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Infectious Disease: Public Health Triumphs & Ongoing Challenges



Missouri's Fentanyl Problem: The China Connection

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Missouri Medicine

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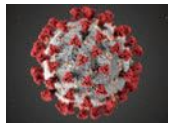
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Keep up with the challenges facing good medicine...

the new normal

What are the risks associated with **telemedicine?**

We're barely making payroll, what if we **can't make a payment?**

I'm a retired doc that wants to help, **will I be covered?**

Will my premium be lower **while I'm closed or not doing certain surgeries?**

What do you do to help burned out physicians **serving on the frontline?**

Am I covered if I get infected?

How do we keep our practice safe?

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I Stuffed Their Mouths with Gold

Part II

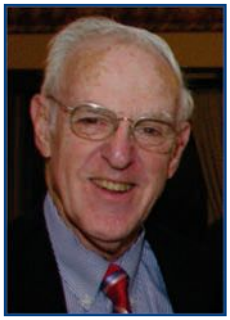
by Arthur Gale, MD

Private Equity Firms Buy Physicians' Practices
Doctors Become Commodities
Cost of Health Care to Consumers Continues to Rise

In 2017 I wrote an article in *Missouri Medicine* titled, "I Stuffed Their Mouths With Gold" with the subtitle "How Hospitals Destroyed the Private Practice of Medicine."

The quote "I stuffed their mouths with gold" was said by British Labor Minister of Health Aneurin Bevan shortly after World War Two ended when the British people voted Prime Minister Winston Churchill and his Conservative party out of office. Bevan, a fiery if crude orator from Welsh coal mining country was the prime mover behind the creation of the British National Health Service (NHS). Under the NHS doctors in Britain are employees of the government. This system is commonly referred to as socialized medicine.

In 1948 Bevan explained that he was able to get doctors in Britain to go along with socialized medicine with the statement, "I stuffed their mouths with gold." What he meant by this famous and oft quoted sentence is that he allowed some British doctors, or consultants as they were called, to continue seeing private paying patients if they accepted NHS patients.



Arthur H. Gale, MD, MSMA member since 1976, is a *Missouri Medicine* Contributing Editor. He practices Internal Medicine in St. Louis.

In the 1990s U.S. hospitals, as part of the managed care revolution, began buying primary care physicians and their practices by "stuffing their mouths with gold." To get doctors to become their employees hospitals initially paid them exorbitant salaries—essentially bribes. The boards of directors of hospitals told the public and doctors that "consultants" (who were never named) advised them that buying medical practices would improve quality and lower health care costs. They would achieve these goals through "integration, coordination, and economy of scale." These three strategies–integration, coordination, and economy of scale–proved to be meaningless slogans as hospital costs in the U.S. continued to rise, and are now by far the highest in the industrialized democracies.[1] Basically hospital boards of directors all across the nation misled the public.

The real reason hospitals employed physicians was that as employees they would refer patients to hospital-owned facilities for tests and procedures which were much costlier than when done in private outpatient offices and facilities. This gave hospitals monopoly power in dealing with private and government payers and increased their profits. Physicians have essentially become profit centers for hospitals. Without ownership of physician practices the overpriced financial structure of hospitals would collapse. This is why hospitals panicked when Medicare recently enacted a rule to pay hospital-owned physicians at the same rate as physicians in private practice if they practiced off the hospital's main campus. This is called site neutral payments. Currently, Medicare pays hospital-owned physicians about 70% more than independent physicians. There is no logical reason for this discrepancy. Thus far, hospitals have been able to block implementation of the site neutral rule.[2]

The initial high salaries paid to primary care doctors eventually ended. Hospital administrators forced physicians to work harder and to see patients faster and faster essentially on an assembly line basis and forced them to use a dysfunctional electronic health record (EHR). This has led to mass physician burnout. Policy makers, academics, and thought leaders continue to blame physicians for the high cost of hospital care when the real cause is high prices charged by hospitals.[3]

In the past few years private equity funds have emulated the hospitals viewing physicians as profitable investments. After all they reason if physicians are profit centers for hospitals why not have non hospital based physicians become profit centers for private equity funds. The private equity funds have never bothered to pretend as have the hospitals that owning physician practices will lower overall health care costs.

Private equity funds anticipate average annual returns on investments of 20% or more. The firms usually take 60 to 80% ownership although this can vary. The initial amount of money paid to physicians varies but may be as high as $1 million to $2 million per physician. After purchase physicians usually receive market rate salaries. The private equity fund will then usually try to sell the practice within three to seven years.[4]

The major focus has been on purchasing emergency room physicians, anesthesiologists, dermatologists, and radiology. More recent acquisitions have been ophthalmology, urology, gastroenterology, orthopedics, and even some primary care doctors.

One of the main inducements to physicians to sell their practices is that their offices will run more efficiently and they will not have to deal with the complexities such as value-based purchasing requirements of both Medicare and private payers.[5] As an aside, value-based purchasing has not been shown to lower health care costs.[6]

Private equity companies also state that their large size allows negotiation of higher payments from insurers, and they also claim it frees up physicians from running the business aspects of their practices and gives them more autonomy and free time.

Nearly all physician practice management companies that publicly traded in the 1990s failed and went bankrupt. Private equity

acquisitions are structured differently and its backers say that won't happen in today's corporate medical environment. Most states bar nonphysicians from owning medical practices. However, states have rarely enforced these laws and private equity firms say that they have addressed and resolved this legal problem.[7]

Some firms want to do a quick flip and cash out. A Young Physicians Section (YPS) report of the American Medical Association (AMA) Annual meeting in 2018 stated that 14% of all private equity acquisitions are in health care and they rapidly "flip" them. One example was a dermatology group being owned by four different groups within an 18-month period! Some practices eventually might even be sold to insurance companies or hospital networks which many doctors wanted to avoid. The same AMA report cites high pressure tactics used by private equity firms to induce doctors to sell ("If you don't sell to us we will open 20 offices in your catchment area to compete with you.")[8] Some dermatologists reported pressure to up code, meet production numbers for procedures, and sell products in their offices.[9]

The same hardball tactics are used when physicians try to leave. One physician reported that the private equity company posted an advertisement in the newspaper that he had retired when he was still in practice. Eventually the private equity fund under pressure posted a notice that he had not retired. A similar tale was told to me by a dermatologist from Michigan whom I met two years ago. He began meeting former patients who told him they were sorry to hear that he retired when he had not retired. He soon realized the private equity firm had given a list of his patients to newly minted dermatologists. He threatened a lawsuit against the private equity firm and eventually it notified and apologized to his former patients. These are anecdotes. But they are a sample of the kinds of folks who run these companies. It's all about their profits.

The main public backlash thus far has come from surprise out of network bills sent to patients from emergency room physicians and anesthesiologists who are owned by private equity firms. This backlash against out of network billing and surprise billing has been fueled by consumer groups and the media and has resulted in Congressional hearings. The public is demanding transparency in all hospital billing. Lawmakers have spent months working on legislation to address this problem. Private equity companies and their allies are worried. They have even sponsored purported grass root consumer groups to oppose such legislation and have thus far been successful in blocking such legislation.[10]

Private equity ownership of physician practices is basically the flip side of hospital ownership of physician practices. Both view the physician as a commodity like cotton or soybean futures—no different from any other commodity in which they can invest and reap a profit. In one sense the private equity firms are more honest than the hospitals. At least they don't pretend as do the hospitals that owning physician practices will lower health care costs.

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MM

Who You Gonna Call?

by George J. Hruza, MD

You get a professional liability insurance bill 50% higher than last year; even worse, your insurance carrier stops writing policies in Missouri. Who you gonna call? Your staff is swamped by prior authorization requests and your patients are unable to get the medications or procedures they urgently need. Who you gonna call? You are laid off and replaced by a non-physician clinician by your hospital employer for "budgetary" reasons. Who you gonna call? Your gym ($3000/yr)? Your cellphone operator ($3000/yr)? Your Internet and TV service provider ($3000/yr)? Maybe your hospital CEO will help? I don't think so—forty years ago, 97% of them were MDs. Today just 3% are. Their interests are rarely aligned with those of physicians.

I submit to you that you should call the Missouri State Medical Association (MSMA, $395/yr) for help. It is the one and only organization that has as its primary mission the support of physicians and their patients in Missouri. I looked over the last 11 years of MSMA advocacy efforts. There has been an impressive array of successes both in passing proactive legislation and in blocking bills that were very harmful for physicians and their patients.

Missouri has gone through three professional liability crises during my medical career. In the 1980s malpractice premiums were skyrocketing. Under the leadership of MSMA, we were able to get a first-ever cap for non-economic damages (pain and suffering) signed into law in 1986. This led to a reduction in frivolous lawsuits and stabilized the insurance market during the next decade.

The courts picked away at the reform law by allowing a multiple of the cap per case equal to the number of named defendants. This basically eviscerated the law. Malpractice lawsuits shot up and premiums soon followed. The crisis got so bad that all traditional malpractice insurers left the state and we were left with mutual insurance companies with limited capitalization and risk for assessment of the insured physicians. MSMA spearheaded our second major tort effort in 2005 that reinstated a single non-economic damage cap per incident. Insurers returned to the market, lawsuits declined and insurance premiums stabilized.

In 2012, the Missouri Supreme court declared the non-economic damage caps to be unconstitutional based on common law principles established at statehood in 1821 (which are in turn based on British common law from 1607). A third malpractice insurance crisis was about to take off. MSMA again swung to action and, in 2015, got the legislature to reestablish the non-economic damage cap. Insurance premiums have again stabilized and even declined.

MSMA has successfully spearheaded additional reforms to reduce lawsuit abuse: expert witness reforms that require testimony to be based on evidence widely accepted by the scientific community, updates to the collateral source rule so plaintiffs can only recover actual monetary damages instead of billed charges and increasing the standard of proof for punitive damage claims. In spite of all these successes, the City of St. Louis makes the list of the top 10 Judicial Hellholes in the United States almost every year. We need the MSMA to be strong to protect the gains we have achieved and continue to fight lawsuit abuse.

The MSMA is active in Jefferson City in all healthcare legislation and has an enviable record of supporting legislation signed into law that is good for Missouri patients and physicians, and stopping legislation harmful to our patients. See Table next page.



George J. Hruza, MD, MBA, FAAD, FACMS, MSMA member since 1989, is the 2020-2021 President. He practices Dermatology in St. Louis.

Select Legislation Important for Physicians and Patients that MSMA Passed or Blocked

2010
- Insurance company prompt pay (signed into law)
- Naturopath licensure and scope expansion (blocked)
- Private Medicaid fraud lawsuits (blocked)
- Statute of limitations expansion for medical malpractice cases and weakening of the collateral source rule (blocked)
- Tiering of physicians (blocked)
- Autism insurance coverage (signed into law)

2011
- Drug testing of surgeons (blocked)
- Chiropractors Medicaid payment (blocked)
- Allowing professional counselors to diagnose (blocked)
- Board of Healing Arts civil penalties (blocked)
- Implementation of concussion protocols for student athletes (signed into law)
- Preemption of local tobacco laws (blocked)

2012
- Increased use of ignition interlock devices (signed into law)
- Regulations on the creation and operation of HIEs (signed into law)
- Lay midwife licensure (blocked)
- CRNA scope expansion (blocked)
- Co-pay equity between primary care physicians and physical therapists (blocked)

2013
- Prompt credentialing improvements (signed into law)
- Telehealth reimbursement parity (signed into law)
- Repeal of collaborative practice act (blocked)
- Volunteer physician malpractice immunity (signed into law)
- Updating of newborn screening requirements (signed into law)
- Mandatory arbitration for claims over 30 days unpaid (blocked)

2014
- Non-physician clinicians scope expansion (blocked)
- Tanning bed parental permission (signed into law)
- Establishment of ECHO telehealth distance learning program (signed into law)
- Statewide Medicaid managed care implementation (blocked)

2015
- Tort reform (signed into law)
- Establishment of direct primary care services (blocked)
- Expansion of APRN scope-of-practice (blocked)
- Parental notification of immunization exemptions (signed into law)

2016
- Telehealth expansion (signed into law)
- Prohibit MOC/MOL for licensure (signed into law)
- Licensure not conditioned on participating in any health insurance plan (signed into law)
- Step therapy reform (signed into law)
- Insurance contracts gag clauses banned (signed into law)
- APRN, athletic trainers, physical therapists, radiology technicians scope expansion (blocked)

2017
- Expert witness reform (signed into law)
- Collateral source rule updated (signed into law)
- Tort reform fix for hospital non-employees (signed into law)
- Requirements for medical student mental health and wellbeing (signed into law)
- APRN opioid prescriptive authority expansion (blocked)
- Implementation of statewide naloxone protocol (signed into law)

2018
- Protection of prudent layperson standard in the ER (signed into law)
- Prohibit pharmacy gag clauses (signed into law)
- Non-physician clinicians, physical therapists, radiology technicians scope expansion (blocked)
- Implementation of workers compensation fee schedule (blocked)
- Increased Medicaid post-partum benefits (signed into law)

2019
- Prior authorization reform (signed into law)
- Prohibit use of virtual credit cards by insurers (signed into law)
- Establishment of pregnancy-associated mortality review board (signed into law)
- Implementation of statewide MAT insurance coverage for opioid disorders (blocked)
- Defeat of various anti-vaccination requirements for physicians (blocked)
- Independent pharmacist prescribing (blocked)

2020
- Punitive damages only for intentional or malicious act (signed into law)
- Prompt credentialing to pay from the date of application (signed into law)
- Overpayment transparency (signed into law)
- Vaping prohibitions (signed into law)
- Criminal penalties for gender dysmorphia treatments (blocked)

This year was a very successful year, in spite of the COVID-19 pandemic. The MSMA has arranged for regular Saturday morning calls with Randall Williams, MD, Missouri Health Director, giving COVID-19 updates to help our members navigate the pandemic. We have gotten significant COVID-19 regulatory waivers in licensure requirements and, especially, in telehealth. We are also working for reasonable liability protection related to COVID-19. With the nationwide shortage of PPE, MSMA has worked with other medical societies to make PPE available for Missouri physicians through a GPO – just visit actionppe.org/3/msma. This enviable record is thanks to the great work of MSMA staff and the support of our members.

