-printed for contour models, guides, splints, and implants. In a patient without a contralateral normal side, other methods are needed for estimating a normative, patient-specific anatomy. In our systematic review, we found that 62% of patients had the mirror technique applied to their 3DP surgical object,[1] making this a very common technique that has significant clinical applications.

Clinical Applications and Techniques of the Four 3DP Types

Our Plastic Surgery center has been utilizing 3D-printed patient-specific objects for patient-specific craniomaxillofacial surgeries for the past 19 years (since the year 2000), as of the writing of this article. These were done at high cost with commercial 3D printers. However, now we have brought 3DP in-house at our academic pediatric hospital since 2017, where we now have faster turn-around, immediate customization, and decreased individual case costs after original investment.

Our in-house 3DP center follows a similar workflow identified by Jacobs and Lin.[1] The most common imaging file we use for 3DP for patient-specific surgery is from the patient's CT scan. Typically, the CT scan is part of the standard of care by the primary treating medical team for diagnostic reasons, and our hospital's radiology department uses as low as possible dosages. In addition, some of our patients have other imaging modalities ordered by their primary treating medical team, including MRIs and ultrasounds, and we are actively testing different methods of utilizing this imaging data. The most common format for imaging is the DICOM format, which we can then utilize multiple commercial software to segmentalize the anatomic structures into the 3DP digital file, which is in the format known as STL. Segmentation can be tedious depending on the area of detail needed, the amount of interference or scatter, and the complexity of the anatomy to be delineated. For contour models, once the segmentalization is done, it is up to surgeon preference the area that has the greatest utilization to be 3D-printed, as the constraints of the print area may prevent the entire anatomic region from being printed as one piece. For guides, which harness the negative space, the software can be used to create a 3DP based on the negative space around an object that needs guidance on the entry or incision point, or the negative space of a defect that needs reconstruction. For splints, additional software is necessary that can perform virtual surgery and simulate cuts and movements on the CT data, to create a virtual final position that a 3DP splint can be printed to represent this final position. Finally for implants, at this point in time hospital-based 3DP hospital centers will not have the manufacturing facilities that can achieve the regulatory requirements of printing an object that can be placed in a human indefinitely, so most 3DP hospital centers will still depend on commercial medical 3DP companies for implants.

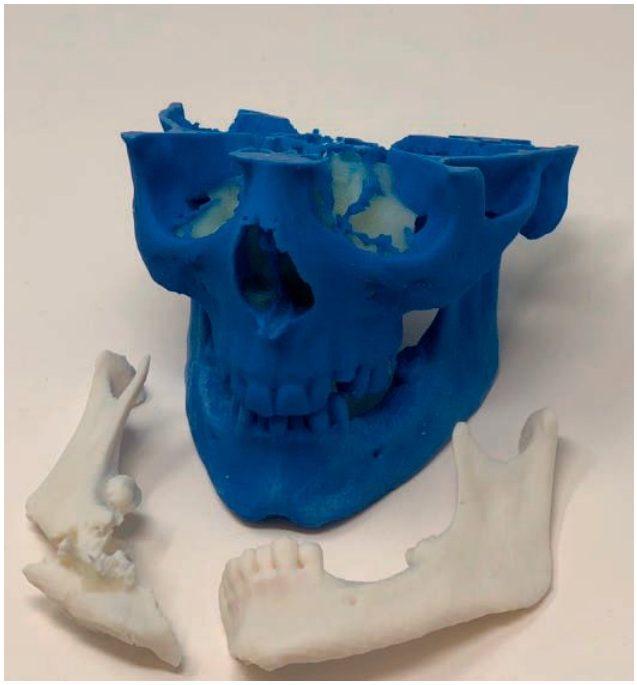
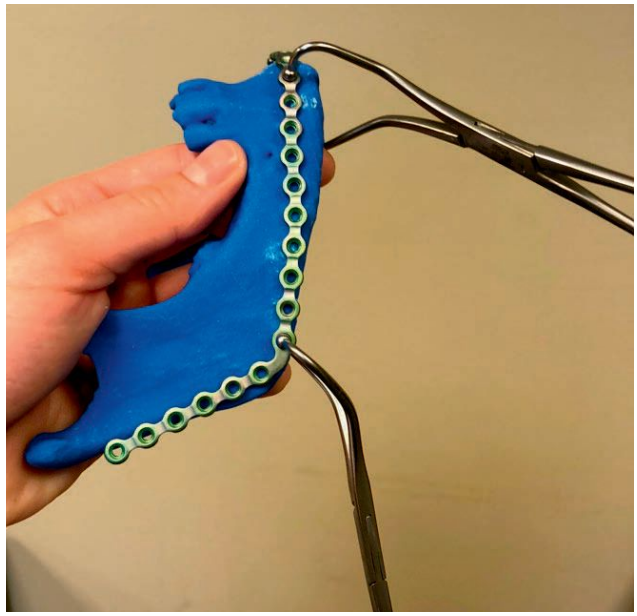
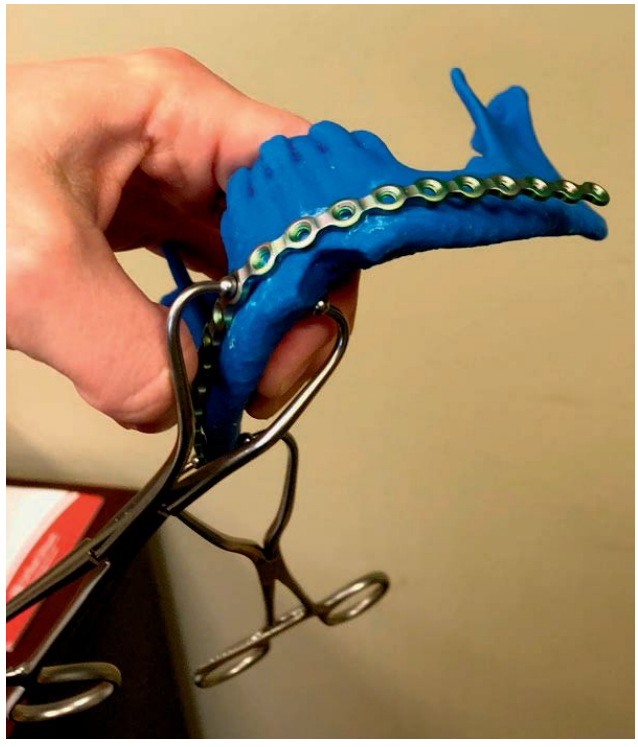


Figure 1. 3D-printed models from our in-house 3D-printer. The white mandible is the patient's injured mandible from the gunshot. The blue mandible was made by taking the less injured left side of the white mandible, and mirroring it to create a theoretically perfect mandible. This predicted preinjury mandible can be used as our contour model. The patient's maxilla is printed as the blue skull to demonstrate that the theoretical blue mandible's condyles were seated within the TMJ joints, indicating the blue mandible has normal functional size and shape.





Figures 2 and 3. These images demonstrate the reconstruction plate being pre-bent to the 3D-printed predicted preinjury model.

Finally, the choice of transferring this STL file to the printing software, is an important team decision with the engineering portion of the team. Careful consideration needs to be given to the type of material, the degree of resolution needed. Typically, the surgeon would prefer a sterilizable material to use the 3DP object intraoperatively, and this will limit the number of choices available. However, for procedures that are not sterile, or for presurgical simulations, a wider variety of materials can be used.

We will go through several typical Plastic Surgery craniofacial and maxillofacial surgeries utilizing this new classification of the four types of patient-specific 3DP objects for surgical application:

Type I. Contour model

Type I models are our most common models used in surgery. The technology is straightforward, and the segmentalization with an engineer and the surgeon is enough to isolate the structures that are needed for surgical visualization. As in-house 3DP becomes more affordable, these models can be utilized in almost any surgery where greater visualization is needed, precision is necessary for appropriate alignment, and where having an intraoperative model reveals hidden anatomy of the patient. This is especially useful in the pediatric population with their finer anatomy and limited incisions. A prime example for our

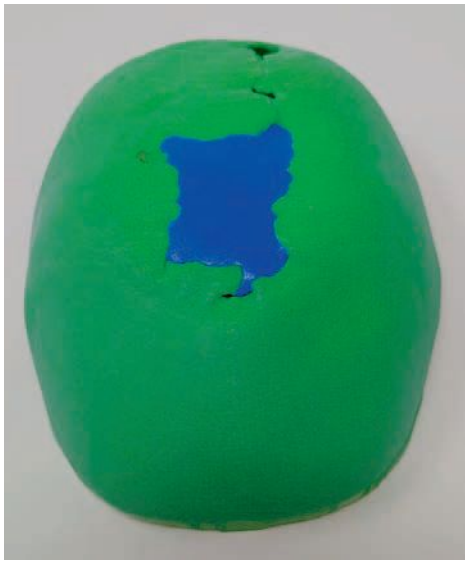




Figure 4. Left, aerial view of a patient's cranium with a significant skull defect, with the 3D-printed guide (blue) fitting perfectly in the cranial defect. This blue printed guide can be used during surgery to harvest a precisely shaped bone graft.

Figure 5. Right, posterior to anterior view of the cranium and cranial defects with a 3DP-guide in one of the two large cranial defects. A separate 3DP-guide was used for this second, distinct skull defect.

center is in facial fractures, as the visualization is difficult because incisions are small to avoid scars in the face, the reduction of the fragments needs to be precise, and the urgent nature of pediatric fractures (that can heal in the incorrect position more quickly than adult fractures due to faster nature of pediatric healing) demands the quicker turnaround that an in-house 3D printer can achieve.

Figures 1-3 demonstrate a patient with a severely comminuted mandible fracture from a gunshot wound. Our in-house 3D printer was used to print a patient-specific model of the mandible that could be used to pre-bend reconstruction plates. The pre-bent hardware was then sterilized and brought in the operating room to be used to internally fixate the mandible fracture. The 3D-printed mandible (white) in figure 1, is the patient's mandible after the gunshot injury – note the free-floating butterfly segment with multiple smaller fragments. Using our software, the uninjured image of the (left) side of the mandible was used to make a mirror image to replace the injured fractured (right) mandible. This theoretically perfect mandible can now have a titanium plate bent to match it before or during surgery (Figures 2-3), and intraoperatively the comminuted pieces can be screwed directly to the plate, resulting in faster and more precise repair of the mandible fracture.

Type II. Guide

Our most common application of guides is in pediatric craniofacial reconstruction, especially bone defects such as those found in skulls, orbits, zygomas. Once the image capture is performed, the DICOM file is converted to an STL file, and then software allows us to capture the negative space to make a guide. For example, in the clinical situation of a child with a skull defect (post-traumatic, post-reconstruction, post-congenital), these are usually irregular skull defects that take significant intraoperative time trying to find an area of skull to use as a donor site, and then fashioning an irregular donor to match the skull defect, then finding out it does not fit well and re-doing it – a time-consuming process. By printing a guide for the skull defect (the negative space representing the defect), we can use this elsewhere on the skull to quickly trace out a perfectly-shaped donor piece of bone, that matches the skull defect precisely. This saves time and bleeding morbidity on pediatric patients, which is important for improving outcomes in pediatric craniofacial surgery.

Figures 4 and 5 show a patient's skull with a large midline cranial skull defect. The skull and the guide were printed using our in-house 3D printer. The printed guide in the figure below (blue) sits perfectly in the cranial defect, demonstrating the precise dimensions of the printed guide. We print the guide by using a type of resin that can withstand deformation temperatures during the sterilization process. Figure 6 shows a complex fronto-orbital craniofacial defect, with a 3DP yellow guide that allows harvest of autologous bone that matches the patient's specific three-dimensional forehead-orbital contour. These guides are used real-time on the surgical field, to harvest a split-cranial bone graft of the exact shape needed, which saves time compared to the traditional method carving and checking until it fits.



Figure 6. Patient with complex fronto-orbital craniofacial defect, with a 3DP yellow guide that is used to harvest autologous bone graft. This yellow guide not only captures the unpredictable shape of the skull defect, but also captures the complex 3D angulation of the lateral aspects of the human forehead where it sweeps into the temple region. This yellow 3D guide allows harvest of bone that has this congruent angle, ensuring an autologous bone graft that matches the patient's specific forehead contour.

Type III. Splint

As in the systematic review study, one of the most common areas that we use splints is for jaw surgeries, especially orthognathic surgery to correct underbite or overbite.[18-24] This surgery is usually done when children reach skeletal maturity at about 16 to 18 years of age or older. Children born with cleft lips have the most severe form, as their midface contains the cleft disease and does not grow normally, leading to a midface that is much smaller than their mandible (lower jaw) – in other words a severe underbite. Before 3DP splints, custom splints would be fashioned by hand with dental impressions made into dental models, on an articulator to simulate "virtual" surgery movements, and manual splints were made to be used intraoperatively. Nowadays, the dental wet lab can be replaced by dental scanners and 3D printers. To successfully perform this virtual surgery, specialized software is necessary to accurately measure cephalometric angles (for example, sella-nasion-A point and sella-nasion-B point) and recognize landmarks such as anterior nasal spine (ANS), as well as simulate the movement to arrive at a final virtual position. Once the program can simulate this virtually, it is a similar process to print the negative space to create a splint that can be used during jaw surgery.

Type IV. Implant

As discussed in the above referenced systematic review, this is the least common type of 3DP object, in part because of the manufacturing sophistication necessary to 3DP biocompatible implantable materials such as porous polyethylene[25] (such as Medpor from Stryker), polyetheretherketone (PEEK from DePuy Synthes), or in the future other biocompatible or even bioengineered constructs. The other significant hurdle is the regulatory concern, which is sensible given that these implants are replacing tissues when there are no other good autologous reconstructive options available, such as a child with small anatomy and therefore limited donor sites. Therefore, currently most hospital 3D printers would not be able to do this. We have applied patient-specific custom implants (some may be additive manufacturing, but there is also another field of subtractive milling that is beyond the scope of this discussion), but only for severe defects. For example, children with large craniofacial defects where there is not enough donor rib or donor bone, will be candidates for implants. Another area is our patients with cleft lip-nose-palate may have such severe maxillary hypoplasia that need a severe advancement and we have used commercial custom titanium plates that are patient-specific for the final virtual position of the maxilla (combining the concept of splints and implants). It is clear that implants will be the subject of significant medical research and advancement.

Conclusions for Plastic Surgery 3DP for Patient Care

Despite the rapid advancement of 3DP in medicine and surgery, 3DP outcomes studies are still in their infancy. Part of this is the lack of a systematic classification of the techniques used, making it more difficult to make comparison studies. Plastic Surgery craniomaxillofacial surgery is an ideal specialty to study patient-specific 3DP

surgeries, as the operations are bone-intensive, and 3DP is currently better at simulating hard tissues. Another area that Plastic Surgery offers for studying outcomes, is the priority placed on normal shape and normal symmetry. Both of these attributes are well-suited for computer processing and virtual simulation. The uniqueness of our recent systematic review and classification[1] is that its sole focus is on 3DP patient-specific anatomy for surgery, which is a patient-centric approach to advancing 3DP applications. This systematic review and analysis of direct surgical applications of patient-specific 3DP revealed four classifications of 3DP: Type I contour models, Type II guides, Type III splints, and Type IV implants. By understanding this classification and the four types of patient-specific 3DP for surgery, this will stimulate new innovations. Multiple examples of these techniques are described above, and can also be seen on our video at https://www.slucare.edu/newsroom/kmov-science-of-healing-faces-of-childhood.php.