We cannot rest on our laurels. There are many groups, including the state's trial attorneys, the hospitals, integrated healthcare systems, pharmacy benefit managers, pharmacy chains, health insurers, and many others that are in Jefferson City every day often pushing positions that are at odds with what is best for our patients. We are looking forward to working on our "to do" list when the 2021 legislative session gets underway in January, including getting a statewide PDMP, meaningful truth-in-advertising in healthcare, eliminating the use of MOC by hospitals and insurers for credentialing and getting a reasonable definition of surgery into law.

To get these proposals from proposed legislation into law, we need the help from many of you, our members. What can you do to help?

1. Recruit your colleagues to join MSMA (MSMA.org/engage). In Jefferson City, numbers matter. The more Missouri physicians that belong to MSMA, the greater is our impact with legislators.

2. Attend our White Coat Day at the Capitol on March 2, 2021.

3. Volunteer to be a Physician of the Day at the Capitol.

3. Respond to our calls to action and contact your legislator to advocate for the issue at hand.

4. Sign up for MSMA's grassroots advocacy tool, Phone2Action, by texting the phrase MOMEDICAL to 52886.

5. Support MMPAC. Think of your MSMA membership as insurance to allow you to continue to practice medicine and keeping the government from getting between you and your patients. The MSMA has been fighting for Missouri physicians and their patients for 170 years. With your support, it will continue to do so for at least 170 more. **MM**

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

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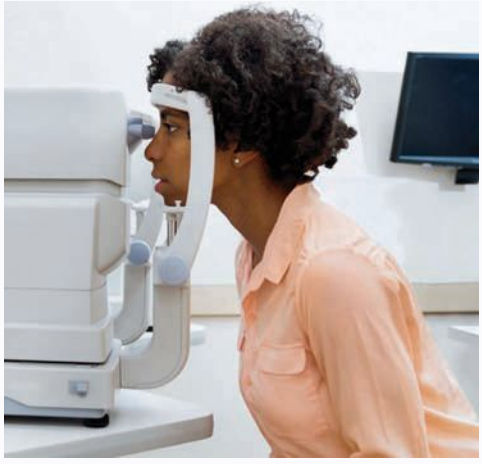
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Direct to Consumer Telemedicine: Is Healthcare From Home Best?

by Suzanne G. Bollmeier, PharmD, Emily Stevenson, Patrick Finnegan, PharmD & Scott K. Griggs, PhD

Optimal medication management requires an effective relationship between the patient and health care professional.

Abstract

Direct-to-consumer (DTC) telemedicine is increasingly popular and enables patients to obtain medical advice and treatment via electronic media (e.g., computer, telephone, or smartphone) without a prior doctor-patient relationship. Convenience, accessibility, and home delivery make DTC telemedicine attractive to patients. Concerns about DTC telemedicine include: a lack of regulation, transparency, and an established patient-provider relationship (physician and pharmacist). In future, researchers, providers, and insurers need to better understand the concerns and challenges that this new form of healthcare poses.

Background

Direct-to-consumer (DTC) advertising of pharmaceutical products has been a "normal" practice for many years. In 1962, Congress passed the Kefauver-Harris Amendments which granted the FDA jurisdiction over the advertising of prescription drugs to patients.[1] Drug manufacturers have used an array of promotional activities and professional marketing techniques in an effort to increase their market share ever since. Consumers in the United States easily see on television, hear on the radio, read about in print media (newspapers, magazines, internet ads), and view on social media, advertisements for prescription medications. Direct-to-consumer pharmaceutical advertising is now the leading type of health communication that the lay public encounters.[2] Disease states often targeted for DTC advertisements with brand-name treatments include high cholesterol, diabetes, depression, erectile dysfunction, and others. Spending for DTC advertising continues to rise, increasing from $2.1 billion (11.9% of total spending) in 1997 to $9.6 billion (32% of total overall prescription drug marketing spending) in 2016.[3] Also, marketing departments are spending more and more on digital promotion including: product websites, online display advertising, search engine marketing, social media campaigns, and even mobile advertising.[2] More recently, a rise in prescription-on-demand services, or direct-to-consumer telemedicine companies, have been seen.

The Institute of Medicine defines telemedicine as "the use of electronic information and communication technologies to provide and support healthcare when distance separates the participants."[4] The term telemedicine has been around since the 1960s and describes using technology to deliver healthcare services and information at a distance in order to improve access, quality, and cost.[5] Similarly, the term telehealth is using electronic information and telecommunications technologies to support long-distance clinical healthcare, health related education, public health, and health administration.[6] Direct-to-consumer telemedicine services, however, are different, with care being provided to patients from



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an organization outside the patient's medical home. There is little or no patient-provider relationship or coordination with the patient's primary medical doctor.[7] When patients utilize multiple pharmacies and/or multiple providers, a complete medication history is often lacking. Drug-drug interactions are often missed if patients do not make their dispensing pharmacist and primary provider aware of medications obtained from outside sources. These direct-to-consumer telemedicine services are providing consumers with around-the-clock access to care for common, nonemergency conditions through phone and live video via Webcam or smartphone applications.[8] These direct-to-consumer telemedicine companies often will have a contract with patients' insurance companies or healthcare organization, or they simply charge patients directly for their services. In response to the growing number of these companies, the American College of Physicians (ACP) released a position statement related to the use of telemedicine in 2015. The ACP supports DTC telemedicine companies within the context of an established patient-provider relationship in a medical home if it meets the same standards of practice as in-person care. DTC telemedicine companies, however, are pushing for telemedicine outside the traditional medical home. Additionally, some state medical boards require an in-person exam before a telemedicine consult can take place.[7]

It appears patients are utilizing telemedicine at an increasing pace despite a lack of research about whether these sites provide comparable care to an in-patient visit. From 2017-2018, telehealth use grew twelve percent.[9] Similarly, the global direct-to-consumer telemedicine market is expected to be a $35 billion-dollar industry by 2020 and an $86.7 billion-dollar industry by 2023.[10] The number of DTC telemedicine website visits in 2015 reached 1.25 million.[11] The novel coronavirus disease 2019 (COVID-19) required the necessary expansion of telehealth for routine care by providers. It is anticipated this type of care will continue to grow in the future as many insurance companies have pivoted to incorporate payments for these services. Little is known if patients prefer this type of care. Several reports have indicated that a majority of patients would be comfortable with telemedicine. These reports do not distinguish between telehealth provided by patients' own provider or by an unknown provider.[7] A nationwide survey (with more than 4,000 respondents) found that patients are less willing to use telehealth as they become further detached from their own provider; these results were statistically significant. Over 50% of respondents were either very willing or willing to use telemedicine with their regular provider, only about one-third were if utilizing a different provider at their same institution, and under 20% were when asked about using a different provider at a different institution.[7]

Procedure

A thorough internet search revealed 21 sites advertising direct-to-consumer medications available for patients with no prior physician-patient relationship (Table 1). The majority of these sites

Table 1. Direct-to-Consumer Telemedicine Sites

Site Name and URL	Prescription item(s) to treat:	Cost to be seen?	Insurance accepted?	Medication mailed to home?	Prescription e-prescribed to local pharmacy?
Hims www.forhims.com	Hair loss, ED, premature ejaculation, performance anxiety	OTC product pricing available on website, once monthly or quarterly subscription cost for Rx	No	Yes	Yes
Roman www.getroman.com/ron	ED, premature ejaculation, cold sores, genital herpes, hair loss, testosterone support	$15 for online visit, refunded if determined unsuitable for telemedicine	No	Yes	Yes through SureScripts
Curology Curology.com	Acne treatment	Starting at $19.95/mo	No -Accepts FSA/HSA	Yes	Yes
Keeps www.keeps.com	Hair loss	$20 annual fee Subscription based: Minoxidil $10/mo, Finasteride $25/mo	No	Yes	Yes
Lemonaid Health www.lemonaidhealth.com	ED, birth control, hair loss, herpes, hypothyroidism, depression, cholesterol, sinus infection, acid reflux, acne, smoking cessation, anxiety	$25 online consultation, $95/mo for anxiety/med, $2/pill Viagra, variable Rx costs	Not for consultation; may for Rx at pharmacy	Yes	Yes
Nurx www.nurx.com	Birth control, STI testing, emergency contraception, HIV preparation, HPV screening	$12 med consultation - includes unlimited messaging for one year, plus cost of drug (if not covered by insurance)	Yes; Medicaid included	Yes	Yes $12 delivery fee
The Pill Club thepillclub.com	Birth control, emergency contraception	$15 med consultation, cost of drug (if not covered by insurance)	Yes; Medicaid in certain states	Yes	Yes
Hers www.forhers.com	Birth control, hypoactive sexual desire disorder, skin/acne treatment, hair loss, performance anxiety	$5 follow up consultation, $30 birth control	No	Yes	Yes
Cove www.withcove.com	Acute and preventative migraine treatment	$15 online consultation - includes messaging access for one year, $3 shipping, cost of drug	No	Yes	Yes
Rory www.hellorory.com	Latisse, cold sores, herpes, sleep, sexual health, hot flashes	$15 online consultation, monthly subscription prices depend on drug	No	Yes	Yes
Zero www.quitwithzero.com	Smoking cessation	$15 online consultation, buproprion: $45/mo, nicotine gum: $42/box	No	Yes	Yes
Sprout Addyi.com	Hypoactive sexual desire disorder	$18 for telemedicine appointment, first 60 days free, $25/mo for subsequent fills	Yes FSA/HSA accepted	Yes	No – filled through home delivery; KippeRx
TwentyEight Health Twentyeighthealth.com	Birth control, emergency contraception	$20 for initial value plus price of drug	Yes; Medicaid	Yes	Yes
Kick Health www.gokick.com	Social anxiety	$49 online consultation, may receive 48 doses if approved	No	Yes	Yes
K Health www.khealth.ai/	Headaches, depression, anxiety	$9/mo, $19/one-time consultation, $99/yr	No; FSA/HAS accepted	Yes for mental health Rx	Yes
Maven https://www.mavenclinic.com/	Birth control, postpartum depression	Contracted with employer, may have additional costs for video chats with specialists	No	No	Yes
Simple Health https://www.simplehealth.com/	Birth control	First consultation $20, free Rx with insurance or $15/mo without	Yes	Yes	Yes
Pandia Health https://www.pandiahealth.com/	Birth control	First consultation $20, free Rx with insurance or $15/mo without	Yes	Yes	Yes
Alpha Medical https://www.helloalpha.com/	Birth control, acne, mental health, UTI, sinus infection	$10 for treatment, $99 annual fee for full access	Yes	Yes	Yes
Blink Health https://www.blinkhealth.com/	Birth control, erectile dysfunction, high cholesterol	Starts at $5 for first month, $9.95/mo thereafter	Yes, with Blink Pharmacy Plus membership	Yes	Yes
Dear Brightly https://www.dearbrightly.com/	Photoaging	Tailored retinoid and consult $29.50/mo	No	Yes	Yes

Table 2. Processes for Obtaining a Prescription from DTC Telemedicine Sites

Site Name	Methods to Obtain Rx
Hims	Online questionnaire, reviewed by a physician, contacted through messaging platform
Roman	Online questionnaire, reviewed by a physician, contacted through messaging platform/phone call/video chat
Curology	Online questionnaire and pictures of affected area, physician determines proper treatment plan
Keeps	Online questionnaire and pictures of affected area, physician determines proper treatment plan
Lemonaid Health	Online questionnaire, reviewed by a physician, contacted through messaging platform/phone call/video chat
Nurx	Online questionnaire, reviewed by a physician, contacted through messaging platform
The Pill Club	Online questionnaire, reviewed by a physician, contacted through messaging platform
Hers	Online questionnaire, reviewed by a physician, contacted through messaging platform
Cove	Online questionnaire, reviewed by a physician, contacted through messaging platform
Rory	Online questionnaire, reviewed by a physician, contacted through messaging platform/phone call/video chat
Zero	Online questionnaire, reviewed by a physician, contacted through messaging platform/phone call/video chat
Sprout	Online questionnaire, reviewed by a physician, contacted by phone call
TwentyEight Health	Online questionnaire, reviewed by a physician, contacted through messaging platform/phone call
Kick Health	Online questionnaire, reviewed by a physician, no virtual interaction with doctor
K Health	Online questionnaire using AI, reviewed by a physician, contacted through messaging platform
Maven	Video chat or messaging platform
Simple Health	Online questionnaire, reviewed by a physician, contacted through messaging platform
Pandia Health	Online questionnaire, reviewed by a physician
Alpha Medical	Online questionnaire, reviewed by a physician, messaging platform available to Alpha Members
Blink Health	Online questionnaire, reviewed by a physician
Dear Brightly	Online questionnaire and pictures of affected area, physician determines proper treatment plan, messaging platform available

focus on promoting prescription items for a limited set of conditions or diseases including: sexual health, hair loss, contraception, dermatologic conditions, performance anxiety, and even primary care. What patients have to complete online to get a prescription varies by site (Table 2). Typical steps include completing an online questionnaire (to rule out any contraindications) followed by a live virtual visit with a provider (physician, nurse practitioner, or physician assistant). In some models, the clinician contacts the patient via messaging, telephone call, or video chat.[12] The company then either e-prescribes a prescription to a local pharmacy (rare) or mails the medication directly to the patient's home (more common).[12]

The cost to the patient varies by telemedicine site and treatment (i.e., medication) alternative. In most cases, there is a patient out-of-pocket cost for the online visit/consultation; this cost is not covered by insurance. For example, Lemonaid Health charges $25 (via credit card) for a typical patient-doctor evaluation and prescription—not including the cost of the medication.[13] In the event that a prescription is not recommended by the physician (e.g., safety), the patient is not charged the consultation fee. Separately, the cost of the medication may be paid in part or total by insurance (depending on the patient's insurance copayment) when picked up at a local pharmacy; alternatively, the medication may be paid for on a monthly basis (cash or insurance) and shipped to the patient's home. The actual medication costs to the patient may vary by telemedicine site, medication, local pharmacy versus mail-order, and prescription insurance (Table 1).

The vast majority of these sites use unaffiliated pharmacies to complete the prescription fulfillment step (mail order pharmacies) or send electronic prescriptions to the patients' local pharmacies. In contrast, the direct-to-consumer telehealth company HIMS and HERS have plans to launch a closed-door pharmacy in Columbus, Ohio, in 2020.[14] The estimated 300,000-400,000 square foot facility will house a mail-order pharmacy, customer support center, and fulfillment center for their online customers. The $1.5 million investment's goal is to speed order fulfillment for its customers instead of relying on alternate pharmacies.[15]

Discussion

DTC telemedicine visits offer significant advantages to patients seeking care, including: improved access, efficiency, and convenience. Obtaining a prescription without leaving the home can be a valuable time-saver. Also, these companies endorse prescriptions for treating conditions some patients would prefer not to discuss during a live face-to-face visit; examples include: erectile dysfunction, hair loss, acne, and genital herpes. The option of visiting with a provider you may never have to see again could be regarded as an advantage for some. Additionally, in this model, overhead costs of a traditional clinic are minimized. Overhead costs like front-end staff, clinic space (rent), and utility bills are minimized, allowing for a reduction in the cost of the primary care visit.[12]

DTC telemedicine likewise has several important disadvantages. These companies offer "solution-oriented" services; therefore, they target their questionnaire to screen for patients who cannot take the medication(s) they offer, rather than investigating the best possible treatment for that patient's medical need.[12] The lack of a patient-provider relationship is also a concern. Patients are now interacting directly with online companies that have a financial interest in the patient (who may or may not have medical knowledge) utilizing the drug(s) they are promoting.[16] Similarly, these interactions may lack transparency, have limited choices for patient treatment, and lack diagnostic testing.[11] The lack of care coordination with patient's primary care provider (PCP) can be problematic, putting the onus on the patient to update his/her current medication list with the PCP. Additionally, telemedicine may intensify legal concerns including HIPAA data disclosure and physician malpractice exposure—as medical malpractice law dictates that a physician's duty exists if there is a patient-physician relationship. Eliminating or modifying the face-to-face visit may make it more difficult to determine if a patient-physician relationship is present. A relationship is typically established if a physician gives personalized medical advice to a patient.[17]

One of the biggest disadvantages to never having a fully developed patient-provider relationship is the lack of follow-up and monitoring required with these therapies. Patients can now choose to completely bypass their PCP in order to seek a swift solution to obtaining a medication due to cost, ease of acquisition, or avoiding embarrassment. These sites are geared toward diagnosis, risk assessment, and ultimately treatment, but offer limited follow up services, including efficacy and safety evaluation of the therapies given. While some of the first drugs available via online providers were lifestyle drugs that required minimal monitoring, as the scope of their services grow, so does the requirement for closer monitoring.

Antibiotics like ciprofloxacin, trimethoprim/sulfamethoxazole, and nitrofurantoin commonly prescribed for urinary tract infections all have clinically relevant adverse effects that can result in significant morbidity and mortality. This is especially true if consumers are not up front with their providers regarding the amount of exposure to drugs such as nitrofurantoin.[18] Similarly, monitoring the routine use of hormone therapies for relief of symptoms associated with menopause is necessary including a range of products from topical to systemic hormone replacement therapy (HRT). While all these sites have extensive screening for appropriate initiation of therapy, none provide any evidence-based recommended monitoring or counseling.[19] Patients who choose to get their medications from these online services may keep this information from their physician, increasing the risk for medical errors and/or drug-drug interactions.

In the state of Missouri, health care providers can provide telehealth or telemedicine services, but this does not include prescribing based solely on an internet questionnaire or prescribing based on a telephone examination without a valid prescriber-

patient relationship. Missouri pharmacies may fill prescriptions issued based on telemedicine exams; these pharmacies are, however, prohibited from filling prescriptions issued without a valid prescriber-patient relationship or based solely on an internet questionnaire.[20]

As discussed, the first closed-door telehealth pharmacy will be opening this year (HIMS and HERS). It is unknown at present how this may affect the traditional healthcare model and if more DTC telemedicine companies will be making this transition. It is anticipated that direct-to-consumer telehealth companies will continue to push for healthcare changes that allow more prescriptions to be prescribed outside of the conventional patient-PCP relationship. As Pat Carroll (a past Walgreens top executive), new chief medical officer of HIMS, wrote in a blog post, "looking forward, we'll add more categories of care so we can keep expanding access."[15] This expansion of DTC telemedicine might include the following therapeutic areas: statins for cholesterol, mental health, menopause, migraines, infections, gastrointestinal disorders, and asthma.[21]

Future Issues

Optimal medication management requires an effective relationship between the patient and health care professional.[22] Exponential growth has been seen in direct-to-consumer telehealth companies in the past decade. The internet will continue to see a rise in these companies offering patients "lifestyle drugs." Looking to the future, direct-to-consumer telehealth will continue to incorporate prescriptions for chronic disease state management and long-term/maintenance medications.

One of the newest ways direct-to-consumer telehealth companies are positioning for increased market share is to offer subscription services. For example, the Alpha Mental Health Service offers patients treatment for anxiety and depression. The cost to belong to the subscription service for a full year is $120. The yearly fee covers all medical consultations, a personalized treatment plan, unlimited messaging with the care team, and insurance coordination.[23]

Several complications in the traditional physician-patient-pharmacist relationship/model can be projected from this shift to "internet doctoring." Patients seeking care from internet providers, with whom they do not have a relationship, may not inform their established provider of these telehealth visits. This lack of a complete and up-to-date medication history hinders medication reconciliation as well as the drug utilization review process that screens for duplicate therapies and drug-drug/drug-disease interactions. Säfholm et al. showed in a study of Swedish primary care patients that medication lists were only accurate 16% of the time.[24] The World Health Organization has stated that these medication errors are the leading cause of avoidable harm in the healthcare system.[25] An incomplete medication list could lead to a disruption in coordination of care amongst specialists the patient may be referred to as well. Patients not informing their providers of medications purchased elsewhere can be problematic at the pharmacy level as well. When patients use more than one pharmacy (that are not linked to one another) for their routine care, screening for drug-drug and drug-disease interactions are limited. Additionally, pharmacists that are not made aware of all of a patient's medications, including items purchased online, non-prescription items, herbal, and dietary supplements, will not be able to catch and correct many preventable medication errors. Also, utilizing mail-order or closed-door pharmacies for medication delivery to a patient's home removes the pharmacist from the patient-pharmacist relationship. Medication counseling by a pharmacist, whereby the patient and pharmacist discuss the medication's directions, side effects, etc. as well as any patient questions, is less likely when the medication is delivered to the patient's home. Patients are forced to simply read a pamphlet regarding the new medication, possible adverse effects, mechanism of action, and how to use or apply the medication/device (e.g., inhaler).

An established, effective provider–patient relationship should encourage and enable patients to ask questions and be a part of the decision-making related to their care and follow-up plans,[22] which happens when patients utilize routine providers for their care.

Conclusions

As the internet and its role in healthcare continue to evolve, patients will expect increased

access, convenience, and speed in their interactions with healthcare providers as well as obtaining prescriptions. In 2009, 80 million households in the U.S. had high speed broadband access. By 2018, that number rose to close to 110.57 million.[26] It is well known that the millennial and Gen Z generations have grown up with digital access and "instant" information which has helped shape not only their personalities but also their perception of healthcare. These are the patients of the future; they want providers that email and text, provide online scheduling, have extended hours, and explain costs of care. Online access to health information is particularly important to the patients of these generations; they often research health and conditions before reaching out to a provider.[27]

The direct-to-consumer telehealth model was initiated with the intent of treating diseases like hair loss and minor dermatologic conditions. The medications used to treat these conditions historically have lacked routine monitoring. However, as these companies expand access and services in the future for digital patients to chronic conditions like oral contraceptives, erectile dysfunction, and even diabetes and hypertension, the ethical, practical, legal, and patient-centered outcomes have not been well defined. It has been shown that patient satisfaction is an indicator of the quality of the health care services received by patients.[22] How satisfied patients are with their care is also a predictor of maintaining a relationship with the health care provider and adhering to a medication regimen.[22] As more and more digital telehealth companies emerge, providers and pharmacists must continue to strive to create meaningful relationships with patients so that patients will see the value in these interactions and obtain optimal health outcomes, both now and in the future.

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The Fight to Save Health Care for Patients and Physicians

In the battle to save medicine for patients and physicians, we are not alone.

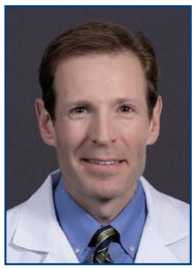
by Scott Hardeman, MD

National grassroots, non-partisan coalition outlines physician-led roadmap to patient-centered care.

Healthcare decisions affect everyone. Patients worry about drug costs, access to affordable insurance, finding a quality physician and pre-existing conditions. While committed to patient care, physicians also have many crucial concerns. These include burdensome government regulations, vertical integration by large predatory hospital and corporate systems, often forcing doctors who prefer to stay independent into an employed status, as well as declining reimbursements. We are in a desperate fight to save healthcare. We need to focus on the physician's vital role in the battle.

In addition to the chronic struggles facing patients and physicians, the COVID-19 pandemic has shed new light on flaws in our delivery model. It has exposed the seemingly corrupt supply-chain industry, exposed the economic vulnerability of physician groups both hospital-employed and private practice groups. All this has allowed increased government bureaucratic intrusion into physician autonomy. It has caused further erosion of the doctor-patient relationship.

I have spent my career working to empower the independent physician. Years ago, my colleagues and I merged groups of otolaryngologists to form a larger single specialty organization in order to maintain our private practices and autonomy. During the last six years, together with others, we formed an independent group of nearly 700 doctors and one of the most successful Accountable Care Organizations (ACOs) in Missouri. It is my passion that physicians be able to care for patients in the way they believe represents the highest level of medical care. More recently, I am pleased to be involved with non-partisan, physician and patient advocacy groups on a national level.



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The Corporatization of Medicine

I am involved in these physician groups because over the last ten years, as the physician work force has moved to a more hospital-employed structure, there has been an escalation of costs and the leveling or even decline in the quality of medicine. Other concerning trends are the insurance industry and private equity firms purchasing medical practices, employing physicians and perhaps putting profit above quality care. Many physicians are embracing the idea of selling their practices and ceding the future practice of medicine to a faceless, profit-driven financial entity. In some southern states, a single insurance company controls over 80% of insured lives, thus cornering health markets. These trends are putting patients and independent medical practice at risk by creating monopolies in the delivery of care model and eliminating choice. It largely is an issue of misaligned incentives. Sadly, this plays out as increased healthcare costs, increased premiums, massive increases in pharmaceutical costs, less accessible care for the underprivileged, escalating physician burnout and greatly diminished free market choice in healthcare.

It is overdue that we physicians take a front seat in all healthcare matters including legislation. To that end, I have the privilege of being connected with hundreds of other physicians, representing many thousands more. These organizations, along with patient advocacy groups, make up a non-partisan grassroots effort to improve healthcare for patients and physicians. One of the group's efforts was to form the movement known as *Free to Care*, (free2care.org). In the spring of 2019, *Free to Care* held a symposium in Washington DC and subsequently produced a white paper with a mission to outline a physician-led path to patient-centered care. This roadmap identifies key issues facing physicians and patients in the battle to keep American medicine at the forefront. This paper also exposes ways to reduce cost and waste.

The Future of Medicine Is in Our Hands Today

Since that meeting, the *Free to Care* movement has continued to gain strength, largely fueled by the fact that healthcare is one of the most important political issues and also it has the support of thousands of physicians and patients. The issues addressed in the *Free to Care* paper resonate with those suffering most under the current burdensome delivery model— patients and their physicians. While I am sure not all physicians will agree with everything laid out in *Free to Care's* white paper, it is clear that physicians need to be integral to major changes in healthcare.

The *Free to Care* Movement is Tackling Five Primary Issues

1. Reduce drug prices and increase supply.

Drug and medical device costs are out of control. Exorbitant pricing is a complex problem. The key factor driving prices can be traced to 1987 when a law passed providing a "Safe Harbor" for 'rebates' (really kickbacks) to the Group Purchasing Organizations (GPOs) in a pay-to-play market. In 2003, this kickback safe harbor was extended to the Pharmacy Benefit Managers (PBMs) industry. Outside of the pharmaceutical and medical-device industries, kickbacks such as these are illegal in any other healthcare endeavor. Multiple Senate Antitrust Subcommittee meetings exposed the safe harbor law as being the root cause of both drug and medical device shortages as well as the increased cost of medicines. It is estimated that this safe harbor allowance adds $250 billion of unnecessary costs to the healthcare bill. Never before have we seen the breakdown in the medical and pharmaceutical supply chain as we have in 2020. The Covid-19 pandemic has exposed just how deeply the corruption in the industry runs. Patients, physicians, medical practices, clinics and hospitals have all suffered under the current paradigm with less access to personal protective equipment and other vital equipment needed to care for suffering patients. Our country has also seen limited access to many medications as well as the basic chemicals to manufacture medications in the United States. Therefore, it is strongly recommended these safe harbor laws be repealed.