Our experience so far with patient-specific 3DP for surgery is that it can make surgeries faster, more accurate, and less invasive with smaller scars. This is especially beneficial to pediatric patients where anatomy is finer and more compressed, length of surgery can lead to more blood loss, which is even more critical in children. This will further improve Plastic Surgery craniomaxillofacial operations, and other medical and surgical subspecialties, to benefit the patients.

References

1. Jacobs CA, Lin AY. A New Classification of Three-Dimensional Printing Technologies: Systematic Review of Three-Dimensional Printing for Patient-Specific Craniomaxillofacial Surgery. Plast Reconstr Surg. 2017;139(5):1211-1220.
2. Lin AY, Losee JE. Pediatric Plastic Surgery. In: Zitelli BJ, McIntire SC, Nowalk AJ, eds. Zitelli and Davis' atlas of pediatric physical diagnosis. 6th ed. Philadelphia, PA: Saunders/Elsevier; 2012.
3. Danelson KA, Gordon ES, David LR, Stitzel JD. Using a three dimensional model of the pediatric skull for pre-operative planning in the treatment of craniosynostosis - biomed 2009. Biomed Sci Instrum. 2009;45:358-363.
4. Engel M, Hoffmann J, Castrillon-Oberndorfer G, Freudlsperger C. The value of three-dimensional printing modelling for surgical correction of orbital hypertelorism. Oral Maxillofac Surg. 2015;19(1):91-95.
5. Hatamleh MM, Cartmill M, Watson J. Management of extensive frontal cranioplasty defects. J Craniofac Surg. 2013;24(6):2018-2022.
6. Horn D, Engel M, Bodem JP, Hoffmann J, Freudlsperger C. Reconstruction of a near-total nasal defect using a precontoured titanium mesh with a converse scalping flap. J Craniofac Surg. 2012;23(5):e410-412.
7. Kozakiewicz M, Szymor P. Comparison of pre-bent titanium mesh versus polyethylene implants in patient specific orbital reconstructions. Head Face Med. 2013;9:32.
8. Lim CG, Campbell DI, Clucas DM. Rapid prototyping technology in orbital floor reconstruction: application in three patients. Craniomaxillofac Trauma Reconstr. 2014;7(2):143-146.
9. Park SW, Choi JW, Koh KS, Oh TS. Mirror-Imaged Rapid Prototype Skull Model and Pre-Molded Synthetic Scaffold to Achieve Optimal Orbital Cavity Reconstruction. J Oral Maxillofac Surg. 2015.
10. Ciocca L, Fantini M, De Crescenzio F, Persiani F, Scotti R. Computer-aided design and manufacturing construction of a surgical template for craniofacial implant positioning to support a definitive nasal prosthesis. Clin Oral Implants Res. 2011;22(8):850-856.
11. Soleman J, Thieringer F, Beinemann J, Kunz C, Guzman R. Computer-assisted virtual planning and surgical template fabrication for frontoorbital advancement. Neurosurg Focus. 2015;38(5):E5.
12. Azuma M, Yanagawa T, Ishibashi-Kanno N, et al. Mandibular reconstruction using plates prebent to fit rapid prototyping 3-dimensional printing models ameliorates contour deformity. Head Face Med. 2014;10:45.
13. Liu YF, Xu LW, Zhu HY, Liu SS. Technical procedures for template-guided surgery for mandibular reconstruction based on digital design and manufacturing. Biomed Eng Online. 2014;13:63.
14. Nkenke E, Eitner S. Complex hemimaxillary rehabilitation with a prefabricated fibula flap and cast-based vacuum-formed surgical template. J Prosthet Dent. 2014;111(6):521-524.
15. Yamada H, Nakaoka K, Horiuchi T, et al. Mandibular reconstruction using custom-made titanium mesh tray and particulate cancellous bone and marrow harvested from bilateral posterior ilia. J Plast Surg Hand Surg. 2014;48(3):183-190.
16. Dong Z, Li Q, Bai S, Zhang L. Application of 3-Dimensional Printing Technology to Kirschner Wire Fixation of Adolescent Condyle Fracture. J Oral Maxillofac Surg. 2015.
17. Flugge TV, Nelson K, Schmelzeisen R, Metzger MC. Three-dimensional plotting and printing of an implant drilling guide: simplifying guided implant surgery. J Oral Maxillofac Surg. 2013;71(8):1340-1346.
18. Li B, Zhang L, Sun H, Yuan J, Shen SG, Wang X. A novel method of computer aided orthognathic surgery using individual CAD/CAM templates: a combination of osteotomy and repositioning guides. Br J Oral Maxillofac Surg. 2013;51(8):e239-244.
19. Mazzoni S, Bianchi A, Schiariti G, Badiali G, Marchetti C. Computer-aided design and computer-aided manufacturing cutting guides and customized titanium plates are useful in upper maxilla waferless repositioning. J Oral Maxillofac Surg. 2015;73(4):701-707.
20. Ye N, Long H, Zhu S, Yang Y, Lai W, Hu J. The Accuracy of Computer Image-Guided Template for Mandibular Angle Ostectomy. Aesthetic Plast Surg. 2014.
21. Kang SH, Kim MK, You TK, Lee JY. Modification of planned postoperative occlusion in orthognathic surgery, based on computer-aided design/computer-aided manufacturing-engineered preoperative surgical simulation. J Oral Maxillofac Surg. 2015;73(1):134-151.
22. Lee UL, Kwon JS, Choi YJ. Keyhole System: A Computer-Assisted Designed and Computer-Assisted Manufactured Maxillomandibular Complex Repositioner in Orthognathic Surgery. J Oral Maxillofac Surg. 2015.
23. Sun Y, Luebbers HT, Agbaje JO, et al. Accuracy of upper jaw positioning with intermediate splint fabrication after virtual planning in bimaxillary orthognathic surgery. J Craniofac Surg. 2013;24(6):1871-1876.
24. Li J, Hsu Y, Luo E, Khadka A, Hu J. Computer-aided design and manufacturing and rapid prototyped nanoscale hydroxyapatite/polyamide (n-HA/PA) construction for condylar defect caused by mandibular angle ostectomy. Aesthetic Plast Surg. 2011;35(4):636-640.
25. Lin AY, Kinsella CR, Jr., Rottgers SA, et al. Custom porous polyethylene implants for large-scale pediatric skull reconstruction: early outcomes. J Craniofac Surg. 2012;23(1):67-70.

Disclosures

None reported.

Acknowledgment

The authors thank our 3D-printing technologist Brian Albers who created the 3D-printed surgical objects shown in the Figures, at our 3D Printing Center of Excellence at SSM Health Cardinal Glennon Children's Hospital at Saint Louis University. **MM**

Surgical Management of Lymphedema

by Aurora M. Kareh, MD & Kyle Y. Xu, MD

Recent advances in the field of lymphatic surgery have given new hope to patients who suffer from this debilitating disease.



Aurora M. Kareh, MD, is a Resident Physician, Division of Plastic and Reconstructive Surgery, and Kyle Y. Xu, MD, (above), is an Attending Physician, Plastic Surgery, Microsurgery and Hand Surgery, Division of Plastic and Reconstructive Surgery, Department of Surgery, Saint Louis University School of Medicine, St. Louis, Missouri.
Contact: kyle.xu@health.slu.edu

Abstract

Lymphedema is a chronic debilitating disease in which impaired drainage of lymphatic fluid causes accumulation of fluid in the soft tissues resulting in a swollen heavy limb. This ultimately leads to severe fibrosis, recurrent infections, non-healing wounds, and a poorly functioning limb that negatively affects a patient's quality of life. Primary lymphedema is due to abnormal development of the lymphatic system and patients can present with lymphedema at birth or later in life. Secondary lymphedema is caused by damage to the lymphatic system from infection, surgery to treat malignancies, trauma, and obesity. In the past, the only treatment was controlling the swelling to prevent progression of the disease by lymphatic therapy and various types of compression which is still currently the first line treatment. Advances in supermicrosurgery (connecting vessels less than 0.8 mm) have made way for surgical treatment options for lymphedema, including lymphovenous bypass and vascularized lymph node transplant. These new surgical treatment options combined with lymphatic therapy and compression have led to better results and improved patient's quality of life. After reading this article, the participant should be familiar with diagnosis, imaging, and surgical treatment of lymphedema.

Introduction

Lymphedema is a chronic, progressive, and incurable disease in which there is impaired drainage of interstitial fluid through the lymphatic system, resulting in accumulation of protein-rich fluid in the interstitial space. This fluid accumulation causes an inflammatory response that induces lipogenesis and fat deposition with connective tissue overgrowth. Eventually patients develop irreversible induration and fibrosis of the affected area.[1]

Primary lymphedema occurs due to structural and functional abnormalities of the lymphatic channels and can become symptomatic at birth, adolescence, or adulthood. Secondary lymphedema develops after disruption of normal lymphatic channels, leading to obstruction of the lymphatic system. The most common cause of secondary lymphedema worldwide is filariasis secondary to infection with Wuscheria bancrofti. In developed countries, however, secondary lymphedema is primarily caused by iatrogenic injury during the treatment of various malignancies including breast, gynecologic, and skin cancers.[2]

Other causes include traumatic injuries, obesity, and infections.

Regardless of etiology, patients with lymphedema exhibit both physical and psychological morbidity that ultimately leads to a decreased quality of life.[3] The affected limb becomes large, swollen, heavy, and painful preventing patients from enjoying hobbies and active lifestyle, exercising, performing activities of daily living, and working which ultimately leads to severe disability. Patients cannot fit into normal clothes and shoes and is a constant painful reminder that they had cancer. As the disease progresses, patients develop recurrent infections and non-healing wounds from even minor trauma requiring intensive wound care, multiple rounds of antibiotics, repeated hospitalization, surgical debridement, and even amputation. This becomes an economic burden on our patients, their families, and our healthcare system.

For many years the first line treatment of lymphedema has been conservative management with complete decongestive therapy (CDT): a combination of compressive garments, skin hygiene, limb compression, manual lymphatic drainage, and exercise. Decongestive lymphatic therapy is labor intensive and requires access to a specialized therapist.[4] CDT requires lifelong patient compliance, as it is not curative and requires continued compression to maintain treatment results.[5]

Multiple surgical options exist for patients whose lymphedema is not adequately controlled with conservative therapy. Debulking procedures such as liposuction and subcutaneous excision decrease extremity size in order to facilitate hygiene and improve functional status.[6] Recent advances in microsurgical techniques have made way for physiologic procedures including lymphovenous bypass and vascularized lymph node transfer which attempt to re-establish normal lymphatic physiology.

Clinical Evaluation

Initial patient evaluation should include a full history and physical exam. Other etiologies of limb edema such as congestive heart failure, renal failure, deep vein thrombosis, and venous insufficiency should be excluded. Venous duplex should be considered to rule out venous incompetence. Physical exam should include a thorough evaluation of the quality of the skin and soft tissue in the affected limb. Particular attention should be paid to the presence of peau d'orange, which indicates soft tissue fibrosis, and Stemmer sign, the inability to grasp the skin overlying the second digit of the foot, as these signs favor a diagnosis of lymphedema over other etiologies of limb swelling.[1] Serial limb circumference should be measured and compared to the contralateral side, as this can be helpful in monitoring treatment response.

The International Society of Lymphedema has described a staging system for the clinical assessment of lymphedema that is a helpful guide in determining the appropriate treatment options for patients presenting with lymphedema.

- Stage 0: Impaired lymph transport, subtle alterations in tissue and fluid composition. Patients may report symptoms, but swelling is not present.
- Stage I: Early accumulation of interstitial fluid that is high in protein. Swelling is present but improves with elevation. Patients may have pitting edema.
- Stage II: Swelling is present and does not improve with elevation. Early on, pitting edema will be present. Later in stage II, pitting will not be present as soft tissue fibrosis develops.
- Stage III: Pitting is absent, trophic skin changes develop, further deposition of fat and fibrosis (lymphostatic elephantiasis).[7]

Imaging

Imaging of the lymphatic system is a vital tool in the assessment of lymphedema, as a variety of morphologic changes in the lymphatic system can lead to similar clinical presentations. Indocyanine green lymphography and radionuclide lymphoscintigraphy are essential to the lymphatic surgeon for surgical planning as well as intraoperative visualization of lymphatic channels that are invisible to the naked eye.

Indocyanine Green Lymphography

Indocyanine green (ICG) lymphography is a minimally invasive imaging technique that allows dynamic visualization of lymphatic channels without radiation exposure. ICG has been used for decades across a number of specialties for evaluation of hepatic function, sentinel lymph node detection, cardiac output, and flap viability.[8] Its use in evaluation of lymphedema was initially described by Ogata et al. in 2007 and it has since become an irreplaceable tool for real-time assessment of lymphatic channels during lymphatic surgery.[9]

ICG lymphography is performed by injecting ICG

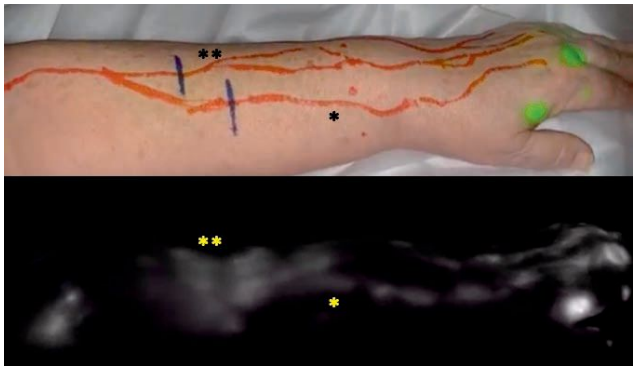


Figure 1. Preoperative left upper extremity ICG lymphography demonstrating normal linear pattern in the distal forearm and hand (*) and abnormal dermal backflow in the proximal forearm (**) in a patient with secondary lymphedema after treatment for left breast cancer. The blue lines represent incisions for lymphovenous bypass to shunt lymphatic fluid into veins upstream from the blockage.

subdermally into the interdigital webspaces of the lymphedematous extremity. Near-infrared light emitted by ICG dye is detected with an infrared camera system. The location, path, and flow of superficial lymphatic channels up to 2cm deep from the skin surface can be detected immediately after injection of ICG.[8]

Findings can be categorized into linear or dermal backflow patterns. Linear patterns correspond to normally functioning lymphatic channels and can be seen in patients with mild clinical findings of lymphedema. Figure 1. Dermal backflow patterns represent nonlinear, pathologic backflow of lymphatic fluid and are seen in more severe cases of lymphedema.[10] Dermal backflow patterns can be further divided into splash, stardust, and diffuse patterns, which correspond to increasing severity of disease and increased fibrosis in the lymphatic channels.[4]

Radionuclide Lymphoscintigraphy

Lymphoscintigraphy is considered the gold standard for evaluation of lymphedema and is frequently used to confirm a clinical suspicion of lymphedema. A Technetium-99 (Tc-99) radiotracer is injected subdermally into the first or second interdigital web space of the affected extremity and uptake is assessed using a high resolution gamma camera.[11] Lymphoscintigraphy gives providers the ability to measure contrast uptake, visualize number and size of lymphatic vessels and nodes, and assess dermal backflow patterns.[12] Lymphatic dysfunction is characterized by delayed, asymmetric, or absent visualization of lymph nodes and lymphatic channels, collateral lymphatic channels, interrupted vascular structures, visualization of the deep lymphatic system, or the presence of dermal back flow.[13]

Surgical Management

Surgical management of lymphedema can be separated into physiologic procedures, which attempt to re-establish normal lymphatic physiology by augmenting clearance of lymphatic fluid, and ablative procedures, which remove excess subcutaneous tissue to improve patient comfort and facilitate conservative therapies.