2. Strengthen the safety net for the vulnerable

It is necessary to create and strengthen the safety net for the most vulnerable of our society. One of the initiatives to help with this is to even the playing field for providers of pro-bono care. Presently, unlike hospitals, physicians are not able to write off charitable care. There is currently a proposed bill called the Physician Pro Bono Care Act of 2019 (HR 856). While it has been introduced, it needs support to move it forward. Passage of this bill will help provide medical care for patients in financial need and would increase access, encouraging more physicians to participate in charitable care. In addition to this bill, there is a specific movement for a tax deduction to be extended to physicians and nurses who donate time in public settings to educate the public on state-based pro-bono care.

3. Foster fresh models to pay for medical care.

There needs to be new and innovative models to pay for medical care. *Free to Care* recommends an expansion of Health Savings Accounts (HSAs) to decrease third party interference. Additionally, expansion of the Direct Primary Care (DPC) model has been shown to increase access and decrease cost of care. This DPC model removes much of the waste associated with claims processing and insurance middleman involvement, producing savings for patients. It can be expanded to include Direct Specialty Care as well.

4. Reverse the impending physician shortage

There is an impending physician shortage and high levels of career dissatisfaction, leading to early retirement. Federal mandates (HITECH, MACRA, ACA, EHR and MIPS) place onerous financial burdens on physicians and private practices. These data collecting initiatives require reporting that is outside the scope of real patient-care efforts. These lead to increased burnout of physicians and financially drive physicians, who often desire to remain in private practice, into an employed status. These mandates need to be corrected by eliminating the Electronic Health Record (EHR) and Merit Based Incentive Payment System (MIPS) requirements for practices with less than 50 physicians. Additionally, the administrative burden of obtaining prior authorizations needs to be eliminated. This directly interferes with the doctor-patient relationship. Also tackled in *Free to Care's* white paper is the need for true medical malpractice reform and the necessity of training more physicians.

5. Make health care prices transparent

There is significant support and efforts being led to create price transparency. While the Executive Order from the President, stood to help in this effort, the battle has just begun. After the Executive Order, the American Hospital Association (AHA) sued to block the transparency order but in June 2020 it lost its legal battle. This means, unless appeals occur, in January 2021 hospitals will be required to publish their pricing structures and more importantly be obligated to publish any rates negotiated with third-party payers. These two groups work in conjunction to drive up the cost of care to maximize their own profits. Included in this effort to make pricing transparent, is eliminating the tax-exempt status of non-for-profit hospitals. Tax-exempt non-profit hospitals may write off charitable care at charge-master level while also receiving Disproportionate Share (DSH) reimbursements from the federal government. This "double-dipping" translates to writing off care while also receiving tax-payer funding for that same charitable care. Among addressed issues, another of significance is to create Site-Neutrality among hospital-based practices with those in private practice. As hospitals are able to charge a facility fee when patients see an employed-physician, an unnecessary cost is passed to the patient. Additionally, it creates more economic incentives for hospitals to employ physicians. While the American Hospital Association often claims that vertical integration reduces cost through consolidation, the increased revenue gained by such consolidation is most often retained by the hospital and not passed back to the patients whose healthcare expenditures increased in the process. This hospital-employed model clearly shows an increase in the overall cost of care to the patients.

Reports recently have also indicated that many large hospital systems have lost money under the shutdown during the pandemic. There have been furloughs of employed "integrated" physicians, nurses and many front-line workers. The shutdown to "flatten the curve" and the pause in non-urgent care has sadly affected rural hospitals and those hospitals not part of a large horizontal system in a more adverse way. Many of the large hospitals systems are receiving money under the CARES act yet smaller hospitals may never recover from the economic impact of closing down. Yet, in the larger systems as clinical staff is taking pay cuts or being relieved of their positions, administrative employment remains at all time levels. This seems woefully out of sync as administrators are not the individuals risking their lives to care for patients.

Call to Action

The *Free to Care* coalition of physicians, patient advocacy groups and business leaders seeks to restore the doctor-patient relationship. While the details of these efforts continue to be evaluated, it is of utmost importance that we stay engaged in the legislative efforts that so greatly affect us and our ability to practice our craft. The future of medicine now more than ever, lies in our hands.

I would encourage you to find out more about these physician-led efforts and know that there is a coalition working for the best interests of doctors and patients. Although we are not alone in our efforts and desires to improve care, our patients and the future generations of physicians need our help. For too long, we have allowed the other players, none of whom have the same level of patient responsibility, to control the direction of healthcare. Visit free2care.org to download the entire white paper and to learn more about its efforts. Most importantly, consider lending your voice to the coalition. **MM**

Legality and Ethics of Lien Uses in Medicine

by Ciara Chambers, JD & Liz LaFoe, JD

Providers must analyze the situation at hand before deciding to enter into a lien with a patient.

The *Wall Street Journal* recently published an article about the "little-known but growing practice" of doctors taking payment through liens tied to wins in court.[1] A lien is a legal right to a portion of an asset. When physicians provide services to treat patients on a lien, it means the patient immediately receives treatment, and payment of the bill is deferred.[2] The treating physician then waits to be paid until the personal injury claim is settled or resolved.[3] After the personal injury attorney has obtained a verdict or a settlement, the personal injury lawyer will pay that medical bill directly from the amount obtained.[4] The *Wall Street Journal* article states that a "spate of legal and legislative changes has led to a proliferation of the practice in California and other states, including Florida, Colorado, Texas, and Georgia. . . ."[5] Financing companies that buy liens from doctors before litigation is complete are also becoming more common with the practice.[6] The purpose of this article is to examine the ethics and legality of health care liens in Missouri, as well as to discuss the logistics, and risks and benefits, of such arrangements.





Ciara Chambers, JD, (left), and Liz LaFoe, JD, (right), from the Kansas City and Jefferson City offices of Husch Blackwell, respectively, wrote this article. They represent a full spectrum of healthcare providers and other businesses in regulatory compliance and litigation 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.

Ethics of Liens in Medicine

According to the American Medical Association (AMA), "physicians must recognize responsibility to patients first and foremost, as well as to society, to other health professionals, and to self."[7] The first AMA principle of medical ethics states: "A physician shall be dedicated to providing competent medical care, with compassion and respect for human dignity and rights."[8] Other principles of the AMA ethics require physicians to respect the rights of others, advance scientific knowledge, contribute to the betterment of public health, and regard responsibility to patients as paramount.[9] The sixth principle states that physicians shall be free to choose whom to serve (except in emergencies), with whom to associate, and the environment in which to provide medical care.[10] The final principle requires physicians to support access to medical care for all people.[11]

Similarly, the American Osteopathic Association (AOA) also has a code of ethics "designed to address the osteopathic and allopathic physician's ethical and professional responsibilities to patients, to society, to the AOA, to others involved in health care, and to self."[12] Section 12 of the AOA Code of Ethics states "Any fee charged by a physician shall compensate the physician for services actually rendered. There shall be no division of professional fees for referrals of patients."[13] Section 13 requires physicians to respect the law.[14]

Although the AMA and the AOA have not publicized a formal written position on the use of

liens by health care providers, and nor have other physician specialty groups (e.g., American Orthopedic Association, the American Academy of Family Physicians), the ethics of such arrangements have been examined in recent articles, and the consensus of medical experts appears to be that the use of liens by health care providers, when permitted by state law, is not unethical.[15] Both the AMA and the AOA ethical principles support that physicians are entitled to fair compensation for their services. The AMA's final principle specifically encourages physicians to support access to medical care for all people. As discussed further in the sections below, liens may allow patients who are uninsured to receive healthcare that they would not otherwise be able to afford. Also as discussed below, healthcare provider liens are lawful by statute in Missouri. Thus, there is no inherent conflict between a physician's ethical duty to follow the law and payment per a lien arrangement in Missouri.

Medical Liens in Missouri

Health care provider liens are allowed by statute in Missouri.[16] The purpose behind Missouri's medical lien statute is to ensure injured patients are promptly treated without consideration of their ability to pay and to also financially protect health care providers to enable them to continue to provide care.[17] Experts in personal injury cases answered that the practice happens in Missouri, but it is not extremely common.[18]

Stephen M. Gorny, a personal injury attorney located in Kansas City, states that ninety-nine percent of his practice is personal injury, including "medical negligence, vehicular collisions, premises liability, and product liability," and that he does not deal with the practice of health care providers working on a lien basis very often.[19] For Mr. Gorny, when clients utilize this type of lien, they have typically suffered a serious injury and as a result, cannot find a physician to offer services as they would be "simply too expensive."[20]

The people who most commonly use these liens are those that are uninsured. Mr. Gorny stated he could not think of a single patient in twenty-six years who opted to use a lien instead of their health insurance.[21] He explained, "The reason is simple. My clients pay for their health insurance. If liability has not yet been established and their contracted-for health insurance is going to pay their expenses, they should get the benefit of that bargain."[22] Instead, their carrier may have a subrogation interest and recover a portion of the amount expended from the ultimate settlement or verdict. Contrast that with a physician lien. In that circumstance, the health care provider will typically request a much higher reimbursement."[23] Additionally, healthcare providers may have to accept a patient's health insurance, depending on the language in the provider's agreement with a health insurer – in these cases, liens are unlikely to be an option.[24, 25]

How the Practice Works

The Missouri Hospital and Health Practitioner lien statute, RSMo. Section 430.225, is the relevant statute for a Missouri's physician lien.[26] Hospitals, clinics, and "health care practitioners" in Missouri can use liens for their services.[27] The "health care practitioners" included in the statute include: (1) chiropractors; (2) podiatrists; (3) dentists; (4) physical therapists; (5) physicians or surgeons; and (6) optometrists.[28] In some circumstances, physicians may also enter into a private agreement with a patient, usually facilitated by an attorney, to receive all or a portion of their medical bills out of a damages award or settlement.[29]

The lien statute is applicable to any person "to whom a health practitioner, hospital, clinic, or other institution delivers treatment, care or maintenance for sickness or injury caused by a tort-feasor from whom such person seeks damages or any insurance carrier which has insured such tortfeasor."[30] The Missouri lien statute applies to anybody with any kind of health insurance, or no insurance at all.[31] Thus, when a person is injured and seeks compensation from the person responsible for the injury, any treating medical providers can assert a legal claim on the settlement to satisfy the medical bills stemming from that injury, except in circumstances where they are barred from doing so by their contract with a specific health insurer, as discussed above.[32]

The lien statute states that, "If the liens of such health practitioners, hospitals, clinics, or other institutions exceed fifty percent of the amount due the patient, every health care practitioner, hospital, clinic or other institution giving notice of its lien, as aforesaid, shall share in up to fifty percent of the net proceeds due the patient, in the proportion that each claim bears to the total amount of all other liens of health care practitioners, hospitals, clinics or

other institutions."[33] The "net proceeds," as used in the statute, means the amount remaining after the payment of contractual attorney fees, if any, and other expenses of recovery.[34]

Providers must "perfect the lien," by sending notice of the bill to the at-fault party.[35] The steps to do this are set out in RSMo. Section 430.240.[36] No lien will be effective without written notice containing: (1) the name and address of the injured person; (2) the date of the accident; (3) the name and location of the hospital; and (4) the name of the person(s), firm(s), or corporation(s) alleged to be liable to the injured party for the injuries received.[37] This notice must be sent by certified mail with return receipt requested to the allegedly liable party or parties.[38] The provider shall also send a certified copy with return receipt requested to the insurance company which has insured such person, firm, or corporation, against such liability.[39]

Therefore, so long as the lien is properly asserted, when the check for the settlement or jury verdict arrives to the plaintiff's lawyer, the lawyer must pay the provider the balance owed to them.[40] However, no matter what happens in the settlement or at trial, the health care practitioner can only receive 50% of the balance of the settlement. Here is a hypothetical example:

If we get a settlement for a car accident for $10,000. And let's say our attorney's fees that we charge are a third so that's $3,300 dollars. And let's say we had some case expenses that we had to advance to get the settlement so let's say when it's all said and done, after attorney's fees and expenses there's $6,000 left to go around. So, $6,000 remains out of that $10,000 global settlement. So what do the facilities get? What do the doctors get? Well, it depends on the amount of the bill. But the law says that out of the remaining $6,000 dollars that is left after our attorney's fees and case costs, all of the facilities, all of the doctors who have liens or bills, will only be able to get a total of $3,000 dollars out of the $6,000. So that statute says that 50% of the remaining balance of the settlement goes to the claimant, being the patient/client.[41]

As for how it works in practice, Mr. Gorny stated that he personally knows "a number of attorneys who work under these provisions for somewhat minor procedures, chiropractic care, and physical therapy," but that most providers who accept liens treat serious injuries.[42]

Brendan Buckley, a personal injury attorney at Edelman & Thompson in Kansas City, also works with Missouri's medical provider liens, in addition to other types of liens.[43] Mr. Buckley stated that when someone comes to him with medical injuries, and they do not have, or do not wish to use, their health insurance, he will suggest three to four providers to contact for treatment who may agree to work under a lien.[44] He assures the providers they will be reimbursed from the damages award or settlement, and he will formally acknowledge the lien.[45] Based on a recent Missouri case, such agreements are still subject to the statutory limitation (fifty percent cap).[46]

Mr. Gorny explained that when a client cannot pay a bill or there are no insurance options or means to pay a health care bill, he is "always happy to speak to a physician to explain the circumstances, the merits of the case, and their likelihood of being compensated from that case."[47] He added that he does not encourage physicians to do "anything other than what they are comfortable with."[48]