Lymphovenous Anastomosis/Bypass

Lymphovenous anastomosis (LVA) is a physiologic microsurgical procedure in which distal lymphatic channels are anastomosed to nearby subdermal veins, allowing bypass of proximal lymphatic obstruction by shunting lymphatic fluid into the venous system. Successful LVA begins with patient selection. Patients with International Society of Lymphedema stage I or II lymphedema who have been compliant with conservative measures but have showed minimal improvement are considered good candidates for LVA.[14,15]

ICG lymphography is performed preoperatively to identify suitable functioning lymphatic channels and guide placement of incisions. Lymphatic channels that are amenable to LVA demonstrate dynamic lymphatic flow that occurs distally to proximally.[14] Local anesthesia is infiltrated into the operative field and isosulfan blue is injected distal to the planned incision. Figure 2. The isosulfan blue stains the lymphatic channels so they may be readily visualized during the dissection. From this point onward, the procedure is performed under microscope

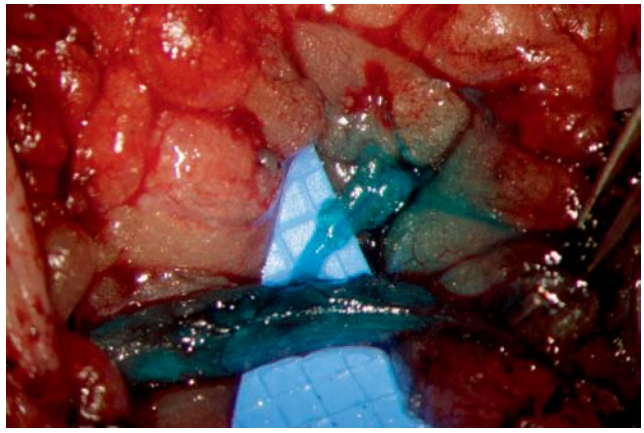


Figure 2. End-to-side lymphovenous anastomosis (end of lymphatic vessel into the side of a vein) with isosulfan blue dye confirming patency. Each square on the blue background is 1 x 1 mm.

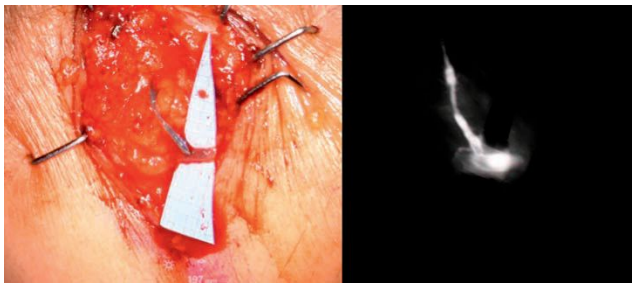


Figure 3. End-to-side lymphovenous anastomosis (left). Patency is confirmed with ICG lymphography (right). Fluorescence is noted flowing from the lymphatic vessel into the anastomosed venule.

magnification. The skin is carefully incised and lymphatic channels are identified within the subcutaneous tissue. Once a satisfactory lymphatic channel has been dissected and transected proximally, a nearby venule with appropriate size match is selected. End-to-end, end-to-side, or side-to-end anastomoses may be performed depending on the size, pressure, and availability of subdermal venules. Lymphatic channels are frequently 0.5-0.8mm in size, making surgeon skill, careful tissue handling, and microsurgical technique paramount to success.[16,17] The vessel may be floated open with heparinized saline or stented with a 6-0 prolene suture in order to avoid back-walling and ensure full-thickness bites are taken.[14] Patency can be confirmed immediately after the anastomosis is completed with ICG lymphography or isosulfan blue injection; fluorescence or dye should flow from the lymphatic duct into the anastomosed venule. Approximately three to four lymphovenous anastomoses are performed per affected limb. Figure 3.

Postoperatively patients are placed in a compression bandage and typically discharged on the day of surgery or admitted overnight for observation. Patients are encouraged to walk but must abstain from vigorous physical activity. At two weeks the compression bandage is transitioned to a compression garment once the incisions are healed. Lymphatic massage is reinitiated at four weeks postoperatively.

Outcomes after LVA have shown promising results in symptoms and disease severity, particularly in upper extremity lymphedema. In a prospective study of 100 patients undergoing LVA, Chang et al. demonstrated symptomatic improvement in 96 percent of patients with upper extremity lymphedema.[15] The same study showed a significant postoperative limb volume reduction at three, six, and 12 months after LVA.[15] Table 1. LVA has consistently been shown to significantly decrease episodes



Figure 4. Bilateral upper extremities six months after left upper extremity lymphovenous anastomosis in the same patient. Arm circumference of the affected (left) and unaffected (right) limbs were equivalent.

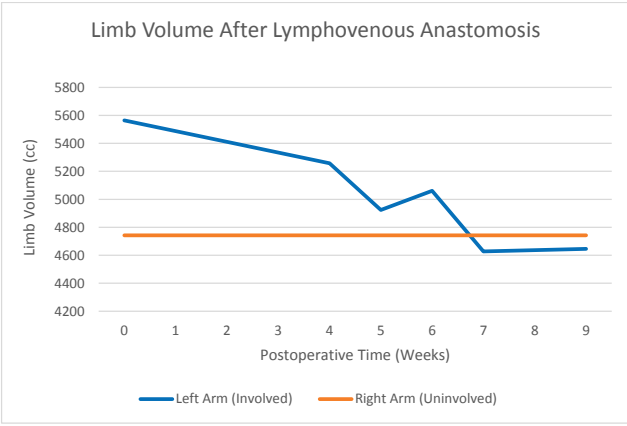


Table 1. Change in limb volume after left arm lymphovenous anastomosis. Limb volume of the affected limb had decreased significantly and was comparable to the unaffected limb by 7 weeks postoperatively.

of cellulitis in the affected limb.[17,18] Disadvantages to LVA include technical difficulty and a paucity of long term outcomes in the literature. Patients should be counseled that LVA is not curative and that fibrosis or failure of the anastomosis could lead to disease relapse. Figure 4.

Vascularized Lymph Node Transfer

In patients whose native lymph node basins are dysfunctional and lymphatic channels are no longer available for LVA, vascularized lymph node transfer (VLNT) may be considered to augment lymphatic drainage of the affected area. The exact mechanism by which VLNT improves lymphedema is still debated, but two leading theories have been described. The first is that transferred

lymph nodes act as a sponge that absorbs local lymphatic fluid and redirects it into the vascular system.[19] The second theory is that transferred lymph nodes produce vascular endothelial growth factor-C (VEGF-C) which induces local lymphangiogenesis by formation of spontaneous efferent and afferent connections between the transferred nodes and the recipient site.[20]

VLNT should be considered in patients with significant dermal backflow with no functioning lymphatic vessels on imaging, those with International Society of Lymphedema stage II lymphedema, and those who have not improved after at least 12 months of CDT.[4,21] In our practice, we will offer VLNT in patients who do not improve and continue to have pitting edema after LVA or in combination with LVA in patients with more advanced disease. Often these patients have undergone lymph node dissections or radiation for treatment of breast or pelvic cancers. The most common donor site for VLNT is the groin, but harvest of nodes from the lateral thoracic, supraclavicular, submental, and omental systems have been described.[19] VLNT using groin and supraclavicular donor sites will be discussed below.

VLNT from the groin is based on the superficial circumflex iliac system or a small medial branch of the femoral artery.[22] Dissection should stay superficial to the deep thigh fascia, superior to the groin crease, and lateral to the femoral artery in order to avoid harvesting nodes that are critical to lower extremity lymphatic drainage.[23] The groin lymph node flap may be transferred alone or in continuity with abdominal flaps in autologous breast reconstruction, making it an ideal donor for secondary lymphedema of the upper extremity in the setting of breast cancer.[23]

When transferring supraclavicular lymph nodes, the right side is preferred so as to avoid the thoracic duct on the left. The nodal basin is bound by the sternocleidomastoid muscle medially, the clavicle inferiorly, and the external jugular vein laterally.[24] The flap is elevated on the transverse cervical artery. The supraclavicular nodes can be transferred with a skin paddle, which can be useful in patients with radiation skin changes who also require contracture releases at the time of VLNT. Advantages to the supraclavicular VLNT include flap reliability, inconspicuous scar, and a low risk for donor site morbidity and secondary lymphedema.[24]

There continues to be controversy surrounding whether orthotopic (i.e. groin, axilla) or heterotopic (i.e. elbow, wrist, knee, ankle) recipient site provides the best outcomes. Until now no study has confirmed superior functional outcomes of one method over the other. Advocates of orthotopic placement report advantages including concurrent removal of scar tissue from the recipient site and a better cosmetic outcome.[25] Orthotopic placement may make drainage of lymphatic fluid from the hand or forearm more difficult, as the lymph nodes must work against distance and gravity to drain excess lymphatic fluid. In addition, these beds are frequently scarred and irradiated, making dissection technically more challenging. Although heterotopic recipient sites leave a more visible scar, they may be favorable over orthotopic recipient sites in patients who have had prolonged or severe symptoms.[22]

A dreaded complication of VLNT is the development of secondary lymphatic dysfunction at the donor site. Careful dissection and knowledge of anatomy is essential in avoiding the harvest of lymph nodes that are critical to donor site drainage. Some have advocated reverse lymph node mapping prior to VLNT to identify and protect nodes that are essential to lymph drainage of the donor site.[25] However, rates of iatrogenic donor site lymphedema after VLNT appear to be quite low.[22]

VLNT has been shown to improve overall quality of life and functional status while decreasing skin infection rates and need for CDT.[3,22] Significant limb volume reduction of upper and lower extremities after VLNT has been consistently seen in the literature.[19,21,22,26] Patients must be counseled on the risk of donor site morbidity and the need for staged revision or debulking procedures in the future.

Ablative Procedures

Ablative procedures remove excess skin and subcutaneous tissue from the affected limb in order to decrease limb volume, improve functional status, and facilitate CDT.[6] These procedures may be considered in patients with late stage II and stage III lymphedema who are not candidates for physiologic procedures due to excess adipose deposition and fibrosis in the affected extremity. These techniques are also used after physiologic procedures to address the fat and fibrosis component of the lymphedematous extremity.

Liposuction is minimally invasive, low risk, and is unlikely to further compromise lymphatic drainage of the affected limb.[27] Significant limb volume reduction is seen almost immediately in the postoperative period, but liposuction is not curative and patients must continue CDT and lifelong compression to maintain results. Suction-

assisted lipectomy may also be used in conjunction with LVA or VLNT to reduce limb size in patients whose lymphatic function has been restored.

The Charles procedure involves radical soft tissue excision to the level of the deep fascia followed by reconstruction with skin grafts. This results in complete disruption of existing distal lymphatic drainage and can lead to exacerbation of distal limb lymphedema.[6] Outcomes of the Charles procedure are aesthetically poor. Complications including graft breakdown, chronic ulceration, and hypertrophic scarring may be seen.[28]

Staged subcutaneous excision is a debulking procedure in which excess subcutaneous tissue is excised from a lymphedematous limb while nerves, blood vessels, and skin are preserved.[28] It is less radical than the Charles procedure and does not require skin grafting for wound closure. Although excision procedures carry high morbidity, they may be beneficial in restoring mobility and limb function in patients with devastating advanced disease.

Conclusion

Lymphedema is a chronic and incurable disease that has been shown to decrease function and quality of life. Recent advances in the field of lymphatic surgery have given new hope to patients who suffer from this debilitating disease. Increased patient satisfaction, limb volume reduction, and a decreased need for CDT has been seen with LVA and VLNT. Ablative procedures in combination with CDT continues to be the mainstay of therapy for patients who are not candidates for physiologic procedures. It is critical for all healthcare providers to be comfortable with the diagnosis and treatment of lymphedema so that timely referral to a lymphatic surgeon can be made.