Legal Issues with Liens

As discussed above, lien arrangements, when utilized properly and in accordance with state law, do not violate medical ethics rules.[49] Ethics aside, there are other concerns. Defense lawyers, such as Greg Minana, a partner at Husch Blackwell in St. Louis, believe lien arrangements can potentially drive up the litigation costs.[50] Mr. Gorny also admitted that these liens can drive up the costs of settling a case.[51] Mr. Buckley stated plaintiffs can receive more in damages because insurance companies usually discount provider rates under health insurance, and when insurance is not used, providers can bill the full amount.[52] This makes it appear the plaintiff has more monetary damages than if they had used their insurance, and the full amount of the provider bill can be submitted to a jury.[53]

Defense counsel may argue that if a treating physician is testifying, the doctor has an interest in the monetary outcome of a case, it may make them biased.[54] Mr. Minana noted his concerns about a doctor's credibility and believed the lien arrangement may be admissible at trial during the provider's testimony.[55] The defense may argue the treating physician has a "bias" because he/she can potentially benefit from a larger verdict or settlement, and therefore, the jury may learn of the arrangement.[56] These sorts of issues in practice are left to the

discretion of the trial judge and may depend on the factual circumstances of the particular case.[57]

One potential problem with liens for health care practitioners is that, under Missouri's statutory liens, the providers can only "share in up to fifty percent of the net proceeds due the patient."[58] Therefore, if a case settles for an amount where the 50% amount will not cover the full extent of the provider's bill, then the provider cannot be paid their full bill.[59] When this occurs, treating health care practitioners receive a pro rata share of the 50% proceeds allocated towards provider bills,[60] and must accept this to satisfy their charges .[61]

In addition to the monetary cap on providers, providers must also "perfect the lien," by sending notice of the bill to the at-fault party.[62] It may be difficult for a provider to determine who the at-fault party is. For example, a plaintiff may not know who caused the accident that resulted in their injuries. In these circumstances, it may help to reach out to the plaintiff's lawyer to help obtain information.[63] Some provider groups gather information up front, such as: (1) How much insurance coverage is involved? (2) Are there liability issues? (3) How significant was the auto crash? (4) Has the client made other personal injury claims in the past? and (5) Does the client have pre-existing issues related to the injured body part?[64] In some situations, such as an emergency after a motor vehicle accident, it will likely be difficult, if not impossible, for a provider, such as a hospital, to obtain the needed information up front.

For those plaintiffs who have health insurance, including Medicare and Medicaid, it may be more valuable for a patient to use their insurance rather than a lien arrangement, depending on the quality of the health insurance and amount of out of pocket costs (*e.g.,* deductible).[65] Mr. Buckley advised that plaintiffs may be able to use a lien rather than their health insurance, but, as discussed above, for most health insurance contracts, there is a contract provision stating that the treating physician must accept the plaintiff's health insurance.[66] Mr. Buckley added that only in a few instances he would encourage a plaintiff to file a lien over their insurance.[67] An example of this may be when someone is in an accident and the commercial insurance carrier involved has unlimited insurance relative to the claim, and the patient's health insurance would not ordinarily pay that much for medical expenses.[68]

The Benefits of Utilizing Liens

One common benefit of using a lien arrangement is that this can give the uninsured patient access to higher quality care, especially with the rising costs of medical care and health insurance in the United States.[69] The physician may also be able to help a patient going through a difficult financial situation, and further their Hippocratic Oath.[70]

For a physician, working on a lien basis can be lucrative.[71] Physicians who work on these liens can receive reimbursement at likely a higher rate than their contractual rate with an insurer.[72] Some plaintiff's attorneys claim they can make a physician more money with a lien than if the physician billed the claims through health insurance.[73]

Should Physicians Work on a Lien Basis?

Not all physicians accept liens as a basis for payment. The largest risk for physicians is that the plaintiff will not win the lawsuit or receive a settlement and the provider will be uncompensated or 50% of the award will not fully compensate the provider.[74] Physicians also cannot be certain if they will be paid the entire portion of the bill for their services.[75] An additional risk is that providers must wait sometimes six months to a year (or years) for the resolution of a plaintiff's case.[76]

The greatest recommendation Mr. Gorny says he can give to a provider who is considering treating a patient on a lien basis is to do his or her homework on the lawyer involved.[77] Mr. Gorny added, "I am certain there are a number of lawyers who will create difficult situations for physicians when the doctor went out of their way to treat the patient on a lien basis."[78] Mr. Gorny explained that he believes the reputation of the lawyer goes a long way.[79] He stressed that providers will work with him because they learn he does not take frivolous cases, he pays all lien holders and subrogation interest holders, and he ensures the provider receives all the information necessary to evaluate whether to treat or continue to treat the client on a lien basis.[80] Mr. Gorny advises that lawyers who have a poor record of paying lien holders and subrogation interest holders, as well as those that do not provide the necessary information to physicians to allow them to appropriately weigh whether to work on the lien basis or not should spark red flags for treating providers.[81] Mr. Gorny mentioned that some physicians simply do not accept liens because they

distrust the legal process or the lawyers involved, or their ability to get paid.[82]

If a physician is going to offer the contractual service, the physician should be prepared to testify on the merits of the case.[83] Failure to testify regarding the case was described by Mr. Gorny as "throwing money away."[84] When testifying at trial, the jury may not ever know the treatment was performed on a lien basis.[85] If the defense chooses to bring up the treatment was performed on a lien basis, then the jury may learn the plaintiff lacks the financial means to pay for the treatment and gain sympathy for the plaintiff.[86]

Mr. Buckley also advised that lawyers, law firms, and medical providers keep relationships professional when liens are involved.[87] He advises lawyers to give their clients multiple options of treating physicians so the decision making process is transparent.[88] Providers should receive information and an agreement from counsel but consider avoiding entering into any type of ongoing relationship.[89] A type of "referral" arrangement is discouraged.[90] Close relationships with plaintiff's counsel and referral arrangements can impact a provider's reputation.

Conclusion

Provider liens can provide a useful tool for uninsured plaintiffs who have been badly injured. However, they also pose risks for the providers who agree to them. Providers must analyze the situation at hand before deciding to enter into a lien with a patient.

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Correspondence

Thank You Missourians Who "Get" the COVID Sacrifices

I'm an emergency physician from St. Louis who has been on the "front lines" of the SARS-CoV-2 pandemic since its start. As such, I've witnessed many gratifying and generous responses by members of the public. An example? Anonymous "Good Samaritans" have sent "free" food to all us in the emergency departments at Barnes Jewish Hospital and Barnes Jewish West County Hospital, recognizing our service.

However, I think we have all been so busy with all things COVID-19 that we may have forgotten to say a meaningful "thank you" back to those good Missourians who have done much to help to blunt the impact of SARS-CoV-2.

Thus, I write to offer such thanks. We should never forget that many Missourians have undergone great personal inconvenience and significant economic pain to do the things needed to keep our health care system in Missouri from being overwhelmed.

Contrast Missouri, since March, to the conditions in February in Italy and Iran, and to the conditions in March in New York City. In Italy and Iran, overwhelmed doctors and nurses were forced to choose who had to die, versus and who could be offered a chance to try to live. So far, we haven't had to do that.

We also know, from the recent surge of cases near Kansas City and elsewhere in Missouri, and from recent experience in locations like Phoenix and Houston, that not all members of the public understand or accept the need for continued vigilance.

However, wearing of masks in our Barnes/Jewish/Children's Hospitals has been required of all for more than two months. We know from experience that masks have enabled a vanishingly low person-to-person transmission rate in our hospitals, and indeed in other hospitals all across the world.

Thus, if your patients express doubt that masks and "social distancing" are useful, perhaps you could point out the recent news from places experiencing a second surge. Also, President Trump, a former "holdout," finally made a supportive statement on July 2 regarding masking. (Governor Parson, are you listening? Your actions suggest you've been a skeptic about masking and "social distancing.")

If your patients ask why masks weren't suggested for everyone back in March, tell them much has been learned as time has passed. Further, advice circulated in March to the public was based at least partly in resource constraints; there simply were not enough masks to go around. Just because advice has changed does not imply some sort of evil conspiracy is afoot. It does mean we are capable of using science to learn, though.

The entire health care team and the public, all want the same thing...a return to economic normalcy. However, in times when we can't get what we want, we can strive for what we need.

We need to be prudent and adopt the updated recommendations of our health leaders, who are advocating for the best that medical science knows now. The major steps needed are "masking" and "social distancing."

When you encounter "doubters," remind them of hospitals' low employee transmission rates enabled by protective measures, and of the second surges of COVID-19 in places where many have gone un-masked.

When you care for patients who "get it," please remember to thank them for their cooperation and sacrifices.

Gary M. Gaddis, MD, PhD, FACEP
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MSMA member since 2002

Post-COVID Rehabilitation Services Emphasizing Telemedicine

I found the May/June 2020 issue of *Missouri Medicine* featuring "Telehealth: The Post-COVID Era," to be both informative and timely. As the COVID-19 pandemic has impacted society and made healthcare providers examine how healthcare

is delivered, the use of telehealth seems to be here to stay. Due to some of the regulatory and reimbursement changes, many physicians in health systems have increased the use of some form of telehealth or telemedicine in their own practice.[1] As physicians, we tend to think of telemedicine as the provision of only our services; however, at the University of Missouri-Columbia, our therapy service department has initiated an interdisciplinary tele-therapy program to assist in both evaluation and therapeutic intervention after hospital discharge of patients with COVID-19. Early data on patients with COVID-19 who require ICU care reveals that sarcopenia, debilitation, and sometimes lung scaring can be causes of increased morbidity that can lead to readmission after discharge from the hospital. Many of our normal post-acute care (PAC) facility options (skilled nursing facilities, inpatient rehabilitation, and home health) have limited access to accept or care for patients post COVID-19 infection. Therefore, it is critical that we find other transition treatment options for patients who are discharged directly from the hospital to home.

As a result of these factors, a team of multi-disciplinary specialists from physical therapy (PT), occupational therapy (OT), speech therapy (ST), and respiratory therapy (RT) developed a post Covid-19 rehabilitation plan that could be provided to patients in their home via Zoom or Skype. Patients at home are initially evaluated using objective measures that include: respiratory rate, pain scale, Borg exertion test, sit to stand test, cognitive screening, and a fatigue scale. Based on each patient's results, an individual program is developed geared toward respiratory mobility and activity of daily living (ADL) needs.

The program consists of two to four visits over a one to three week time frame based on each individual's severity, needs, and clinician judgment. The visits are stratified as follows:

- Visit 1: 2-4 days post-discharge; evaluation and service needs.
- Visit 2: 2-4 days post Visit 1; evaluate progress and need to continue program.
- Visit 3: 7-10 days post Visit 1; assess tolerance and progress exercise recommendations.
- Visit 4: 3 weeks post initial evaluation; discharge to home wellness program or to outpatient therapy program.

By standardizing our treatment plan for delivering therapy services in the home setting, we hope to have a positive impact on readmission rates, costs, and satisfaction (provider and patients). Also, arranging therapy sessions during the first 10 to 14 days ensures that a medical professional has contact with patients soon after the transition home. This allows contact with the primary medical team if there are any acute concerns early in the patient's post-hospital transition. Initial observations reveal that patients are in need of more OT and ST services than initially expected. However, just like physician services different, payors may or may not cover these services. While we are excited about further developing this and other teletherapy programs, it will be critical for physicians to understand options of treatment, to advocate for payment, and continue to push for innovation to help the patients that we serve.

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Letters to the Editor

Submissions reflect readers' opinions and may be edited for length. Use in subject line: "For Publication"

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Missouri Medicine in the News

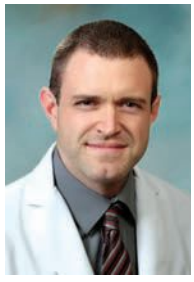
The *Missouri Medicine* Publications Committee announces that David Fleming, MD and Charles Van Way, III, MD, will receive our Distinguished Editorial Service Award for 2020. They join Art Gale, MD, in this distinguished circle of esteemed, long-time contributors to our nationally-known medical journal. Together the three represent the longest serving members of our board.



Dr. Fleming has edited the book *Care of the Dying Patient* (University of Missouri Press) based on articles published in our Journal, served as a long-standing liaison with University of Missouri, and worked with us to create the first ever two theme issues in Nov/Dec 2002 and Jan/Feb 2003. This set the model of using our state medical schools to present theme issues which has insured both high quality and adequate volume for the past 17 years.



Dr. Van Way has contributed numerous editorials and perspectives. He has been an excellent liaison with the University of Missouri - Kansas City School of Medicine and helped with faculty recruitment to MSMA. He is also a past President of MSMA and a Missouri Delegate to the American Medical Association.



Congratulations are due to John Bustle, MD, MHCM, Chief Executive Officer for Bates County Memorial Hospital, who received his Master in Health Care Management degree from Harvard University, T.H. Chan School of Public Health. Thank you for your membership support since 2010.



Kristyn Menendez, MD, recently joined Golden Valley Memorial Healthcare as an ob/gyn in Clinton. MSMA appreciates your support as a member since 2008.

Congratulations to the following medical students who recently graduated from a school of medicine in Missouri, and received the MSMA Graduate Award.



A.T. Still University: Joshua Buell



Kansas City University: Kellen Smutz



University of Missouri-Columbia: Calli Morris







Saint Louis University: Jared Schaefer, Carly Therese Thaxton, and Marah Van Diest







University of Missouri-Kansas City: Landon Rohowetz, Emily Boschert, and Keerthi Gondi.



Jaswinder Singh, MD, has been a valued MSMA member since 2009 and MSMA commends him on expanding his oncology practice to the patients of Bates County Memorial Hospital.

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

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Finding Hope

by Mary Anne Jackson, MD

As we address the uptick of COVID-19 cases in our communities within the state of Missouri, our goals are clear. Limiting viral transmission, improving treatment, and vaccine development are the top priorities, while assuring healthcare capacity and the economic health of our communities, as cases continue to increase, present competing priorities.