References

1. Warren AG, Brorson H, Borud LJ, Slavin SA. Lymphedema. Annals of Plastic Surgery. 2007;59(4):464-472.
2. Rockson SG, Rivera KK. Estimating the Population Burden of Lymphedema. Annals of the New York Academy of Sciences. 2008;1131(1):147-154.
3. De Brucker B, Zeltzer A, Seidenstuecker K, Hendrickx B, Adriaenssens N, Hamdi M. Breast Cancer-Related Lymphedema: Quality of Life after Lymph Node Transfer. Plast Reconstr Surg. 2016;137(6):1673-1680.
4. Chang DW, Masia J, Garza R, 3rd, Skoracki R, Neligan PC. Lymphedema: Surgical and Medical Therapy. Plast Reconstr Surg. 2016;138(3 Suppl):209S-218S.
5. Lasinski BB, McKillip Thrift K, Squire D, et al. A systematic review of the evidence for complete decongestive therapy in the treatment of lymphedema from 2004 to 2011. PM R. 2012;4(8):580-601.
6. Kung TA, Champaneria MC, Maki JH, Neligan PC. Current Concepts in the Surgical Management of Lymphedema. Plast Reconstr Surg. 2017;139(4):1003e-1013e.
7. The Diagnosis and Treatment of Peripheral Lymphedema: 2016 Consensus Document of the International Society of Lymphology. Lymphology. 2016;49(4):170-184.
8. Narushima M, Yamamoto T, Ogata F, Yoshimatsu H, Mihara M, Koshima I. Indocyanine Green Lymphography Findings in Limb Lymphedema. J Reconstr Microsurg. 2016;32(1):72-79.
9. Ogata F, Azuma R, Kikuchi M, Koshima I, Morimoto Y. Novel lymphography using indocyanine green dye for near-infrared fluorescence labeling. Ann Plast Surg. 2007;58(6):652-655.
10. Yamamoto T, Narushima M, Doi K, et al. Characteristic indocyanine green lymphography findings in lower extremity lymphedema: the generation of a novel lymphedema severity staging system using dermal backflow patterns. Plast Reconstr Surg. 2011;127(5):1979-1986.
11. Yoshida RY, Kariya S, Ha-Kawa S, Tanigawa N. Lymphoscintigraphy for Imaging of the Lymphatic Flow Disorders. Tech Vasc Interv Radiol. 2016;19(4):273-276.
12. Garza RM, Chang DW. Lymphovenous bypass for the treatment of lymphedema. Journal of Surgical Oncology. 2018;118(5):743-749.
13. Tiwari P, Coriddi M, Salani R, Povoski SP. Breast and gynecologic cancer-related extremity lymphedema: a review of diagnostic modalities and management options. World journal of surgical oncology. 2013;11:237.
14. Baltzer HL, Winocour S, Harless C, Saint-Cyr M. Lymphaticovenous Bypass: Adaptations and Lessons Learned. Plast Reconstr Surg Glob Open. 2017;5(6):e1328.
15. Chang DW, Suami H, Skoracki R. A prospective analysis of 100 consecutive lymphovenous bypass cases for treatment of extremity lymphedema. Plast Reconstr Surg. 2013;132(5):1305-1314.
16. Chang EI, Skoracki RJ, Chang DW. Lymphovenous Anastomosis Bypass Surgery. Semin Plast Surg. 2018;32(1):22-27.
17. AlJindan FK, Lin C-Y, Cheng M-H. Comparison of Outcomes between Side-to-End and End-to-End Lymphovenous Anastomoses for Early-Grade Extremity Lymphedema. Plastic and Reconstructive Surgery. 2019;144(2):486-496.
18. Scaglioni MF, Fontein DBY, Arvanitakis M, Giovanoli P. Systematic review of lymphovenous anastomosis (LVA) for the treatment of lymphedema. Microsurgery. 2017;37(8):947-953.
19. Scaglioni MF, Arvanitakis M, Chen YC, Giovanoli P, Chia-Shen Yang J, Chang EI. Comprehensive review of vascularized lymph node transfers for lymphedema: Outcomes and complications. Microsurgery. 2018;38(2):222-229.
20. Pappalardo M, Patel K, Cheng MH. Vascularized lymph node transfer for treatment of extremity lymphedema: An overview of current controversies regarding donor sites, recipient sites and outcomes. J Surg Oncol. 2018;117(7):1420-1431.
21. Schaverien MV, Coroneos CJ. Surgical Treatment of Lymphedema. Plast Reconstr Surg. 2019;144(3):738-758.
22. Cheng MH, Chen SC, Henry SL, Tan BK, Lin MC, Huang JJ. Vascularized groin lymph node flap transfer for postmastectomy upper limb lymphedema: flap anatomy, recipient sites, and outcomes. Plast Reconstr Surg. 2013;131(6):1286-1298.
23. Tourani SS, Taylor GI, Ashton MW. Vascularized Lymph Node Transfer: A Review of the Current Evidence. Plast Reconstr Surg. 2016;137(3):985-993.
24. Maldonado AA, Chen R, Chang DW. The use of supraclavicular free flap with vascularized lymph node transfer for treatment of lymphedema: A prospective study of 100 consecutive cases. J Surg Oncol. 2017;115(1):68-71.
25. Liu HL, Pang SY, Lee CC, Wong MM, Chung HP, Chan YW. Orthotopic transfer of vascularized groin lymph node flap in the treatment of breast cancer-related lymphedema: Clinical results, lymphoscintigraphy findings, and proposed mechanism. J Plast Reconstr Aesthet Surg. 2018;71(7):1033-1040.
26. Cook KH, Park MC, Lee IJ, Lim SY, Jung YS. Vascularized Free Lymph Node Flap Transfer in Advanced Lymphedema Patient after Axillary Lymph Node Dissection. J Breast Cancer. 2016;19(1):92-95.
27. Boyages J, Kastanias K, Koelmeyer LA, et al. Liposuction for Advanced Lymphedema: A Multidisciplinary Approach for Complete Reduction of Arm and Leg Swelling. Ann Surg Oncol. 2015;22 Suppl 3:S1263-1270.
28. Miller TA, Wyatt LE, Rudkin GH. Staged skin and subcutaneous excision for lymphedema: a favorable report of long-term results. Plast Reconstr Surg. 1998;102(5):1486-1498; discussion 1499-1501.

Disclosure

None reported.

MM

Use of Robotic Technology in the Management of Complex Colorectal Pathology

by Claire Wunker, MD & Grace Montenegro, MD

Robotic surgery, in experienced hands, has been shown to be safe and feasible in complex colorectal surgery.



Claire Wunker, MD, is a Resident Physician and Grace Montenegro, MD, MS, (above), is Assistant Professor, Department of Surgery, Colon and Rectal Surgery, Saint Louis University School of Medicine, St. Louis, Missouri.
Contact: grace.montenegro@health.slu.edu

Abstract

Use of robotic surgery is increasing in multiple surgical specialties including colorectal. We argue that the improved visualization and better instrumentation outweigh the increased cost and operating room time. However, the indications for its use are not clearly defined. This is especially true in complex pathologies such as rectal cancer and complicated diverticulitis. We explore the limited clinical data on the subject to support or dismiss the use of this currently developing technology.

Introduction

Laparoscopic surgery has been used for over two decades in the field of colon and rectal surgery.[1] A conventional laparoscopic approach is challenging as it utilizes unarticulated rigid instruments (Figure 1) through the abdominal wall, which creates a fulcrum, reversing the surgeon's movements. The surgeon's view is through a two-dimensional monitor receiving the image from a camera held by an assistant. All these factors contribute to the steep learning curve of laparoscopic colorectal surgery.[2] Despite this, it has proven to be as safe and effective as open surgery which was demonstrated by the Clinical Outcomes of Surgical Therapy Group (COST) in 2004.[3] Even with this knowledge, there has been slow adoption of this technique.[4] In addition, it has become the standard of care for benign and malignant colonic disease as it is associated with less postoperative pain and shorter length of stay (LOS).[5]

The era of robotic surgery began in 1994 with the first FDA approved voice controlled camera holder.[6] Since then, multiple other systems have been developed to increase and improve utility in robotic surgery.[7] In 1997, Intuitive Surgical Inc. introduced their first robotic prototype called the da Vinci and the first robot assisted abdominal procedure, a cholecystectomy, was performed in March of 1998.[8] Intuitive Surgical has cornered the market and currently the da Vinci robot is the most widely used model for robotic assisted procedures since approval by the FDA in 2000. Its system consists of three main components: the robotic cart, a surgeon console, and a vision cart. The surgeon is seated at the console which controls the arms on the robotic cart in a master-slave organization.[9] A high definition three-dimensional camera and interchangeable instruments are fastened into each effector arm. The technology allows multidirectional motion of endoscopic instrument tips, similar to that of the human wrist - 7° of freedom, 180° articulation and 540° rotation.[9] Motion scaling results in reduced tremors, superior dexterity, and greater ergonomic comfort. The learning curve on the robot is similar to that of laparoscopic surgery and surgeons already trained in laparoscopy



Figure 1. Laparoscopic surgery has been used for over two decades in the field of colon and rectal surgery.

can master the robot in as little as 30 cases.[10,11] The 3D camera controlled by the surgeon, use of three endo-wristed instruments, and ability to reach and operate precisely in tight, hard to reach fields are clear advantages of robotic assisted surgery over traditional laparoscopic surgery. The ability to operate in this field with optimal ergonomics for the surgeon is one reason why robotic rectal surgery has gained popularity. Due in part to this it has been widely adopted in prostate surgery but has been much more slowly introduced in rectal surgery.[12]

Rectal Cancer

Colorectal cancer (CRC) is the third most common malignancy in the US. The American Cancer Society (ACS) found a 51% increase between 1994 and 2014 in the population, from 6% to 11%.[13] In response, ACS modified their colonoscopy screening recommendations to start at age 45. Lu et al. investigated the anatomic distribution of CRC in young patients using the National Cancer Database files from 2004 to 2015 and they found that patients <50 years of age had significantly more left-sided tumors compared to patients >50, (74.4% vs 56.1%, ($p<0.001$)).[14] A significant limitation to this retrospective study was the inclusion of young patients with familial syndromes. Interestingly, among all patients with left sided cancers, the rectum had the highest percent distribution among other locations (splenic flexure, descending, sigmoid and recto-sigmoid).

Total Mesorectal Excision (TME) has been established as the standard of care technique in rectal cancer surgery. Bill Heald describes the "holy plane" of rectal cancer surgery, aimed to excise the rectum and surrounding mesorectum within an intact visceral fascial "envelope", and achieve a wide circumferential radial margin (CRM).[15] CRM involvement is a strong predictor of local recurrence, as well as distant metastasis and poor survival.[16] Laparoscopic TME is fully feasible but remains a technically demanding procedure. The reported high conversion rates and involvement of the CRM (16%) are thought to reflect the high level of difficulty associated with laparoscopic TME.[17] More specifically, the fulcrum effect of laparoscopic surgery results in reduced range of motion, especially during pelvic dissection. This is exacerbated in the narrow male pelvis, obese abdomens, and by the non-articulating rigid instruments.[18]

Case series, comparative and multicenter studies have demonstrated robotic rectal surgery is feasible and safe for minimally invasive TME. Studies demonstrate robotic surgeries have lower rates of positive CRM and lower genitourinary complications.[19] Liao et al. reported a meta-analysis of four randomized control trials (RCT) comparing robotic to lap colorectal surgery.[20] Two studies involved only rectal cancer patients, one included right sided colon cancer, and one with sigmoid and rectal cancers. They found advantages of robotic approach including reduced estimated blood loss (EBL) and lower conversion rates to open laparotomy, with no heterogeneity among the studies.

Return of bowel function was shorter in the robotic group. No significant differences in complication rates, LOS, proximal margin, distal margin or harvested lymph nodes were found.

In 2017, the ROLARR data was published which was the first randomized multicenter investigation, including 471 rectal cancer patients, from 29 sites in 10 countries involving 40 surgeons.[17] The study compared robotic to conventional laparoscopic approach among patients undergoing resection for rectal cancer. The primary outcome was conversion to open laparotomy. Interestingly, the study did not show a significantly reduced risk of conversion to open surgery with robotic approach. Conversion from laparoscopy to open 12.2% vs. 8.1% in robotic group ($p = 0.16$). Rate of positive CRM also had no difference between techniques. The study did find a lower CRM positive rate (5.7%) in the robotic group than previous RCTs investigating laparoscopy for rectal cancer: COLOR II, ACOSOG Z6051 and ALaCaRT.[21–23] Other secondary endpoints including, intraoperative and postoperative complications, bladder dysfunction, and sexual dysfunction did not show a statistically significant difference between the groups. Among the patients who were converted to open, a multilevel logistic regression model showed increased odds of conversion in obese patients and males. In subgroup analysis of these groups robotic trended towards lower conversion however it was not statistically significant. The study concluded that robotic-assisted surgery does not have an advantage in rectal cancer resection when performed by surgeons with varying robotic experience. Sensitivity analysis demonstrated that when robotic operative experience was accounted for, the odds ratios for conversion to open decreased from 0.96 in the lower experienced group to 0.30 in the experienced group. This was regardless of their laparoscopic case numbers, suggesting that the greater benefit of robotic surgery becomes clear once a surgeon becomes more experienced on the robot.

Complicated Diverticulitis

Colectomy for diverticulitis is considered a more difficult operation than colectomy for cancer, regardless of surgical method, due to ill-defined planes, significant inflammation and, bulky mesentery. Laparoscopic colectomy for non-complicated and complicated diverticulitis is the preferred approach as there is less EBL, less postoperative pain, shorter LOS, and less postoperative morbidity.[24–26]

Complicated diverticulitis creates an even more difficult surgical procedure due to obliterated anatomic planes; chronically inflamed tissues; along with involvement of pelvic organs from abscess, stricture, and fistula. Higher conversion rates from laparoscopic to open are quoted in patients with complicated diverticulitis.[26–28] This should not be seen as a separate complication as it is most commonly done for the safety of the patient and to reduce the risk of complications. Conversions to open are associated with longer hospital stay and higher postoperative complications.[2] Robotic surgery for complicated diverticulitis has been shown to be safe and feasible although data is limited.[26,28–30]

Two separate case series looked at the use of robotic assisted surgery for diverticulitis.[26,29] Ragupathi et al. published one of the earliest and largest North American case series that looked at 24 patients, nine who had complicated disease and underwent anterior sigmoid resection. Xia et. al had a single surgeon series looking at 68 patients, 36 who had complicated disease (20 with abscess, 11 with fistula and 5 with stricture). Operating time (OT) was similar in both studies but Xia et al found a longer OT in the complicated group by 23.8 minutes ($p=0.011$). The mean LOS in Ragupathi et al. was 3.4 days with a post-op complication rate of 12.5% and no conversions to open. Xia et al had a longer LOS and higher rate of complications in the complicated group though it was not statistically significant but conversion to laparotomy was higher in the complicated group, 8 vs. 1 case ($p = 0.03$). Creation of ostomy and drain placement were also higher in the complicated group (3 vs. 12 cases, $p = 0.037$ and 1 vs. 10 cases, $p = 0.015$, respectively).[26] A point was made by Ragupathi et al. that patients with complicated diverticular disease defined as stricture, enterocolic fistula, colovesicular fistula or pelvic abscess benefit the most from the robotic approach as it helps to overcome the challenging dissections in fibrotic tissue planes.

There have also been two single center studies that look at the comparison of laparoscopic versus robotic assisted procedures in the context of fistulas.[28,30] Maciel et al. published their experience with colovesical fistula while Elliot et al. looked at multiple fistula types including colovesical, colovaginal, and colocutaneous. Both groups had more laparoscopic cases (55 and 20 vs 20 and 11 respectively). While Maciel et. al had a large range in OT from 126.7 minutes laparoscopically to 207.7 minutes robotically, Elliott et. al had similar times in both groups (247 minutes vs 250 minutes). Interestingly they also had opposite results in rates of conversion with Maciel's group

having none in the robotic group (14.6% in laparoscopic, p=0.001) while Elliott's group had none in the laparoscopic (18% in robotic). It was noted that the robotic group in Elliott's cohort had a larger proportion of patients with prior abdominopelvic surgeries and a larger proportion of colovaginal fistulas. These studies also had differing results on length of stay (not significant[30] vs longer in the robotic group 6.5 vs 4.2 days, p=0.007[28]) and complication rates (38% laparoscopic and 20% robotic[30] vs similar in both groups[28]).

With the lack of RCT or large multicenter meta-analyses, the impact of robotic surgery in complicated diverticulitis remains unknown. Retrospective case series and reviews demonstrate that robotic assisted surgery for complicated diverticulitis is safe and feasible. Overall complication rates are comparable to laparoscopic approach, 20%, 27% and 38.9% in robotic groups and 29% and 30% in the laparoscopic groups.[28,30–32] Mean EBL was not statistically significant when compared to laparoscopic approach (101.3 mL, 200 mL and 142.5 mL in robotic groups versus 187.6 mL and 150 mL in laparoscopic groups).[28,30] Conversion from laparoscopic to open in complicated diverticulitis has reported range from 20-61%.[32–34] Elliot et. al reported conversion in two patients and this was attributed to morbid obesity, dense intra-abdominal and pelvic adhesions, prior laparotomy, and chronic abscess. Xia et. al reported a single conversion in 8 patients. They too faced the challenge of a morbidly obese patient with active phlegmon and inability to visualize structures.

Additional Considerations and Technology

Identification and preservation of the ureters is critical during pelvic surgery and is especially important after complicated diverticulitis when the planes have been disrupted. Ureteral injury is an uncommon but devastating complication with a reported incidence of 0.2%-7.6%.[35] Prophylactic ureteral stents are used at the discretion of the surgeon to facilitate early repair of injury in cases of reoperative pelvic surgery, chronic inflammation, or previous radiation. Only one of the papers previously mentioned placed ureteral stents for complicated diverticulitis which was only done in 11.1% of patients and no injuries were reported.[26]

Several methods have been used to help identify the ureters. Lighted ureteral stents were shown to prevent ureteral injury in a retrospective study with over 400 patients undergoing laparoscopic colorectal surgery.[36] Indocyanine green (ICG), a fluorescent dye that can be seen under near-infrared fluorescence, can be visualized with FIREFLY a tool integrated on the robot. This has been utilized to assess perfusion and identify relevant anatomy.[37] ICG reversibly binds to proteins in the urothelial layer when injected into ureteral stents or through a catheter intubating the ureteral orifice, causing the ureters to fluoresce green when FIREFLY is used.[37,38] Only a few case series exist reporting ICG technology, and no complications or adverse reactions have been reported.[38]

Disadvanages of Robotic Surgery

By far, the most criticized aspect of the robotic platform is the cost. Intuitive Surgical is virtually the sole company employed globally at the time of publishing. Purchase and maintenance of the system increases the average cost of a minimally invasive surgery by at least $3000 compared to laparoscopy.[39] Each upgrade and addition to maintain the robot and compete with laparoscopy is an additional cost. It was believed that the cost would be defrayed by shorter LOS and decreased conversion rate, but this has not been demonstrated.[17,40] An experienced surgeon and a dedicated OR team both maximize outcomes and efficiency leading to decreased operative time which also contributes to decreased cost. Increased competition should decrease costs but it will take time for other companies to get their products to market. As these are complicated technologies regular maintenance is required by specially trained personnel which is costly and time consuming. Unfortunately, there is no easy solution to these problems. Ultimately RCTs are necessary to determine if the financial burden is offset by other benefits, but for more global adoption, cost must be improved.

Conclusion

Robotic assisted surgery has dramatically changed the landscape of the minimally invasive approach to colon and rectal surgery. This is especially true for the most challenging cases when dissection is required in confined spaces where precise movements are critical and anatomy may be skewed. Robotic surgery, in experienced hands, has been shown to be safe and feasible in complex colorectal surgery. However, utilization will not become global until the cost is reduced. As with any relatively new technology, challenging cases are not pursued until surgeons become more comfortable and thus further research is warranted.

References

1. Jacobs M, Verdeja J, Goldstein H. Minimally invasive colon resection (laparoscopic colectomy. Surg Laparosc Endosc. 1991;1(3):144-145-150.
2. Tekkis P, Senagore A, Gudgeon M, Fazio V. Evaluation of the learning curve in laparoscopic colorectal surgery: comparison of right-sided and left-sided resections. Ann Surg. 2005;242(1):83-84-91.
3. A Comparison of Laparoscopically Assisted and Open Colectomy for Colon Cancer. N Engl J Med. 2004;350(20):2050-2059. doi:10.1056/NEJMoa032651
4. Moghadamyeghaneh Z, Carmichael JC, Mills S, Pigazzi A, Nguyen NT, Stamos MJ. Variations in Laparoscopic Colectomy Utilization in the United States. Dis Colon Rectum. 2015;58(10):950-956. doi:10.1097/DCR.0000000000000448
5. Gaertner WB, Kwaan MR, Madoff RD, et al. The evolving role of laparoscopy in colonic diverticular disease: a systematic review. World J Surg. 2013;37(3):629-638. doi:10.1007/s00268-012-1872-x
6. Sackier JM, Wang Y. Robotically assisted laparoscopic surgery. From concept to development. Surg Endosc. 1994;8(1):63-66. doi:10.1007/bf02909496
7. Palep JH. Robotic assisted minimally invasive surgery. J Minimal Access Surg. 2009;5(1):1-7. doi:10.4103/0972-9941.51313
8. Himpens J, Leman G, Cadiere GB. Telesurgical laparoscopic cholecystectomy. Surg Endosc. 1998;12(8):1091. doi:10.1007/s004649900788
9. Intuitive | da Vinci | Robotic Surgical Systems. Intuitive Surgical. https://www.intuitive.com/en-us/products-and-services/da-vinci. Accessed October 21, 2019.
10. Park EJ, Kim CW, Cho MS, et al. Is the learning curve of robotic low anterior resection shorter than laparoscopic low anterior resection for rectal cancer?: a comparative analysis of clinicopathologic outcomes between robotic and laparoscopic surgeries. Medicine (Baltimore). 2014;93(25):e109. doi:10.1097/MD.0000000000000109
11. Kim HJ, Choi G-S, Park JS, Park SY. Multidimensional analysis of the learning curve for robotic total mesorectal excision for rectal cancer: lessons from a single surgeon's experience. Dis Colon Rectum. 2014;57(9):1066-1074. doi:10.1097/DCR.0000000000000174
12. Wexner SD, Bergamaschi R, Lacy A, et al. The current status of robotic pelvic surgery: results of a multinational interdisciplinary consensus conference. Surg Endosc. 2009;23(2):438-443. doi:10.1007/s00464-008-0202-8
13. Wolf AMD, Fontham ETH, Church TR, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA Cancer J Clin. 2018;68(4):250-281. doi:10.3322/caac.21457
14. Lu P, Fields AC, Vise AS, et al. Anatomic Distribution of Colorectal Adenocarcinoma in Young Patients. Dis Colon Rectum. 2019;62(8):920-924. doi:10.1097/DCR.0000000000001422
15. Heald RJ. The "Holy Plane" of rectal surgery. J R Soc Med. 1988;81(9):503-508.
16. Nagtegaal ID, Quirke P. What is the role for the circumferential margin in the modern treatment of rectal cancer? J Clin Oncol Off J Am Soc Clin Oncol. 2008;26(2):303-312. doi:10.1200/JCO.2007.12.7027
17. Jayne D, Pigazzi A, Marshall H, et al. Effect of Robotic-Assisted vs Conventional Laparoscopic Surgery on Risk of Conversion to Open Laparotomy Among Patients Undergoing Resection for Rectal Cancer: The ROLARR Randomized Clinical Trial. JAMA. 2017;318(16):1569-1580. doi:10.1001/jama.2017.7219
18. Keller DS, Madhoun N, Flores-Gonzalez JR, Ibarra S, Tahilramani R, Haas EM. Effect of BMI on Short-Term Outcomes with Robotic-Assisted Laparoscopic Surgery: a Case-Matched Study. J Gastrointest Surg Off J Soc Surg Aliment Tract. 2016;20(3):488-493. doi:10.1007/s11605-015-3016-8
19. Xiong B, Ma L, Huang W, Zhao Q, Cheng Y, Liu J. Robotic versus laparoscopic total mesorectal excision for rectal cancer: a meta-analysis of eight studies. J Gastrointest Surg Off J Soc Surg Aliment Tract. 2015;19(3):516-526. doi:10.1007/s11605-014-2697-8
20. Liao G, Zhao Z, Lin S, et al. Robotic-assisted versus laparoscopic colorectal surgery: a meta-analysis of four randomized controlled trials. World J Surg Oncol. 2014;12:122. doi:10.1186/1477-7819-12-122
21. Fleshman J, Branda M, Sargent DJ, et al. Effect of Laparoscopic-Assisted Resection vs Open Resection of Stage II or III Rectal Cancer on Pathologic Outcomes: The ACOSOG Z6051 Randomized Clinical Trial. JAMA. 2015;314(13):1346-1355. doi:10.1001/jama.2015.10529
22. Bonjer HJ, Deijen CL, Abis GA, et al. A Randomized Trial of Laparoscopic versus Open Surgery for Rectal Cancer. N Engl J Med. 2015;372(14):1324-1332. doi:10.1056/NEJMoa1414882
23. Stevenson ARL, Solomon MJ, Lumley JW, et al. Effect of Laparoscopic-Assisted Resection vs Open Resection on Pathological Outcomes in Rectal Cancer: The ALaCaRT Randomized Clinical Trial. JAMA. 2015;314(13):1356-1363. doi:10.1001/jama.2015.12009
24. Klarenbeek BR, Veenhof AA, Bergamaschi R, et al. Laparoscopic sigmoid resection for diverticulitis decreases major morbidity rates: a randomized control trial: short-term results of the Sigma Trial. Ann Surg. 2009;249(1):39-44. doi:10.1097/SLA.0b013e31818e416a
25. Köckerling F, Schneider C, Reymond MA, et al. Laparoscopic resection of sigmoid diverticulitis. Results of a multicenter study. Laparoscopic Colorectal Surgery Study Group. Surg Endosc. 1999;13(6):567-571. doi:10.1007/s004649901042
26. Xia J, Paul Olson TJ, Rosen SA. Robotic-assisted surgery for complicated and non-complicated diverticulitis: a single-surgeon case series. J Robot Surg. January 2019. doi:10.1007/s11701-018-00914-x
27. Haas JM, Singh M, Vakil N. Mortality and complications following surgery for diverticulitis: Systematic review and meta-analysis. United Eur Gastroenterol J. 2016;4(5):706-713. doi:10.1177/2050640615617357
28. Elliott PA, McLemore EC, Abbass MA, Abbas MA. Robotic versus laparoscopic resection for sigmoid diverticulitis with fistula. J Robot Surg. 2015;9(2):137-142. doi:10.1007/s11701-015-0503-6
29. Ragupathi M, Ramos-Valadez DI, Patel CB, Haas EM. Robotic-assisted laparoscopic surgery for recurrent diverticulitis: experience in consecutive cases and a review of the literature. Surg Endosc. 2011;25(1):199-206. doi:10.1007/s00464-010-1159-y
30. Maciel V, Lujan HJ, Plasencia G, et al. Diverticular Disease Complicated With Colovesical Fistula: Laparoscopic Versus Robotic Management. Int Surg. 2014;99(3):203-210. doi:10.9738/INTSURG-D-13-00201.1
31. Bhakta A, Tafen M, Glotzer O, et al. Laparoscopic sigmoid colectomy for complicated diverticulitis is safe: review of 576 consecutive colectomies. Surg Endosc. 2016;30(4):1629-1634. doi:10.1007/s00464-015-4393-5
32. Laurent SR, Detroz B, Detry O, Degauque C, Honoré P, Meurisse M. Laparoscopic Sigmoidectomy for Fistulized Diverticulitis. Dis Colon Rectum. 2005;48(1):148-152. doi:10.1007/s10350-004-0745-2
33. Bartus CM, Lipof T, Sarwar CMS, et al. Colovesical fistula: not a contraindication to elective laparoscopic colectomy. Dis Colon Rectum. 2005;48(2):233-236. doi:10.1007/s10350-004-0849-8
34. Vargas HD, Ramirez RT, Hoffman GC, et al. Defining the role of laparoscopic-assisted sigmoid colectomy for diverticulitis. Dis Colon Rectum. 2000;43(12):1726-1731. doi:10.1007/BF02236858
35. Silva G da, Boutros M, Wexner SD. Role of prophylactic ureteric stents in colorectal surgery. Asian J Endosc Surg. 2012;5(3):105-110. doi:10.1111/j.1758-5910.2012.00134.x
36. Boyan WP, Lavy D, Dinallo A, et al. Lighted ureteral stents in laparoscopic colorectal surgery; a five-year experience. Ann Transl Med. 2017;5(3). doi:10.21037/atm.2017.02.01
37. Jafari MD, Lee KH, Halabi WJ, et al. The use of indocyanine green fluorescence to assess anastomotic perfusion during robotic assisted laparoscopic rectal surgery. Surg Endosc. 2013;27(8):3003-3008. doi:10.1007/s00464-013-2832-8
38. Siddighi S, Yune JJ, Hardesty J. Indocyanine green for intraoperative localization of ureter. Am J Obstet Gynecol. 2014;211(4):436.e1-436.e2. doi:10.1016/j.ajog.2014.05.017
39. Tyler JA, Fox JP, Desai MM, Perry WB, Glasgow SC. Outcomes and costs associated with robotic colectomy in the minimally invasive era. Dis Colon Rectum. 2013;56(4):458-466. doi:10.1097/DCR.0b013e31827085ec
40. Kim CW, Baik SH, Roh YH, et al. Cost-effectiveness of robotic surgery for rectal cancer focusing on short-term outcomes: a propensity score-matching analysis. Medicine (Baltimore). 2015;94(22):e823. doi:10.1097/MD.0000000000000823

Disclosure

None reported.

MM

Colorectal Surgery Review for Primary Care Providers

by Rakesh Hegde, MD, John M. Trombold, MD & José M. Dominguez, MD

This article is Part I of a three-part mini-series on Colorectal Surgery.

Though anorectal conditions have overlapping symptoms, careful history and good physical examination can usually confirm diagnosis.



Rakesh Hegde, MD, (above), John M. Trombold, MD & José M. Dominguez, MD, MSMA member since 1996, are in the Department of Colon and Rectal Surgery, Ferrell-Duncan Clinic, CoxHealth, Springfield, Missouri.
Contact: Rakesh.Hegde@coxhealth.com

Abstract

Anorectal conditions are one of the most common problems evaluated by primary care physicians. Most patients present with rectal pain, rectal bleeding, or purulent drainage per rectum. Colorectal conditions have overlapping symptoms. Thorough history and careful anorectal examination can differentiate common anorectal conditions like hemorrhoids, anorectal abscesses, anal fistula, anal fissure, and anal condyloma. Most of these conditions can be diagnosed and treated without imaging.

Introduction

Anorectal disorders are commonly encountered in primary care practices. There are overlapping symptoms in these disorders causing confusion and misdiagnosis. This paper will review anorectal abscesses, anal fistula, hemorrhoids, anal fissure and anal condyloma.

Anorectal Abscesses

Anorectal abscess results from obstruction of anal glands. Anorectal abscesses are defined by the anatomic space in which they develop. These most commonly involve the perianal and ischiorectal spaces; less often the intersphincteric, supralevator and submucosal spaces.[1] The incidence of anorectal abscesses is 8.6-20/100,000, with a male: female ratio of 3:1. They may occur at any age with a peak incidence between 20 and 40 years of age.[2]

The diagnosis of anorectal abscess is usually based on the patient's history and physical examination. Perianal pain and swelling are common with superficial abscesses.[2] Deeper abscesses also present with pain that is referred to the perineum or buttock but visualized swelling is less common. Inspection of the perineum may reveal superficial erythema and fluctuance with tenderness to palpation. Digital rectal exam commonly elicits severe pain. Imaging is rarely needed.[3]

The primary treatment of anorectal abscess remains surgical drainage. In general, the incision should be kept as close as possible to the anal verge to minimize the length of a potential fistula. Bedside or in-office drainage with local anesthetic and a scalpel is usually adequate. Relief is immediate. Sometimes, examination under anesthesia is needed to confirm deeper more occult abscesses and to drain more complicated abscesses.[4]

After drainage, abscess recurrence has been observed in up to 44% of patients, most often within one year of initial treatment. Inadequate drainage (such as using a needle), loculations, horseshoe-type abscess and failure to perform primary fistulotomy have been identified as risk factors for recurrent anorectal abscess.[5]

Antibiotics should be reserved for patients with anorectal abscess complicated by cellulitis, systemic signs of infection or underlying immunosuppression. The sole treatment of anorectal abscesses with antibiotics is inadequate.