As we continue our face-off against the novel coronavirus, the crushing effect on every physician, our families, and every member of society across the United States, has been ever increasing.

Seven months into the global coronavirus pandemic, we are up over four million cases and more than 140,000 deaths in the U.S. Colleagues have worked front line caring for critically-ill patients with COVID-19 when personal protective equipment has been in short supply, and healthcare systems have been pushed to the brink. As healthcare professionals, we understand and embrace the strategies necessary to flatten the epidemic curve, to protect ourselves, our families and those around us. We do so because it is our duty and privilege and to see us through the next three months when a COVID-19 vaccine becomes a reality.

Since the onset of the pandemic in the U.S. on January 22, 2020, the fall-out has changed what "normal life" looks like. For medical schools across the country, stay-at-home orders in our community that were enacted on March 11 triggered us to quickly move to an online biomedical science curriculum and clinical pauses for medical students, and required us to teach clinical medicine using virtual clinical encounters. Like schools across the U.S., all of the faculty and staff at our School of Medicine went above and beyond to make sure students stayed on path to promote and graduate. Now, as students entered back into the healthcare environment to continue their clinical phase of training on June 20, we are facing challenges like no other as we tackle a surge in cases.

Since the pandemic onset 178 days ago, July 18 brought with it, a global record for number of new cases—260,000 in one day with 74,000 of those new cases across the U.S. Hospitalizations and deaths from COVID-19 are again on the rise as the median age of those infected decreases owing to a rise in cases in younger people. We've listened to Anthony Fauci, MD, guide the entire country on the best public health strategies to keep us safe, based on the evolving science, and all the while demonstrating how one provides leadership with grit and integrity. We've seen the financial fall out from the virus, and the painful impact of the pandemic on communities and even those we love.



Mary Anne Jackson, MD, FAAP, FIDSA, FPIDS, MSMA member since 2019, is Dean and Professor of Pediatrics at the University of Missouri-Kansas City School of Medicine, Kansas City, Missouri.

We've also confronted a dual crisis as on May 30, protests across the U.S., outraged after George Floyd's death while in police custody, called on us to confront structural racism in our society. I was proud to participate with my colleagues here and across the country at the White Coat for BLM event at Hospital Hill Park on June 8, 2020, which symbolized this recognition for our medical community. This call to action began by naming racism as a determinant of health. At this School of Medicine, we have heard the voices of our students, staff and faculty and made the commitment to change as we promote racial justice in our community, demand racial justice in medical care, and transform our medical school curriculum to keep current and future physicians educated about the history of and expressions of racism in medicine. We will use activism and advocacy, to move forward and stress that knowledge, love, grace and compassion can change the course of human kind.

As we address the uptick of COVID-19 cases in our communities within the state of Missouri, our goals are clear. Limiting viral transmission, improving treatment, and vaccine development are the top priorities, while assuring healthcare capacity and the economic health of our communities, as cases continue to increase, present competing priorities. Understanding where we still have gaps and providing resources are necessary to advance COVID testing capacity, speed testing turnaround time, ramp up contact tracing and to continue to address PPE shortages. Urgently addressing needs of vulnerable populations who remain at risk, require us to respond to rises in cases of domestic abuse, eviction, and suicide rates. We need a safe and effective path toward bringing our youth back to in-person education. And we need to ensure societal compliance with mask wearing and social distancing. The reason: masks work to effectively limit transmission and prevent disease. In Springfield, Missouri, two hair stylists with active COVID-19, had face to face contact with 139 clients who ranged in age from 20-93 years for appointments lasting 15-45 minutes—both parties wore masks, and no cases of transmission occurred.

So as we navigate the "new normal," and try to hang in there, where is the space for hope? There are at least 26 COVID-19 vaccines that are in human trials and four progressing forward to Phase 3 efficacy trials. Vaccines from Pfizer Inc, BioNtech SE, Moderna Inc., and AstraZeneca are leading the way and ready to recruit adult volunteers in the next few weeks. My colleague, Barbara Pahud, MD, UMKC School of Medicine Associate Professor in Pediatrics and Research Director of Pediatric Infectious Diseases at Children's Mercy with Mario Castro, MD, '88 UMKC School of Medicine alum and Vice Chair of Clinical and Translational Research at Kansas University Medical Center, will lead the AstraZeneca/ University of Oxford Phase III study in our Kansas City community. And our colleagues at Washington University will be recruiting for that same vaccine trial in St. Louis. It is expected that federal funding will facilitate move to licensure for five or more vaccine initiatives by December 2020.

And more reason for hope? On August 3, our newest medical students—the future of our profession- will be welcomed to the medical community, but for the first time ever, with a virtual white coat ceremony. As they don their white coats, we ask them to embrace the call to action. The lessons we teach along the way as we address both COVID-19 and our path to racial justice will guide our student's to grow and develop as healers who care for patients with compassion and empathy. We call on them to ensure that we are successful in our mission to use cutting-edge science and transformative changes in our healthcare system to address health inequity. Wearing our white coats is a daily reminder of our commitment to patients, to learning, and to understanding that struggle and reward is the opportunity to grow.

MM



Trends in Sexually Transmitted Infections

by David M. Bamberger, MD

Clinicians need to be thorough in obtaining an appropriate sexual history and basing screening decisions accordingly.



David M. Bamberger, MD, is Chief, Infectious Diseases, Truman Medical Center, Medical Director, Sexual Health Clinic, Kansas City Health Department, and Professor of Medicine, University of Missouri - Kansas City School of Medicine, Kansas City, Missouri.

Abstract

Sexually transmitted infections have increased dramatically in the past 10 years. Rates are higher in Missouri than nationally, and higher in the large urban areas, in young adults, racial minority groups, among men having sex with men, and are associated with injection drug and methamphetamine use. Clinicians need to perform an appropriate sexual history and follow guidelines for screening and treatment. There is increasing concern for resistance among gonococcal isolates which limits future treatment options.

Introduction

After previous declines in morbidity, sexually transmitted infections (STIs) have been increasing in the United States.[1] STIs have long been associated with stigma and social inequality. The Institute of Medicine report in 1997 noted that despite the tremendous health and economic burden of STIs, the scope and impact of the STI epidemic are underappreciated and the STI epidemic is largely hidden from public discourse.[2] More than twenty years later, the burden of STIs is increasing.

Disease Burden

Gonorrhea cases in the United States reached a historic low of 98 cases per 100,000 population in 2009 but has increased 82.6% to 179 in 2018, a rate not seen since 1992 (Table 1).[1] The rate in Missouri and its two largest metropolitan areas are higher than the national average. Nationally, the rate is 46% higher among males than females, and highest among those aged 20-24. There is a marked disparity among racial/Hispanic ethnicity groups. Provisional data from 2019 show a further increase in cases in 2019 in Missouri.[3]

Chlamydia is three-fold more common than gonorrhea.[1] Cases in the United States have increased by 33.3% since 2009. Similar to gonorrhea, the rates in Missouri and its two largest metropolitan areas are higher than the national average. In contrast to gonorrhea, the rate in females is higher than in males. The ages most affected are among 15-24 year olds, and there remains a marked disparity among racial/Hispanic ethnicity groups. Provisional data from 2019 in Missouri show a similar number of cases as in 2018.[3]

Syphilis rates (all stages) have increased 315% in 2018 since reaching a low in 2000.[1] Congenital syphilis increased 394% since 2012, representing 1306 cases in the United States. Syphilis is approximately six-fold more common in men than in women. The most common age group is 25-29 in men, and 20-24 in women. Similar to gonorrhea and chlamydia, there is a marked disparity among racial/Hispanic ethnicity groups.

Table 1. Rates of reported cases of gonorrhea (GC), chlamydia (CT) and syphilis per 100,000 population.[1]

	GC	CT	Syphilis			
			All stages	Primary and Secondary	Early non-primary and secondary	Congenital*
National US Rate 2018	177	540	35.3	10.8	11.8	33.1
National US Rate 2009	98	405	14.6	4.6	4.3	10.4
Missouri 2018 Rate	247	568	31.3	13.2	8.9	22.8
Kansas City Metro 2018 Rate	266	604	37.3	16.7	11.6	
St. Louis Metro 2018 Rate	259	613	31.2	12.3	8.3	
National rate by Sex 2018						
Male	211	381		18.7		
Female	144	693		3.0		
National rate by Age 2018						
15-19	432	2110		4.3		
20-24	713	2899		10.0		
National Rate by Race/ Hispanic Ethnicity 2018						
Blacks	549	1192		28.1		86.6
Whites	71	212		6.0		13.5
Hispanics	116	393		13.0		44.7

**Congenital syphilis rates are per 100,000 live births.*

High-Risk Populations

Men who have sex with men (MSM) account for 64.3% of national reported primary and secondary syphilis cases, and account for 66.6% of the cases among men.[1] 35% of the MSM cases were in those who also reported to be HIV positive. The rate of primary and secondary syphilis infection per 100,000 MSM in Missouri is 462.

Nationally, data for chlamydial and gonorrheal disease are not reported according to sexual partners. In a study at the Kansas City Health Department Sexual Health Clinic, we observed gonococcal infections approximately twice as commonly among MSM than among men having sex with women (MSW).[4] As has been reported widely, more than 80% of the gonococcal disease burden among MSM would be missed if testing at pharyngeal and rectal sites were not performed. Similarly for chlamydia, rectal chlamydia is more than twice as common as urogenital chlamydia among MSM engaging in anal receptive sex, and more than 90% would be missed if not tested at the extragenital site. Almost all of those tested at extragenital sites were asymptomatic.

Although most primary and secondary syphilis is observed in MSM, rates of infection between 2014 and 2018 are increasing at a faster rate in MSW (99%) and in women (156%) than in MSM (48%).[1] This increasing rate of infection in MSW and women is associated with a marked increase in infections associated with injection drug use, methamphetamine use, heroin use and in sex with a person who injects drugs. This has been particularly observed among MSW and women living in Western and Midwestern states. As an example, in 2014 only 2.4% of MSW and 3.4% of women with primary and secondary syphilis in the Midwest reported methamphetamine use in the prior 12 months, compared to 14.8% of MSW and 22.4% of women in 2018. During this time, there was a decline in the primary and secondary syphilis cases among MSM that were associated with methamphetamine use from 8.3% in 2014 to 6.3% in 2018. In Kansas City, 47% of primary and secondary syphilis cases reported substance use of any kind during sex in 2019 compared to 31% in 2018 (data provided by Lesha Dennis, KC Health Department)

The higher rates of STIs in MSM may be exacerbated by the uptake in the use of preexposure prophylaxis (PrEP) among MSM. In an Australian study, 48% of those entering a PrEP trial developed an STI in a mean follow-up of 1.1 years.[5] Among

Table 2 Questions for assessment of risk for STIs. (modified from Savoy, et al.[6])

1. Are you currently sexually active? Have you been?
2. What is your gender? How do you identify?
3. How do your partners identify? Do they identify as male, female or another? What are the genders of your partners?
4. How many partners have you had in the last month? In the last six months? Your lifetime?
5. Do you participate in vaginal sex? Oral sex? Anal sex?
6. Have you been tested for STIs and HIV?
7. Have you ever had any STIs? Have your sex partners?
8. Do you or your sexual partners use intravenous drugs and/or methamphetamines?
9. How do you protect yourself from STIs and HIV?

those with preenrollment data, the number of STIs increased by 12% after being initiated on PrEP and after adjusting for testing frequency. Risk factors for STIs included younger age, greater partner number and group sex.

Clinical Care

Clinicians should obtain a sexual history in a nonjudgmental approach avoiding terms that make assumptions regarding behavior or orientation. Questions that should be asked when evaluating a patient for the risk of STIs are found in table 2.

Screening

The United States Preventive Services Task Force recommends screening for HIV for all people age 15 to 65, and to also include those younger and older who are at increased risk.[7] Repeat screening is recommended for person who are increased risk, including sexually active MSM, a person with a sex partner with HIV, injection drug users, sex partners of injection drug users, exchanging sex for drugs or money, having another STI or a sex partner with a STI, or having a new sex partner whose HIV status is unknown. Key to obtaining appropriate screening is obtaining a thorough history for risks of STIs.

All sexually active females <25 years old should be screened for chlamydia and gonorrhea annually, and screened for syphilis if there are risk factors, including new or multiple sex partners, recent STI diagnosis, HIV disease, exchanging sex for money or drugs, or intravenous drug use or methamphetamine use.[7,8] Women ≥ 25 should be screened for chlamydia, gonorrhea and syphilis if there are similar risk factors, including a STI in the previous 24 months.

Pregnant women should be screened for chlamydia and gonorrhea in the first trimester if <25 or if there is an increased risk.[7,8] All women should be screened for HIV, HBV and syphilis in the first trimester. Repeat screening should be done in the third trimester if there is an increased risk. Pregnant women with HIV should also be screened for trichomonas in the first trimester.

MSW without HIV should be screened for gonorrhea, chlamydia and syphilis if they had a previous STI in the last two years, on the basis of exposure to a known infection, or in targeted settings, such as adolescent and STI clinics and correctional facilities.[7,8]

MSM should be screened for genital chlamydia and gonorrhea, rectal chlamydia, rectal gonorrhea and pharyngeal gonorrhea if exposed, and syphilis annually.[7,8] More frequent screening (every three months) should be done for those with multiple or anonymous sexual partners, and those who engage or whose sexual partners engage in injection drug or methamphetamine use.