Figure 1. Perianal abscess

Anal Fistula

A fistula is an abnormal connection between two epithelialized structures. An anal fistula results from chronic infection and epithelialization of prior abscess drainage site. The incidence is 2/100,000/year. Anal fistulae are usually cryptoglandular/abscess-related in over 90% of cases. Blockage of anal crypts/glands leads to infection and abscess formation.[6] Following routine abscess drainage, a failure of the tract to heal may lead to fistula formation. Less common causes include trauma and inflammatory bowel disease. Anal fistulae are classified in relationship to sphincter complex as intersphincteric, transphincteric, suprasphincteric and extrasphincteric.[7] Intershincteric and low transphicteric are most common.

Patients who present with anal fistula after resolution of the abscess typically report intermittent perianal swelling and drainage. Inspection of the perineum should include a search for surgical scars, signs of perianal Crohn's disease and the presence of the external opening of the fistula. Probing a fistula during office exam is not necessary. Goodsall's rule, generally predicts short radial tracts for anterior fistulae close to the anus. Posterior fistulae and those far from the anus are more variable in their course.[8]

Simple fistulae, in general, do not require diagnostic imaging. If persistent for more than six weeks, examination under anesthesia and treatment is indicated, as they will not resolve spontaneously. Complex and recurrent anal fistula may require imaging such as CT, MRI, ultrasound and fistulogram.

The primary goal of treatment of anal fistula is fistula resolution without compromising continence. Fistula cause, prior treatments, fistula anatomy, underlying continence, and comorbidities must all be considered when formulating a treatment plan. Regardless, recurrences are common

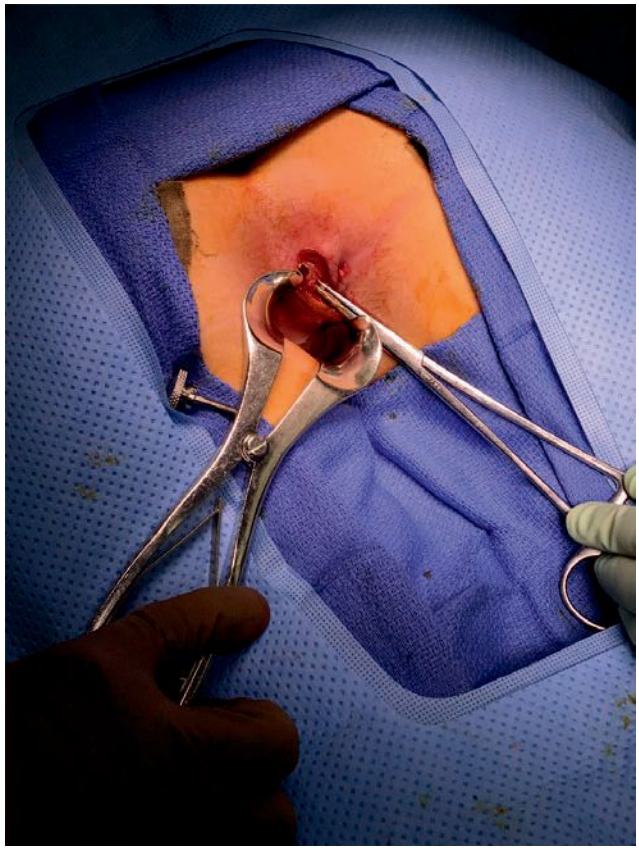


Figure 2. LIFT (ligation of intersphincteric fistula tract) procedure for anal fistula

and the potential need for multiple procedures must be discussed preoperatively.[9]

Fistulotomy (cutting open) is effective treatment for simple anal fistula that results in healing in over 90% of patients and a low chance of continence issues. More complex fistulae involving more sphincter muscle can be treated with rectal advancement flap, ligation of intersphincteric fistula tract (LIFT), fibrin glue, fistula plug, cutting or draining setons (rubber bands).[10] The existence of many treatment options reflects that lack of a perfect solution and treatment requires careful counseling and individualization to each patient's unique presentation. Complicated or multiply recurrent fistulae, fistula in setting of Crohn's disease, or fistula in patients with poor sphincter function as baseline may even require colostomy.

Hemorrhoids

"Hemorrhoids" represent one of the most common medical and surgical disease processes encountered in the United States. It is estimated that more than 50% of the population over 50 years of age have experienced hemorrhoid problems. Unfortunately, many anorectal



Figure 3. Thombosed external hemorrhoids

conditions, such as cancer and inflammatory bowel disease, are inappropriately attributed to hemorrhoids.[11]

Hemorrhoids are normally occurring vascular cushions containing blood vessels, smooth muscles, and elastic tissue that serve to maintain closure of anal canal and aid in fecal continence. Symptomatic hemorrhoids develop because of chronic constipation, prolonged straining, poor bowel hygiene, pregnancy, ascites, pelvic mass and pelvic dysfunction that increase abdominal pressure.[12]

Hemorrhoids are divided into internal and external. Internal hemorrhoids originate proximal to dentate line and external hemorrhoids are located distal to dentate line. Internal hemorrhoidal symptoms typically include painless bright red bleeding, itching, burning, pain, prolapse and swelling.[13] The physical examination should typically include visual inspection of the anus and digital examination. Anoscopy can allow direct visualization in the office. Colonoscopy is helpful to rule out other pathology in patients of appropriate age who have not been screened or when reported symptoms are not clearly explained by physical exam.[13] Since colorectal cancer can also cause painless anorectal bleedings, the presence of enlarged hemorrhoids does not rule out malignancy.

Internal Hemorrhoids classified into four grades: 1) Prominent internal hemorrhoidal tissue without prolapse; 2) Prolapse with defecation and spontaneous reduction; 3) Prolapse with defecation requiring manual reduction; and 4) Chronically prolapsed and irreducible.[1]

Dietary modification focusing on adequate fluid intake (64 ounces daily) and fiber intake (approximately 30 grams daily) are primary non-operative strategies for patients with symptomatic hemorrhoid disease. Minimizing straining and time on the commode are also helpful. Most patients with grade I, II, and III hemorrhoid disease, in whom medical treatment fails, may benefit from office-based procedures. These include rubber band ligation, sclerotherapy, and infrared coagulation. Hemorrhoid banding is typically well tolerated is painless, repeatable and requires no alteration in daily activities.[12]

Surgical hemorrhoidectomy is indicated for patients who fail nonoperative and office-based procedures or have more advanced disease at presentation. Surgical hemorrhoidectomy involves complete removal of all pathologic hemorrhoid tissue, under general or spinal anesthesia. Complications of hemorrhoidectomy include severe pain, bleeding, wound complications and anal stenosis. Significant, lasting fecal incontinence is quite uncommon, urinary retention and rarely infection.[14]

External hemorrhoids are distal to the dentate line therefore innervated by somatic nerves. Combined internal and external hemorrhoids that are causing symptoms frequently require operative removal as described above. External hemorrhoids thrombosis causes sudden severe anal pain usually precipitated by an episode of constipation or diarrhea. A firm, exquisitely tender lump (often resembling a blueberry) typically accompanies the pain. It rapidly progresses and peaks at 48 hours but can then start to diminish. Bleeding often indicates spontaneous clot drainage.[15] Management is directed at pain control with topical anesthetic cream, sitz bath, and oral pain medication. If resolution does not occur or if examined early in its course, simple bedside clot excision with local anesthetic can offer immediate relief. Excision of the thrombosed hemorrhoids in the office or operating room may be required,[16] for severe pain presenting in the first few days. If pain is mild and patient presents several days into symptoms, excision is best avoided, as it would likely worsen the pain.

Anal Fissure

Anal fissures are common and often present advertised as "hemorrhoids". Patients frequently have bright red bleeding and severe tearing/stabbing pain made worse with bowel movements. They generally represent a traumatic tear, usually caused by passage of a hard stool or conversely, diarrhea. They are almost always in the midline, most often posteriorly. The fissures cause severe spasm of the internal sphincter, which leads to an elevated resting pressure and tissue hypoxia, which prevents healing.[17]

Fissures that are deeper lateral or multiple in number are considered atypical fissures. The differential diagnosis of an atypical fissure includes Crohn's disease,



Figure 4. Posterior midline anal fissure

hematologic malignancies, HIV/AIDS, sexually transmitted diseases, dermatologic conditions, tuberculosis and anal carcinoma.[18] Further workup under these circumstances is warranted.

An acute anal fissure can be diagnosed with gentle buttock spreading and inspection. They are often quite small and difficult to see unless the provider has seen many of them. Digital exam causes severe pain and should be avoided if fissure is suggested by symptoms and identified by simple inspection. A chronic anal fissure may be associated with an enlarged anal papilla proximally, sentinel tag or pile distally (which causes many to be misdiagnosed as hemorrhoids). Internal sphincter muscle fibers are frequently visible in the base of the fissure.[18]

Many acute fissures heal spontaneously but are considered chronic if present greater than six to eight weeks. Medical treatment for an acute anal fissure focuses on improving the bowel function. Resolving the causative constipation with increased water intake and fiber is paramount.[19] Treating the underlying cause for a diarrheal illness is recommended. Topical anesthetic such, as lidocaine, may be used for symptomatic relief. Warm sitz baths help decrease sphincter spasm.

Highly symptomatic acute and chronic anal fissures will need more specific treatment, which usually focuses on decreasing sphincter tone. Topical nitroglycerin (0.2-0.4%) can be used to relax the internal sphincter. Rectiv (0.4% nitroglycerin) is commercially available. Headache caused by the nitroglycerin limits its use. Do not use 2% nitroglycerin intended for cardiac disease. Topical calcium channel blockers, such as nifedipine (0.2–2%) and diltiazem (2%) also cause relaxation of the internal sphincter. These medications must be prepared at a compounding pharmacy and do not cause headaches, making them better choice for primary use. It is frequently mixed with lidocaine and other agents for additional symptom relief. Topical therapy combined with stool softening with fiber is effective in up to 80% of cases.[20]

Surgical management is indicated with failed medical treatment, associated infection, and concern for other pathology like malignancy. Lateral internal sphincterotomy is the gold standard for surgical management and over 95% effective. Many surgeons try to avoid sphincterotomy in women of childbearing age due to the possibility of obstetrical sphincter injury. Sphincterotomy carries with it a risk of incontinence of 8-30%.[20] Botulinum toxin can achieve sphincter relaxation of medium duration to allow fissure healing. It has a higher long-term fissure recurrence rate but much lower long-term incontinence risk.[20] Other surgical options include fissurectomy and anal flap advancement procedures. The decision of what surgical procedure to use requires discussion between the surgeon and patient.

Anal Condyloma

Anal condyloma are caused by human papillomavirus (HPV). The condyloma or "warts" can be on the perianal skin as well as within the anal canal. It is very important that the treating physician is comfortable with anoscopy so the extent of intra-anal disease can be identified. Anal condyloma are sexually transmitted by both heterosexual and homosexual intercourse. Transmission is most common with unprotected anal receptive intercourse but can occur without. Condoms may not completely prevent transmission of HPV.[21]

There are more than 120 subtypes of HPV. Subtypes 6 and 11 have a low malignant potential. Other, more oncogenic, subtypes of HPV may affect the anal region. HPV is the leading cause of squamous cell carcinoma of the anus. Patients with HIV/AIDS and other immunosuppressed conditions are at higher risk for HPV disease and development of malignancies.[21]

The patient generally complains about the presence of lesions. Itching, bleeding, and pain may be associated. Difficulty with perineal hygiene is common with a large volume of disease.[22] Condyloma may be mistaken as hemorrhoids by the patient.

Diagnosis is by inspection of the perianal skin as well as anoscopy to visualize the anoderm. Condyloma may vary in number and size of lesions. Screening for other



Figure 5. Anal condyloma

sexually transmitted diseases should be part of the initial evaluation. A complete genitourinary examination is important to try to identify other sites of infection.[23]

After diagnosis, a treatment plan is established. If there is no intra-anal disease, topical therapies may be used. These include imiquimod (Aldara), podophyllotoxin (Condylox) and sinecatechins (Veregen). Physician administered treatments include cryotherapy, trichloroacetic acid application, surgical excision, electrosurgical fulguration and laser ablative therapy. Imiquimod (Aldara) may be used following complete excision to decrease recurrence.[24] More extensive disease mandates frequent trips to the operating room for surgical treatment. It is important to obtain a biopsy, especially in high-risk individuals. Condyloma may have varying degrees of dysplasia, carcinoma in situ and invasive carcinoma.[25]

Treatment, whether patient applied or physician administered, requires extensive follow-up up. Recurrence is common regardless of treatment choice. Vaccination for HPV should be discussed and screening for sexual partners is recommended.

Conclusion

Though anorectal conditions have overlapping symptoms, careful history and good physical examination can usually confirm diagnosis. If a patient mentions a symptom, they require examination. If a patient fails their initial treatment regimen or if the underlying diagnosis is unclear, referral to a colorectal surgeon is recommended.

References

1. Eisenhammer S. The internal anal sphincter and the anorectal abscess. Surg Gynecol Obstet. 1956; 103:501–506.
2. Cox SW, Senagore AJ, Luchtefeld MA, Mazier WP. Outcome after incision and drainage with fistulotomy for ischiorectal abscess. Am Surg. 1997; 63:686–689.
3. Gosselink M P, Van Onkelen RS, Schouten W R. The cryptoglandular theory revisited. Colorectal Dis. 2015; 17:1041–1043.
4. Ommer A, Herold A, Berg E, Fürst A, Schiedeck T, Sailer M. Germans 3-Guideline: rectovaginal fistula. Ger Med Sci. 2012;10:Doc15. doi: 10.3205/000166.
5. Nelson R. Anorectal abscess fistula: what do we know? Surg Clin North Am. 2002; 82:1139–51.
6. Sainio P. Fistula-in-ano in a defined population. Incidence and epidemiological aspects. Ann Chir Gynaecol. 1984; 73:219–224.
7. Hall JF, Bordeianou L, Hyman N. Outcomes after operations for anal fistula: results of a prospective, multicenter, regional study. Dis Colon Rectum. 2014; 57:1304–1308.
8. Abramowitz L, Soudan D, Souffran M ; Groupe de Recher- che en Proctologie de la Société Nationale Française de Colo- Proctologie and the Club de Réflexion des Cabinets et Groupe d'Hépato-Gastroentérologie. The outcome of fistulotomy for anal fistula at 1 year: a prospective multicentre French study.Colorectal Dis. 2016; 18:279–285.
9. Garcia-Aguilar J, Belmonte C, Wong WD, Goldberg SM, Madoff RD. Anal fistula surgery. Factors associated with recurrence and incontinence. Dis Colon Rectum. 1996; 39:723–729.
10. Rojanasakul et al Total anal sphincter saving technique for fistula-in-ano J Med ASS 2007; 90581-6.
11. Muldoon JP. The completely closed hemorrhoidectomy: a reliable and trusted friend for 25 years. Dis Colon and Rectum 1981: 24(3):211-14
12. Cataldo P, Ellis CN, Gregorcyk S, Hyman N, Buie WD, Church J, Chen J Fleshner P. Practice parameters for the management of hemorrhoids (revised). Dis Colon Rectum.2005;48:189 –194.
13. Wexner SD.The quest for painless surgical treatment of hemorrhoids continues. J Am Coll Surg. 2001; 193:174 –178.
14. Parks AG. The surgical treatment of hemorrhoids. Br J Surg.1956; 43:337–351.
15.Todd IP, Fielding LP eds. Rob & Smith's Operative Surgery Alimentary Tract and Abdominal Wall 3, Colon, Rectum and Anus. Fourth ed. London: Butterworths; 1983:480 – 488.
16. Sharif HI, Lee L, Alexander-Williams J. Diathermy hemorrhoidectomy. Int J Colorectal Dis. 1991; 6:217–219.
17. Gough MJ, Lewis A. The conservative treatment of fissure-in- ano. Br J Surg. 1983; 70:175–176.
18. Jensen SL.Treatment of first episodes of acute anal fissure: prospective randomised study of lignocaine ointment versus hydrocortisone ointment or warm sitz baths plus bran. BMJ. 1986; 292: 1167–1169.
19.Shub H A, Salvati EP, Rubin RJ. Conservative treatment of anal fissure: an unselected, retrospective and continuous study. Dis Colon Rectum. 1978;21:582–583.
20. Jones O M,Ramalingam T, Merrie A .Randomized clinical trial of botulinum toxin plus glyceryl trinitrate vs. botulinum toxin alone for medically resistant chronic anal fissure: overall poor healing rates. Dis Colon Rectum. 2006; 49:1574 –1580.
21.Welton ML, Sharkey FE, Kahlenberg MS. The etiology and epidemiology of anal cancer. Surg Oncol Clin N Am 2004; 13:263–75.
22. Zbar A P, Fenger C, Efron J, Beer-Gabel M, Wexner SD. The pathology and molecular biology of anal intraepithelial neoplasia: comparisons with cervical and vulvar intraepithelial carcinoma. Int J Colorectal Dis 2002; 17:203–15.
23. DeToma G, Cavallaro G, Bitonti A, Polistena A, Onesti MG, Scuderi N. Surgical management of perianal giant condyloma accuminatum. Eur Surg Res 2006; 38:418–22
24.Wieland U, Brockmeyer NJ, Weissenborn SJ, Hochdorfer B, Stucker M, Swoboda J, Altmeyer P, Pfister H, Kreuter A. Imiquimod treatment of anal intraepithelial neoplasia in HIV-positive men. Arch Dermatol 2006; 142:1438–44.
25. Shepherd N. Anal intraepithelial neoplasia and other neoplastic precursor lesions of the anal canal and perianal region. Gastroenterology Clinic North Am 2007; 36: 969–87.

Disclosure

None reported.

MM

The Dangers of Vaping

by Peter Laucks, DO & Gary A. Salzman, MD



UMKC School of Medicine

A year after the patent for vaping was submitted in 1963, the Surgeon General released his report "Smoking and Health" on the potential health consequences of cigarette smoking.





Peter Laucks, DO, MSMEd, (left), is in the Department of Internal Medicine, Pulmonary and Critical Care Fellowship at Truman Medical Centers, Kansas City, Missouri. Gary A. Salzman, MD, (right), MSMA member since 2007, is Professor of Medicine; University of Missouri-Kansas City School of Medicine, Kansas City, Missouri.
Contact: salzmang@umkc.edu

Abstract

As our nation turns away from smoking tobacco and toward legalization of marijuana, vaporization of both plants has increased in popularity. There are medical and cultural implications of this new trend which are just recently being reported and investigated. The purpose of this article is to review the scientific and sociological literature as it pertains to the vaporization of both marijuana and tobacco products and the potential medical and cultural implications of this new phenomenon.

Background

The invention of vaping is attributed to Herbert Gilbert, a cigarette smoker and scrap metal dealer from Pennsylvania. Gilbert's device was battery-powered to vaporize a liquid for inhalation, very similar to modern electronic cigarettes. He admitted to the *Smithsonian* magazine that he believed it to be a breakthrough alternative to cigarette smoking to save people from tobacco's harmful effects as it did not contain nicotine. After multiple permutations, the device was never mass-produced but its patent has been cited by many companies since then. He actually proposed an alternative use for the device for people that were dieting and believed that they could vaporize the tastes of their favorite foods to quench food cravings. He initially proposed a handful of flavorings including cinnamon, rum, orange, and mint.[1-2] A year after the patent was submitted in 1963, the Surgeon General Luther Terry released his report "Smoking and Health" on the potential health consequences of cigarette smoking. This was the first report implicating cigarettes in a causal relationship with lung cancer and heart disease as well as laryngeal cancer and chronic bronchitis.[3]

Since that time, "vaping" as it is called has diverged into two very separate activities with some common elements. The practice of vaporizing tobacco products and nicotine-containing liquids continued to be developed and has manifested in the modern day in the form of both commercial and custom-made dedicated devices. Separately, in the early 1990s vaping emerged as a new method to use marijuana both recreationally and medicinally.[4] These behaviors have significant overlap in the devices used for inhalation, the cultural changes associated with their acceptance, and the potential health effects. In this article, we will examine the cultural and medical implications of vaping as well as some obstacles to good scientific study.

Cultural

Although vaping tobacco was initially conceived as a healthier way

to smoke, it took on a life and an industry of its own. In 2019, vaping tobacco is a new gateway to nicotine abuse that frequently skips the initial phase of addiction to cigarettes. It has been perceived as safer, better tasting, more efficient, and more discrete. Vaping tobacco provides new users with an overall better initial experience when compared to the first time smoking cigarettes.[4-5]Eighty years ago, cigarette smoking was culturally accepted and even considered "cool." In the present day, vaping tobacco has its own culture that is often separate from cigarette smoking. Substantial marketing investment by tobacco companies in response to a decrease in combustible cigarette consumption in the last few years has led to an overall normalization of vaping tobacco and a change in perception that it is safe. Combustible cigarette smoking has become culturally stigmatized, with many cities outlawing tobacco smoking in bars and restaurants and sometimes even on the street. Vaping is a method by which people can consume tobacco products without being part of a fringe and marginalized group.[4-6]

Marijuana has always had its own culture. Induction into this culture previously required a supplier of the illegal drug that would also provide education about how to smoke it, either through pipes or rolled into cigarette form. There are many generations of marijuana smokers who are now considering the long-term health effects of smoking. Much like with vaping tobacco products, chronic marijuana smokers are vaporizing marijuana as a potentially healthier alternative. This is especially true of the "Baby Boomer" generation.[7] The legalization of marijuana has drastically changed the landscape of the use of this drug, both in terms of the potency of available products and the methods by which it can be ingested or inhaled. In states where marijuana has become legal, vaporizing marijuana oils is more convenient and more popular.[6,7]

A final cultural consideration of vaporization of tobacco is the misunderstanding that vaporizing tobacco is somehow a viable way to quit smoking cigarettes. No clinical trials have been able to show that vaping helps reduce cigarette smoking, but there are some trials that show that dual-use is common and that many people who start vaping with the intention to quit smoking end up smoking cigarettes and vaping tobacco. They are acquiring the risk profiles of both activities without benefit.[8] It is common to see patients in this group feel somehow encouraged that through vaping they have been able to reduce their intake of combustible cigarettes, with no consideration to the unknown possible dangers of vaporizing.[9]

Problems with Studies

Good clinical evidence is lacking regarding the potential harm of vaping or the potential benefits. There are some problems with studying something like vaping. For one thing, any research has to make a distinction between vaporizing marijuana and vaporizing tobacco and this is not always possible. Additionally, the methods by which people vaporize tobacco and marijuana differ. As far as tobacco devices go, there are many brands with many different compositions and construction designs. Regarding the vaporization of marijuana, there are no standardized devices and there are no standard formulations.

Studies to prove a benefit of vaporizing tobacco over smoking cigarettes have been confounded by the lack of a direct correlation between the number of puffs of an electronic cigarette and the number of conventional cigarettes smoked. With different brands of electronic cigarettes having different chemical ingredients and different concentrations of nicotine, the issue is even more complicated.[9,10] Many of the studies performed on electronic cigarettes used a Nicorette inhaler as a control for comparison. It is important to note that the Nicorette inhaler does not heat its component chemical liquid, where vaporization does heat the internal components and the liquids.[11]

The studies on the safety or dangers of vaporizing marijuana are limited in number because the marijuana itself is difficult to acquire. There were a small number of the plants released in the early 90s for clinical research.[12] Most of those studies utilized the same device, manufactured under the name "Volcano". This device is expensive and is drastically different from any of the modern handheld devices for vaporizing marijuana and tobacco. It does not serve as a good facsimile for comparison to modern day vaporization technology.

Many of the clinical research studies available focus on aspects of vaping such as the amount of nicotine or marijuana delivered but there's not a great deal of evidence on the analysis of other toxins released both from vaporizing tobacco leaf products and marijuana. With all of these limitations, most of the available studies are non-clinical or have very small numbers of study subjects. A strong and thorough assessment of the potential dangers of vaporizing tobacco and marijuana products has not been forthcoming.[12,13]

Medical Dangers of Vaping

All of the medical dangers of vaping are unknown. Only a small number of people who admit to vaping marijuana are doing so for medical reasons, and there are almost no studies. A large number of people believe that vaping tobacco is a healthy way to quit, and this belief has been fostered by the tobacco industry.[6,14] There is no strong clinical signal in the direction of using electronic cigarettes as an effective method of quitting smoking. It is difficult to hold an informed discussion with patients about the potential risks and benefits of vaping. Potential risks come from multiple places: device specific concerns, the makeup of the liquid products being vaporized, and the potential for toxicity of both nicotine and marijuana when inhaled in concentrated forms.

Chemical Composition of the Liquid Products

The pharmacologically active components of vaping products are not regulated, and the methods by which they are extracted and suspended in solution vary greatly. The user believes they are inhaling a pure form of THC (the active component of marijuana) or nicotine but there is often little regard for what else is being inhaled concomitantly. The risk profiles of these inhaled chemical mixtures change significantly depending upon the method by which they are vaporized or heated.[15-17]

The conventional solvents for the dissolution of nicotine or THC have been propylene glycol and glycerol, and these are the best studied. Initially thought to be benign, there is now some research demonstrating that propylene glycol when vaporized causes significant respiratory irritation and even increases the incidence of asthma. The breakdown products from heating propylene glycol and glycerol to target temperatures include formaldehyde and hemiacetals such as acetaldehyde. Formaldehyde is a Group 1 carcinogen that contributes a 5-15 times higher lifetime risk of cancer. It is present in traditional smoked tobacco in much lower quantities. Hemiacetals such as acrolein and acetone have been implicated in nasal irritation, cardiovascular effects, and lung mucosal damage and these byproducts are produced in higher quantities with higher voltage devices. Basically, as the temperature of the coil increases, the carcinogenic risk of vaping approaches that of traditionally smoked cigarettes.[9,10,16-18]

The flavorings added to the nicotine and THC extracts represent a separate but no less worrisome health risk. We tend to think of food additives as safe, and we sometimes learn empirically about the hazards they pose when people are exposed to them in ways other than direct ingestion. Diacetyl is a food additive that is also used in flavoring electronic cigarettes that approximates the flavor of butter. In the early 2000s, diacetyl was implicated as a cause of bronchiolitis obliterans organizing pneumonia (BOOP) in factory workers exposed to it in large quantities. Although it is considered safe to eat, exposure to this chemical is regulated and limited by OSHA due to its proven health effects.[8,19] The flavoring additives of electronic cigarettes on the mass market are typically passed through the FDA under a provision that these chemicals, almost exclusively synthetic, are "generally accepted as safe" for human consumption. The caveat with this provision is that consumption refers to oral ingestion. It is unknown what potential health effects result when something perfectly safe to eat and digest is vaporized at 500 degrees and inhaled. Some research is demonstrating that the flavorings incorporated into electronic cigarettes have cytotoxic effects.[8] Furthermore, sweeter flavorings tend to contain stronger oxidizers. One study used a murine model of lung epithelial cells and demonstrated a higher release of inflammatory cytokines IL-6 and IL-8 as well as fibroblastic changes in the subjects exposed to sweeter electronic cigarette flavorings, with the mice appearing to lose redox balance.[20]

Problems with Manufacturing of E-Cigarettes

There is no real regulation of either nicotine-containing electronic cigarette products or marijuana extracts for vaping. Every part of the manufacturing process allows for error and contamination, with

too many unknowns about the potential dangers of vaporizing each individual component. With marijuana still being illegal in many states and on the federal level, this is even more of a problem with THC containing products available on the black market. Recent research has shown that Vitamin E is a new solvent into which these THC extracts are dissolved, probably due to its relative ease of acquisition. All of the health effects of inhaling vaporized vitamin E are unknown.[21] There is recent evidence that vaporized vitamin E oil may be a cause of Electronic cigarette and Vaping Associated Lung Injury (EVALI). The simplest and highest-yield method of extracting THC oil from marijuana buds utilizes a rudimentary setup that exploits certain properties of compressed butane gas, called "supercritical fluid extraction". The traditional backyard equipment setup is a PVC pipe and a butane lighter refill canister which, under the right conditions, can explode with multiple case reports of severe burns. Most of those who self-report home extraction of THC oil learned how to do so from materials available on the internet, and by watching videos on Youtube.[22,23]

Toxicity of Nicotine and THC

It bears noting that when vaping is successful and delivers concentrated nicotine or THC to the user, the amount of drug delivered is much higher than would typically be inhaled by burning and smoking the raw tobacco or marijuana plant. Sociological questionnaires on vaping habits reveal a trend toward dabbing THC contributing to addictive behavior not reported by those users who smoke marijuana in a non-concentrated form. The same pattern of addiction, tolerance, and withdrawal that has been observed in drugs like heroin, traditionally considered "hard drugs", is now being reported in those vaping THC.[5,6,15,24] There have been some cases of nicotine poisoning from using electronic cigarettes, with an increased risk of toxicity associated with customized devices and higher nicotine concentrations in the liquids. Finally, many of those who attempted to quit cigarettes by transitioning to vaping are reporting that quitting vaping is actually significantly harder than quitting smoking traditional cigarettes, with some respondents even turning back to cigarettes as a way to help wean off their vaporizer device.[25-27]

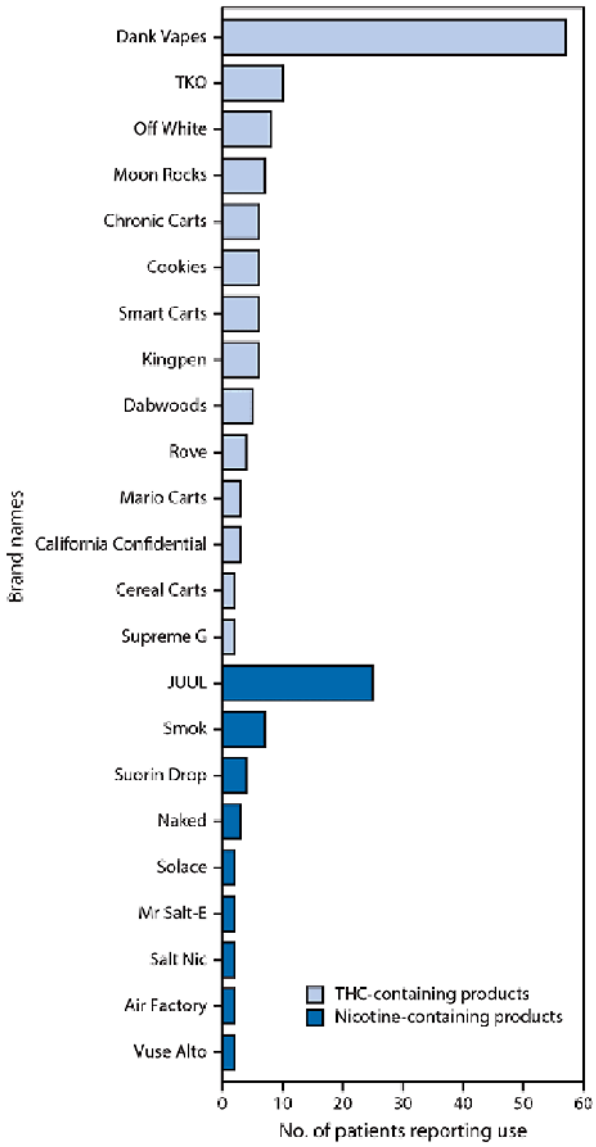


Figure 1. Vaping Brands Chart- E-cigarette Product Use, or Vaping, Among Persons with Associated Lung Injury — Illinois and Wisconsin, April–September 2019.
Ghinai I, Pray IW, Navon L, et al. MMWR Morb Mortal Wkly Rep 2019;68:865–869.