Newer Aspects of Treatment and Prevention

Current guidelines for the treatment of cervical, urethral, rectal and pharyngeal gonorrhea in the United States is the combination of ceftriaxone 250 mg intramuscularly in addition to 1g of oral azithromycin.[9] Although the combination was initially advocated for the high rate of coinfection with chlamydia, which has been reported as high as 46% in older national surveys,[10] is also advocated even in those not co-infected with chlamydia because of concerns of rising minimum inhibitory concentrations (MIC) and the hope that the combination would lessen the chance of further development of resistance of gonococci to ceftriaxone. Ceftriaxone remains the best treatment option for all forms of gonococcal infections but there is a trend in the US and word-wide noting higher MICs associated with mosaic penA alleles that can lead to treatment failure.[11,12] Drug resistant gonococci has been listed by the CDC as one of the five urgent antibiotic threats in the US. [13] There is also a recent trend for higher MICs for azithromycin and frank azithromycin resistance, and it has not been clear that the combination of the two agents is beneficial in the absence of concomitant chlamydia infection. Guidelines in the UK and Japan utilize higher doses of ceftriaxone to reflect the concern for rising MICs, and it is anticipated that US guidelines may also evolve.

Pharyngeal gonorrhea infections are usually asymptomatic but are of concern because they may act as a reservoir promoting sustained infection, be less susceptible to treatment, and contribute to the evolution of antimicrobial resistance. In our study at the Kansas City Sexual Health Clinic, pharyngeal

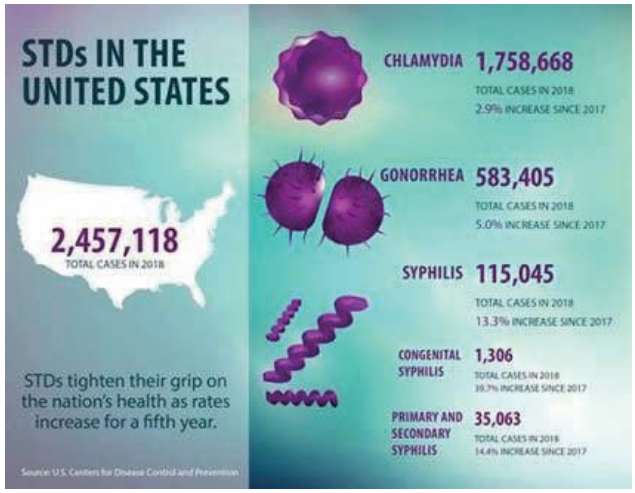
gonorrhea was found in 8.5% of MSM, but also in 3.8% of women and 3.1% of MSW.[4] Extragenital infection in the absence of genitourinary infection is particularly common in MSM, but also was noted in about a third of MSW and women and would be missed in absence of extragenital screening. Current US guidelines recommend that providers should ask their patients with urogenital or rectal gonorrhea about oral sexual exposure and that any person with pharyngeal gonorrhea who is treated with a regimen other than the combination of ceftriaxone plus azithromycin should return 14 days after treatment for a test-of cure.[9]

Mycoplasma genitalium is likely the second most common cause of nongonococcal urethritis in males and has been associated with cervicitis and pelvic inflammatory disease in women. Macrolide resistance rates vary from 50 to 88% and when utilized, a five-day treatment is more effective than a single dose.[14] Moxifloxacin is also recommended for suspected or confirmed *Mycoplasma genitalium*, but resistance to quinolones is also increasing. The organism is on the CDC's Watch List for antimicrobial resistance threats for 2019.[13] In 2019, the first Food and Drug Administration approved assay became available on the market. Concerns for single dose azithromycin in the treatment of nongonococcal urethritis, along with evidence of greater efficacy of doxycycline given for seven days over single-dose azithromycin for rectal chlamydia have called into question the routine use of single-dose azithromycin in the management of nongonococcal urethritis.

A French study among MSM using tenofovir disoproxil and emtricitabine for preexposure prophylaxis for HIV randomized participants to taking doxycycline 200 mg within 24h after sex or no prophylaxis.[15] 42% of those in the control group developed a STI over a nine-month period. Those receiving doxycycline had a 70% lower rates of both chlamydia and syphilis, but no decrease in rate of gonorrhea. Most of the infections were asymptomatic.

Conclusions

Sexually transmitted infections are increasing in the United States. Although chlamydia is more common, of concern is marked increase in cases of gonorrhea and syphilis, including cases of congenital syphilis. Clinicians need to be thorough in obtaining an appropriate sexual history and basing screening decisions accordingly. Antimicrobial resistance, particularly for Neisseria gonorrhea and *Mycoplasma genitalium*, is increasing, with concerns that available therapies will lose efficacy.



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Disclosure

None reported. **MM**



Updates on Rapid Diagnostic Tests in Infectious Diseases

by Masako Mizusawa, MD

Rapid diagnostic tests are powerful tools for the timely optimization of antimicrobial use.



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Abstract

In the last two decades there have been dramatic advances in development of rapid diagnostic tests. Turnaround time of the assays have significantly been shortened which led to reductions in time to appropriate antimicrobial therapy and improvement of patient clinical outcomes. Molecular-based assays generally have better sensitivity than conventional methods, but the cost is higher. The results need to be interpreted cautiously as detection of colonized organisms, pathogen detection in asymptomatic patients, and false negative/positive can occur. Indications and cost-effectiveness need to be considered for appropriate utilization of rapid diagnostic tests.

Introduction

Detection of pathogens plays a major role in the clinical care of the patients with infectious diseases. Traditional diagnostic testing for infectious diseases such as microscopic examination, antigen detection, serology, cultures, and biochemical reactions are still being used, and sometimes essential for determination of infectious disease etiologies. However, those traditional methods tend to suffer from long turn-around time. For example, bacteria generally require 1-2 days to have growth on culture media, and conventional biochemical identification and susceptibility tests require additional one to two days to result. In the meantime, the patients tend to remain on empiric broad spectrum antibiotics which could lead to selection of antimicrobial resistance.

New technologies such as nucleic-acid amplification, mass spectrometry, and genomic sequencing have revolutionized diagnostic testing for infectious diseases by providing rapid and robust results. Introduction of rapid diagnostic testing in collaboration with antimicrobial stewardship has led to appropriate antimicrobial use and improvement of clinical outcomes.[1]

This article is a concise summary of rapid diagnostic tests for infectious diseases currently available in the United States.

Rapid Molecular Assays

Molecular Multiplex Syndromic Panel Testing

There are currently 4 molecular multiplex syndromic panels available in the U.S.: Blood stream infections, respiratory tract infections, gastrointestinal infections and meningitis/encephalitis. The common advantages of those panels are simultaneous detection of multiple targets and rapid turnaround time that could shorten time to appropriate antimicrobial treatment and improve associated

clinical outcomes. The common disadvantages of those panels are the limited numbers of detectable pathogens and higher cost than conventional methods.

Blood Stream Infections

Blood stream infections are often associated with significant morbidity and mortality.[2] Multiple studies demonstrated associations between delay in initiation of appropriate antimicrobial therapy and increased mortality for patients with blood stream infections.[3–6] Identification of the pathogens in blood cultures is essential for directing appropriate antimicrobial therapy and improving patient outcomes. There are currently four FDA-cleared molecular multiplex assays for blood culture pathogen identification: FilmArray BCID panel (bioMérieux, Marcy l'Etoile, France), Verigene Gram Positive Blood Culture ID assay (BCID-GP) and Gram Negative Blood Culture ID assay (BCID-GN) (Luminex Molecular Diagnostics, Toronto, Canada), Accelerate PhenoTest BC kit (Accelerate Diagnostics, Tucson, AZ), and ePlex Blood Culture Identification Gram-Positive Panel (BCID-GP) and Gram-Negative Panel (BCID-GN) (GenMark Diagnostics, Carlsbad, CA).

The assays are performed directly on positive blood culture specimens detected by a continuous monitoring blood culture system. The turnaround time and pathogen targets in each panel are shown in Table 1. While FilmArray BCID and PhenoTest BC include targets for both Gram positive and Gram negative organisms in one test kit, Verigene and ePlex have Gram-positive and Gram-negative panels separately and Gram staining results determines selection of the appropriate test panels. Of note the PhenoTest BC is currently the only assay that enables rapid antimicrobial susceptibility testing in addition to pathogen identification. The antimicrobial susceptibility panel of the PhenoTest BC includes amikacin, ampicillin, ampicillin/sulbactam, aztreonam, ceftazidime, ceftaroline, cefepime, ceftriaxone, ciprofloxacin, daptomycin, erythromycin, ertapenem, gentamicin, linezolid, meropenem, piperacillin/tazobactam, tobramycin, and vancomycin. There have been no major differences in the performance of those multiplex blood culture panels to support superiority one over another.[7–22] In general, their performance is lower with polymicrobial blood culture specimens than monomicrobial ones.[7,8,13,14,19,20,22] Improvement of clinical outcomes such as length of stay, time to optimal antibiotic therapy, and 30-day mortality rate with antimicrobial stewardship interventions based on the results of rapid blood culture identification have been demonstrated.[23–34]

Meningitis and Encephalitis

Meningitis and encephalitis are potentially life-threatening infections and could leave severe neurological sequela. Rapid pathogen detection to guide appropriate treatment is critically important to improve clinical outcomes. Currently FilmArray Meningitis/Encephalitis (ME) panel (bioMérieux, Marcy l'Etoile, France) is the only FDA-cleared assay available in the U.S. The pathogen targets included in the FilmArray ME panel are *Escherichia coli* K1, *Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitidis* (encapsulated), *Streptococcus agalactiae, Streptococcus pneumoniae*, Cytomegalovirus, Enterovirus, Herpes simplex virus 1, Herpes simplex virus 2, Human herpesvirus 6, Human parechovirus, Varicella zoster virus, and *Cryptococcus neoformans/gattii*. The advantages of the FilmArray ME panel compared to conventional cultures and individual molecular-based tests are rapid turnaround time (one hour) and a small amount of CSF (0.2mL) required for detection of 14 targets. In the meta-analysis of eight studies accounting for 3,059 patients met the inclusion criteria of the diagnostic accuracy test review of the FilmArray ME panel, mean sensitivity was 90% (95% CI 86 - 93%) and mean specificity was 97% (95% CI 94 - 99%).[35] The studies that specifically evaluated false positive and negative results were also analyzed, and it was found that 4% and 1.5% of specimens were determined as false positive and false negative respectively by the FilmArray ME panel compared with reference standard methods after implementing adjudication for discrepant results.[35] The highest proportion of false positive was observed for *Streptococcus pneumoniae* followed by *Streptococcus agalactiae*, and the highest proportion of false negative was observed for Herpes simplex virus 1 and 2, enterovirus, and *Cryptococcus neoformans/gattii*.[35] Most of the false negative *Cryptococcus neoformans/gattii* cases were those who were on antifungal treatment.[35]

Respiratory Tract Infections

There are currently five FDA-cleared multiplex panels for respiratory pathogens: NxTAG Respiratory Pathogen Panel (Luminex Molecular Diagnostics, Toronto, Canada), FilmArray Respiratory Panel (bioMérieux, Marcy l'Etoile, France), Verigene

Table 1. Turnaround time and pathogen targets of FDA-cleared multiplex blood culture identification panels

	FilmArray	Verigene	PhenoTest	ePlex
Turnaround time	1 hour	2-2.5 hours	7 hours[a]	1.5 hours
Pathogen targets				
Gram positive bacteria				
Staphylococcus species	X	X		X
S. aureus	X	X	X	X
Coagulase-negative *Staphylococcus* spp.			X	
S. epidermidis		X		X
S. lugdunensis		X	X	X
Streptococcus species	X	X	X	X
S. pneumoniae	X	X		X
S. pyogenes	X	X		X
S. agalactiae	X	X		X
S. anginosus group		X		X
Enterococcus species	X			X
E. faecalis		X	X	X
E. faecium		X	X	X
Listeria species		X		X
L. monocytogenes	X			X
Lactobacillus species				X
Micrococcus species				X
Bacillus cereus group				X
Bacillus subtilis group				X
Corynebacterium species				X
Cutibacterium acnes				X
Gram negative bacteria				
Enterobacteriaceae	X			
Escherichia coli	X	X	X	X
Klebsiella species			X	
Klebsiella pneumoniae	X	X		X
Klebsiella oxytoca	X	X		X
Proteus species	X	X	X	X
Proteus mirabilis				X
Enterobacter species		X	X	
Enterobacter (non-*cloacae* complex)				X
Enterobacter cloacae complex	X			X
Citrobacter species		X	X	X
Serratia species				X
Serratia marcescens	X		X	X
Pseudomonas aeruginosa	X	X	X	X
Acinetobacter species		X		
Acinetobacter baumanii	X		X	X
Haemophilus influenzae	X			X
Neisseria meningitidis	X			X
Bacteroides fragilis				X
Fusobacterium necrophorum				X
Fusobacterium nucleatum				X
Morganella morganii				X
Coronobacter sakazakii				X
Salmonella species				X
Stenotrophomonas maltophilia				X
Yeast				
Candida species				X
Candida albicans	X		X	
Candida glabrata	X		X	
Candida krusei	X			
Candida parapsilosis	X			
Candida tropicalis	X			
Antimicrobial resistance markers				
mecA	X	X		X
mecC				X
VanA/B	X			
VanA		X		X
VanB		X		X
KPC (*bla*$_{KPC}$)	X	X		X
OXA (*bla*$_{oxa}$)		X		X
VIM (*bla*$_{VIM}$)		X		X
IMP (*bla*$_{IMP}$)		X		X
CTX-M (*bla*$_{CTX-M}$)		X		X
NDM (*bla*$_{NDM}$)		X		X

[a] Including antimicrobial susceptibility testing for amikacin, ampicillin, ampicillin/sulbactam, aztreonam, ceftazidime, ceftaroline, cefepime, ceftriaxone, ciprofloxacin, daptomycin, erythromycin, ertapenem, gentamicin, linezolid, meropenem, piperacillin/tazobactam, tobramycin, and vancomycin.