Device-Specific Concerns

The basic design of the device, in the case of vaping both tobacco and marijuana, is largely unchanged from the original patent by Gilbert. There is a reservoir that holds an oil or liquid, a mouthpiece, and a heating element. Theoretically, vaporizing the liquid does not combust it and saves the person vaping from exposure to byproducts generated by high heat. However, there is no regulation of these devices and no agreed upon standard temperature. There appears to be a wide variance in the quality of the

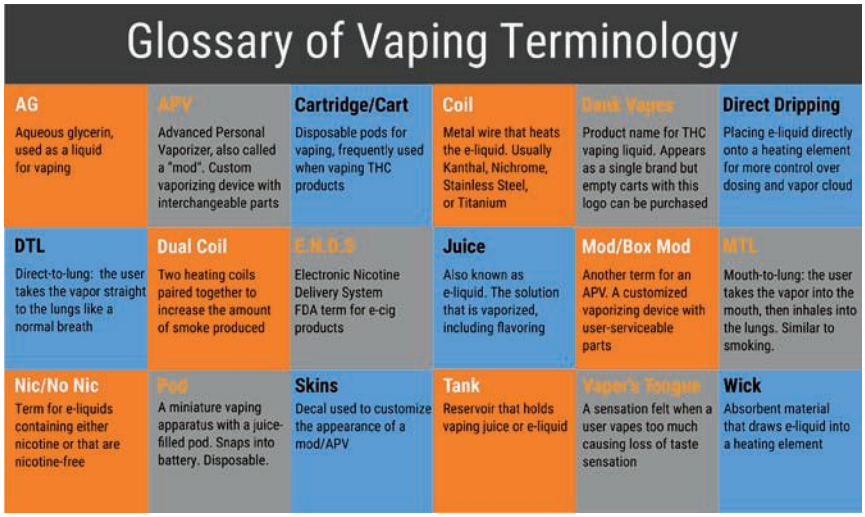


Figure 2. Vaping Terminology

components of these devices depending on the price of purchase.[2,10,11,16,28]

There are multiple different metals used for the heating element, including: Nichrome (nickel-chrome), tungsten, stainless steel, and Kanthal (Ferritic iron chromium aluminum alloy) among others. Powered by a battery, the element wire is heated to a temperature range around 375-525 degrees. The long term effects of sustained exposure to the oxide products of these metals are unknown.[2,16,28]

There are manufactured electronic cigarettes under various brand names (Figure 1), but there is also a subculture of people who vape either tobacco and marijuana (or both) through devices that they custom build, referred to as "mods". There are many websites and physical stores catering to this hobby, and there are many different accessories and components available to change different aspects of device performance. A user can find stronger batteries, a wide array of device designs, and an even broader selection of metals for the heating element in different lengths and diameters. The practice of "direct dripping" involves users directly dripping the vaping liquid onto a heated coil with the express intention of increasing the quantity of vapor as well as increasing the concentration of the active ingredients being vaped.[6,16,20,29] This practice increases toxin exposure and often goes along with modified devices that increase temperature by increasing voltage. Increasing the voltage of the device with stronger batteries and driving higher temperatures on the heating coils has been shown to approach equivalency with cigarettes in terms of exposure to carcinogens. It is unknown what other potential health effects are caused by modifying these properties of the device.[10]

Shifting Perspectives on Vaping

The smoking of tobacco in pipes and cigarettes used to be much more common, and it took a long time to realize the true dangers of combustible cigarette smoking. The terminology used can be confusing (Figure 2). The available body of medical literature regarding the potential harms of vaping consists of data from animal models, observational studies with small numbers of subjects, and single case reports and series. One observational study utilized pulmonary function tests to show that vaping decreases FeNO and increases respiratory impedance.[30] There have been multiple case reports of vaping-associated lipoid pneumonia. As previously mentioned, there have been reports of both THC and nicotine toxicity. There are many reports of mechanical injury and burns from malfunctioning devices. The perception that vaping is safe is starting to change.

An additional common theme has been that many of the electronic cigarette and vaping associate lung injury (EVALI) cases are related to black-market THC products marketed under a variety of brand names. In one study, approximately 96% of THC for vaping was typically sold in pre-filled cartridges or "carts". A clear majority, over 60%, were sold under the label 'Dank Vapes.' This does not represent an actual brand, but rather a type of empty packaging readily available online and in vaping shops which can then be filled with whatever homemade product a dealer has at their disposal. It is not widely known by consumers that Dank Vapes is not a brand, and this may contribute to a sense of false trust.[31,32]

Conclusion

The cultural phenomenon of vaping both marijuana and nicotine were billed as a healthy alternative to smoking and at times even seen as an option to aid in cessation. With the current body of evidence and the outbreak of EVALI in 2019, it is incumbent upon all healthcare practitioners to advise patients that vaping should not be considered safer than smoking and that there are very real and new dangers associated with vaping that still require further study. Providers must learn more about the dangers of vaping and identify adverse health effects from this practice in patients. An evidence-based approach to smoking cessation based on established data and practice patterns is needed.

References

1. White, A. (2018, December). Plans for the First E-cigarette Went Up in Smoke 50 Years Ago. Smithsonian Magazine.
2. Bekki, K., Uchiyama, S., Ohta, K., Inaba, Y., Nakagome, H., & Kunugita, N. (2014). Carbonyl Compounds Generated from Electronic Cigarettes. International Journal of Environmental Research and Public Health, 11(11), 11192–11200.
3. US Department of Health, Education, and Welfare. Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service. Washington, DC: US Department of Health, Education, and Welfare, Public Health Service; 1964. (Public Health Service Publication No. 1103)
4. Giroud, C., Cesare, M. D., Berthet, A., Varlet, V., Concha-Lozano, N., & Favrat, B. (2015). E-Cigarettes: A Review of New Trends in Cannabis Use. International Journal of Environmental Research and Public Health, 12(8), 9988–10008.
5. Budney, A. J., Sargent, J. D., & Lee, D. C. (2015). Vaping cannabis (marijuana): parallel concerns to e-cigs? Addiction, 110(11), 1699–1704.
6. Schauer, G. L., King, B. A., Bunnell, R. E., Promoff, G., & Mcafee, T. A. (2016). Toking, Vaping, and Eating for Health or Fun. American Journal of Preventive Medicine, 50(1), 1–8.
7. Murphy, F., Sales, P., Murphy, S., Averill, S., Lau, N., & Sato, S.-O. (2015). Baby Boomers and Cannabis Delivery Systems. Journal of Drug Issues, 45(3), 293–313.
8. Barrington-Trimis, J. L., Samet, J. M., & Mcconnell, R. (2014). Flavorings in Electronic Cigarettes. Jama, 312(23), 2493.
9. Jensen, R. P., Luo, W., Pankow, J. F., Strongin, R. M., & Peyton, D. H. (2015). Hidden Formaldehyde in E-Cigarette Aerosols. New England Journal of Medicine, 372(4), 392–394.
10. Kosmider, L., Sobczak, A., Fik, M., Knysak, J., Zaciera, M., Kurek, J., & Goniewicz, M. L. (2014). Carbonyl Compounds in Electronic Cigarette Vapors: Effects of Nicotine Solvent and Battery Output Voltage. Nicotine & Tobacco Research, 16(10), 1319–1326.
11. Goniewicz, M. L., Knysak, J., Gawron, M., Kosmider, L., Sobczak, A., Kurek, J., … Benowitz, N. (2013). Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. Tobacco Control, 23(2), 133–139.
12. NIH (National Institutes of Health). 1997. Workshop on the Medical Utility of Marijuana. Report to the Director, National Institutes of Health by the Ad Hoc Group of Experts. Bethesda, MD, February 19–20, 1997. Bethesda, MD: National Institutes of Health.
13. Hazekamp, A., Ruhaak, R., Zuurman, L., Gerven, J. V., & Verpoorte, R. (2006). Evaluation of a vaporizing device (Volcano®) for the pulmonary administration of tetrahydrocannabinol. Journal of Pharmaceutical Sciences, 95(6), 1308–1317.
14. Krauss, M. J., Sowles, S. J., Mylvaganam, S., Zewdie, K., Bierut, L. J., & Cavazos-Rehg, P. A. (2015). Displays of dabbing marijuana extracts on YouTube. Drug and Alcohol Dependence, 155, 45–51.
15. Loflin, M., & Earleywine, M. (2014). A new method of cannabis ingestion: The dangers of dabs? Addictive Behaviors, 39(10), 1430–1433.
16. Talih, S., Balhas, Z., Salman, R., Karaoghlanian, N., & Shihadeh, A. (2016). "Direct Dripping": A High-Temperature, High-Formaldehyde Emission Electronic Cigarette Use Method. Nicotine & Tobacco Research, 18(4), 453–459.
17. Talih S, Salman R, Karaoghlanian N, et al. "Juice Monsters": Sub-Ohm Vaping and Toxic Volatile Aldehyde Emissions. Chemical Research in Toxicology. 2017;30(10):1791-1793.
18. Farsalinos, K. E., Voudris, V., & Poulas, K. (2015). E-cigarettes generate high levels of aldehydes only in 'dry puff' conditions. Addiction, 110(8), 1352–1356.
19. Harber P, Saechao K, Boomus C. Diacetyl-Induced Lung Disease. Toxicological Reviews. 2006;25(4):261-272.
20. Lerner CA, Sundar IK, Yao H, et al. Vapors Produced by Electronic Cigarettes and E-Juices with Flavorings Induce Toxicity, Oxidative Stress, and Inflammatory Response in Lung Epithelial Cells and in Mouse Lung. Plos One. 2015;10(2).
21. Lewis N, McCaffrey K, Sage K, et al. E-cigarette Use, or Vaping, Practices and Characteristics Among Persons with Associated Lung Injury - Utah, April-October 2019. MMWR Morb Mortal Wkly Rep. 2019;68(42):953–956. Published 2019 Oct 25.
22. Gussow, L. (2014). Toxicology Rounds: Dangerous new drugs hit the streets. Emergency Medicine News, 36(5), 1.
23. Sugie, H., Sasaki, C., Hashimoto, C., Takeshita, H., Nagai, T., Nakamura, S., … Kurihara, K. (2004). Three cases of sudden death due to butane or propane gas inhalation: analysis of tissues for gas components. Forensic Science International, 143(2-3), 211–214.
24. Daniulaityte, R., Nahhas, R. W., Wijeratne, S., Carlson, R. G., Lamy, F. R., Martins, S. S., … Sheth, A. (2015). "Time for dabs": Analyzing Twitter data on marijuana concentrates across the U.S. Drug and Alcohol Dependence, 155, 307–311.
25. Chen. FDA Summary of Adverse Events on Electronic Cigarettes. Nicotine & Tobacco Research. 2012;15(2):615-616.
26. Monroy, A.E.; Hommel, E.; Smith, S.T.; Raji, M. (2012). Paroxysmal Atrial Fibrillation Following Electronic Cigarette Use in an Elderly Woman. Clin. Geriatrics, 20, 28–32.
27. Hua M, Alfi M, Talbot P. Health-Related Effects Reported by Electronic Cigarette Users in Online Forums. Journal of Medical Internet Research. 2013;15(4).
28. Hutzler, C., Paschke, M., Kruschinski, S., Henkler, F., Hahn, J., & Luch, A. (2014). Chemical hazards present in liquids and vapors of electronic cigarettes. Archives of Toxicology, 88(7), 1295–1308.
29. Morean, M. E., Kong, G., Camenga, D. R., Cavallo, D. A., & Krishnan-Sarin, S. (2015). High School Students Use of Electronic Cigarettes to Vaporize Cannabis. Pediatrics, 136(4), 611–616.
30. Chaumont M, Borne PVD, Bernard A, et al. Fourth generation e-cigarette vaping induces transient lung inflammation and gas exchange disturbances: results from two randomized clinical trials. American Journal of Physiology-Lung Cellular and Molecular Physiology. 2019;316(5).
31. Ghinai I, Pray IW, Navon L, et al. E-cigarette Product Use, or Vaping, Among Persons with Associated Lung Injury — Illinois and Wisconsin, April–September 2019. MMWR Morb Mortal Wkly Rep 2019;68:865–869.
32. Aubrey A. Many Vaping Illnesses Linked To Black Market 'Dank Vapes' Or Other THC Products. NPR. September 2019. https://www.npr.org/sections/health-shots/2019/09/27/765151187/many-vaping-illnesses-linked-to-black-market-dank-vapes-or-other-thc-products.

Disclosure

None reported.

MM

Hindsight 2020



New Loss Prevention Seminar for Physicians

The medical professional liability industry is currently experiencing an increase in the severity of jury verdicts. While jurors are not permitted to use hindsight in arriving at their decisions, they often do.

Join us as we retrospectively examine factors affecting verdict severity and will demonstrate how fundamental risk management principles can help result in a successful defense.

Looking back allows us to see what went right and what went wrong. **That's why hindsight is 20/20**.

PROASSURANCE LOSS PREVENTION SEMINARS 2020

ProAssurance
Treated Fairly

Healthcare Professional Liability Insurance & Risk Resource Services

Visit ProAssurance.com/Hindsight to find a seminar near you!

800.282.6242



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