Respiratory Pathogens Flex Nucleic Acid Test (RP Flex) (Luminex Molecular Diagnostics, Toronto, Canada), eSensor Respiratory Viral Panel (RVP) (GenMark Diagnostics, Carlsbad, CA), and ePlex Respiratory Pathogen (RP) Panel (GenMark Diagnostics, Carlsbad, CA). The assays are performed on nasopharyngeal swab specimens collected from individuals who are suspected to have respiratory tract infections. NxTAG Respiratory Pathogen Panel and Verigene RP Flex allow panel customization to avoid detection of unnecessary targets and minimize the cost. The turnaround time and pathogen targets included in each panel are shown in Table 2. The assay performance generally demonstrated high concordance rates with positive percent agreement 84.5 - 98.8% and negative percent agreement 99.2 - 100% when compared between different multiplex panels or with a laboratory-developed polymerase chain reaction (PCR) assay as a reference method.[36–40] However, more frequent discrepancies have been reported for adenovirus,[36,40] influenza B virus,[36] human metapneumovirus,[39] parainfluenza 3,[39] coronavirus,[40] and rhinovirus/enterovirus.[40] It is important to keep in mind that detection of a certain virus does not necessarily mean that the virus is a causative pathogen of respiratory symptoms that a patient has because viruses can be colonized in the respiratory tract asymptomatically. In addition, detection of multiple targets is not uncommon.[36,37] Although immunocompromised patients can develop severe viral respiratory infections and are more likely to benefit from the multiplex panel testing than immunocompetent individuals, they can shed viruses for a prolonged period of time without clinical symptoms. The results of the multiplex respiratory panel testing need to be interpreted carefully in a clinical context. Further work up may be indicated as there are many respiratory pathogens that are not included in multiplex respiratory panels.

Gastrointestinal Infections

Infectious diarrheal illness is very common worldwide. Since 1990, diarrhea has been ranked among the top ten causes of death and disability-adjusted life-years (DALYs) among all ages, and one of the top five causes of death and DALYs for children younger than five years.[41] Conventional methods for diarrheal pathogen detections include microscopic examination, culture, and enzyme-linked immunosorbent assays (ELISA). Microscopic examination for parasite detection requires specific expertise and the results are operator dependent which causes variability in sensitivity. Stool culture is labor intensive and takes two to three days to result. ELISA assays are generally less sensitive than PCR.[42–44] There are currently three FDA-cleared multiplex gastrointestinal pathogen panels in one kit available in the U.S. FilmArray Gastrointestinal (GI) Panel (bioMérieux, Marcy l'Etoile, France), Verigene Enteric Pathogen Test (Luminex Molecular Diagnostics, Toronto, Canada), and xTAG Gastrointestinal Pathogen Panel (Luminex Molecular Diagnostics, Toronto, Canada). BD MAX (BD Diagnostics, Sparks, Maryland, USA) is also a FDA-cleared multiplex assay, but has 4 separate panels for gastrointestinal pathogens: Enteric Bacterial Panel, Extended Enteric Bacterial Panel, Enteric Parasite Panel, and Enteric Viral Panel. The turnaround time and pathogen targets included in those assays are shown in Table 3. Overall multiplex panel tests had higher positivity rates compared to conventional methods in performance evaluation studies.[45–52] Simultaneous detection of multiple pathogens is not uncommon as well as detection of pathogens in asymptomatic patients which can make interpretation of the test results and management challenging for clinicians.[53,54]

Point-of-care Molecular Based Tests

There are a variety of FDA-cleared nucleic acid amplification tests available for one to several targets for surveillance as well as diagnosis of specific infections. Examples include methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, Carbapenem resistance genes (bla_{KPC}, bla_{NDM}, bla_{VIM}, bla_{OXA-48}, and bla_{IMP}), Group A *Streptococcus*, Group B *Streptococcus*, Influenza virus A & B/RSV, *Clostridium difficile* with or without NAP 027, Norovirus, Human simplex virus 1 & 2, *Mycobacterium tuberculosis* with rifampin resistance, *Trichomonas vaginalis, Chlamydia trachomatis/Neisseria gonorrhea*, and *Bordetella pertussis/Bordetella parapertussis*.

T2 System

Candidemia is associated with high mortality rates. Although the rates are variable depending on the clinical setting, mortality rates range from 20% to 60%.[55,56] Blood culture is the gold standard for diagnosis of Candidemia. However, sensitivity of blood culture is as low as 50%.[57,58] T2Candida

Table 2. Turnaround time and pathogen targets of FDA-cleared multiplex respiratory panels

	FilmArray	Verigene	NxTAG	eSensor	ePlex
Turnaround time	1 hour	2 hours	5 hours[a]	6 hours	1.5 hours
Pathogen targets					
Viruses					
Influenza A	X	X	X	X	X
Influenza A H1	X	X	X	X	X
Influenza A H3	X	X	X	X	X
Influenza 2009 H1N1	X			X	X
Influenza B	X	X	X	X	X
Respiratory Syncytial Virus	X				
Respiratory Syncytial Virus A		X	X	X	X
Respiratory Syncytial Virus B		X	X	X	X
Parainfluenza virus 1	X	X	X	X	X
Parainfluenza virus 2	X	X	X	X	X
Parainfluenza virus 3	X	X	X	X	X
Parainfluenza virus 4	X	X	X		X
Coronavirus (229E/HKU1/NL63/OC43)					X
Coronavirus HKU1	X	X	X		
Coronavirus NL63	X		X		
Coronavirus 229E	X		X		
Coronavirus OC43	X		X		
Adenovirus	X		X		X
Adenovirus B/E				X	
Adenovirus C				X	
Rhinovirus		X		X	
Rhinovirus/Enterovirus	X		X		X
Human Metapneumovirus			X	X	X
Human Bocavirus			X		
Bacteria					
Mycoplasma pneumoniae	X		X		X
Chlamydophila pneumoniae	X		X		X
Bordetella pertussis	X	X			
Bordetella parapertussis/ Bordetella bronchiseptica		X			
Bordetella holmesii		X			

[a] *For 96 samples*

Panel (T2 Biosystems, Lexington, Massachusetts, USA) is an FDA-cleared qualitative T2 Magnetic Resonance (T2MR) assay for detection of Candida species directly from whole blood specimens. In T2 system blood-compatible polymerase chain reaction is followed by hybridization of the amplified pathogen DNA to capture probe–decorated nanoparticles. Hybridization yields nanoparticle micro-clusters that cause large changes in the sample's T2MR signal.[59] T2Candida Panel identifies five species of Candida by categorizing them in three groups: Candida albicans/ Candida tropicalis, Candida parapsilosis, and Candida glabrata /Candida krusei. Time to result is three to four hours. In a multicenter clinical trial including 14 centers, the assay sensitivity was 89%.[60] In patients receiving antifungal therapy, T2Candida Panel identified bloodstream infections that were missed by conventional blood cultures.[60] In another multicenter clinical trial including 12 centers, the overall sensitivity was 91.1% and specificity was 99.4%. [61] The pooled analysis including eight studies conducted to evaluate accuracy of T2Candida Panel demonstrated the pooled sensitivity of 91% and specificity of 94%.[62] T2 system also has FDA-cleared Bacterial Panel which can detect *Enterococcus faecium*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* directly from whole blood samples. In a diagnostic accuracy study T2Bacterial Panel sensitivity and specificity for proven blood stream infections were 90% and 90% respectively.[63] Mean time to identification was 3.61 hours (SD, 0.2) for one sample and 7.70 hours (SD, 1.38) for seven samples.[63]

MALDI-TOF MS

Matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry (MS) is a rapid, accurate, and cost-effective identification

method for bacterial and fungal culture isolates with direct smear. In mass spectrometry analysis, sample protein molecules are converted into ions in the gas phase by laser ablation. The ionized molecules are subsequently accelerated by a potential difference and fly through the flight tube towards the detector, and the system measures the analytes' time of flight to the detector which produces a characteristic spectrum. The advantages of MALDI-TOF MS are ability to identify broad range of pathogens and low cost. Turnaround time for the MALDI-TOF MS assay itself is short, but it takes one to two days until the culture isolate for direct smear becomes available. In an effort to shorten time to pathogen identification in blood culture, various sample preparation procedures including Sepsityper kit (Bruker Daltonics, Bremen, Germany) and in-house methods were developed to perform MALDI-TOF MS directly from positive blood culture bottles without subculture. Overall correct identification rates to species level and genus level range 39.9 - 89.7% and 76.4 -100% respectively, and the rates were higher in Gram negative organisms compared to Gram positive organisms.[64–79] Performance was poor in polymicrobial cultures[65,67–69,71–73,75–78] and yeast identifications.[66,70,71,79] Recently, an alternative method with subculture has been developed. The positive blood culture specimens are plated on solid media. After short incubation (four to six hours) 1 - 2 mm of the bacterial lawn is transferred with a 1 µL inoculation loop for direct smear. Using short incubation overall correct identification rates to species level range 69.7 - 99.5%.[80–83]

Table 3. Turnaround time and pathogen targets of FDA-cleared multiplex gastrointestinal panels

	FilmArray	Verigene	xTAG	BD Max[a]
Turnaround time	1 hour	2 hours	6 hours[b]	3-4 hours[b]
Pathogen targets				
Bacteria				
Campylobacter	X	X	X	X
Salmonella	X	X	X	X
Shigella		X	X	
Shigella/Enteroinvasive E. coli	X			X
Shiga-like toxin producing E. coli St1/St2	X		X	X
Shiga Toxin 1		X		
Shiga Toxin 2		X		
Vibrio	X	X		X
Vibrio cholerae	X		X	
Yersinia enterocolitica	X	X	X	X
Plesiomonas shigelloides	X			X
Enteroaggregative E. coli	X			
Enteropathogenic E. coli	X			
Enterotoxigenic E. coli LT/ST	X		X	X
E. coli O 157	X		X	
Clostridium difficile (toxinA/B)	X		X	
Viruses				
Adenovirus F40/41	X		X	X
Astrovirus	X			X
Norovirus GI/GII	X	X	X	X
Rotavirus A	X	X	X	X
Sapovirus (I, II, IV and V)	X			X
Parasites				
Cryptosporidium			X	X
Cyclospora cayetanensis	X			
Entamoeba histolytica	X		X	X
Giardia lamblia	X		X	X

[a] Consists of 4 separate panels (Enteric Bacterial Panel, Extended Enteric Bacterial Panel, Enteric Viral Panel and Enteric Parasite Panel)
[b] For 24 samples

Conclusions

Rapid diagnostic tests are powerful tools for the timely optimization of antimicrobial use. However, interpretations of the results such as potential false positive or negative and detection of colonized microorganisms require careful evaluation of the clinical settings and background of the patients. Cost-effectiveness also needs to be considered to determine indications for expensive rapid diagnostic tests to prevent overutilization of those tests.

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SARS-CoV-2 Serology Testing: An Epilogue

There are currently more than 200 SARS-CoV-2 commercial serology tests available in the U.S. Serology assays for SARS-CoV-2 initially did not require FDA emergency use authorization (EUA), and submission of assay validation data to Food and Drug Administration (FDA) was a voluntary process until May 4, 2020. Therefore, many laboratories notified FDA that they had validated their assays and started patient testing, but their assay performances were not reviewed by FDA prior to market release. A revised guidance from FDA has provided specific assay performance thresholds, and validation data submission for EUA has become manufacturers' requirements. A list of SARS-Co-V-2 serology tests that have been removed from the notification list due to manufacturers' voluntary withdrawal and lack of pending EUA request or issued EUA is available on the FDA website (https://www.fda.gov/medical-devices/emergency-situations-medical-devices/faqs-testing-sars-cov-2#nolonger). There is also a list of EUA authorized serology tests (https://www.fda.gov/medical-devices/emergency-situations-medical-devices/eua-authorized-serology-test-performance). It is advised to select an EUA authorized SARS-Co-V-2 serology test to assure the appropriate assay performance.

Commercial serology assays for SARS-CoV-2 are variable in different formats (lateral flow assays, enzyme immunosorbent assays, and chemiluminescent immunoassays) and antibody classes (IgM, IgA, IgG, and IgM/IgG total antibody) with using different antigens (nucleocapsid, S1 and/or S2 spike glycoproteins, and spike glycoprotein receptor binding protein).[1] The majority of patients seem to develop antibody response between seven and eleven

SARS-CoV-2 Serology Testing: An Epilogue, continued

days following exposure to SARS-CoV-2[2] although available data regarding timing of antibody appearance following disease onset are variable.[2–6] Wu et al. collected plasma samples from 175 COVID-19 recovered patients with mild symptoms and found that SARS-CoV-2 specific neutralizing antibodies were detected in patients from day 10-15 after the onset of disease.[7] They also found that elderly and middle-age patients had significantly higher plasma neutralizing antibody titers than young patients, and approximately 30% of recovered patients generated a very low level of neutralizing antibody titers (10 patients had undetectable levels).[7]

Antibody testing can be used for surveillance to identify how many people have been exposed to SARS-CoV-2 in the community as well as contact tracing. Another use of antibody testing is donor screening for convalescent plasma which is used to treat patients with SARS-CoV-2 infection. In the future, when a vaccine for SARS-CoV-2 becomes available, antibody testing would play a role in screening vaccine candidates and monitoring immune responses of vaccinated individuals.

Not all the antibodies produced are neutralizing antibodies that block viral entry to host cells.[8] Commercial serology assays do not distinguish between neutralizing antibodies and other antibodies. Therefore, detection of IgG antibodies by those assays does not mean that detectable levels of neutralizing antibodies are present, and antibody testing should not be used as a surrogate marker for protective immunity against SARS-CoV-2 infection. Even if a serology test that specifically detects neutralizing antibodies is developed, detection of neutralizing antibodies still does not equal to protective immunity because what levels of antibody titers would protect patients from SARS-CoV-2 infection is still unknown.

Antibody testing should not be used for diagnosing acute/recent SARS-Co-V-2 infection by itself because antibody may not be detected in the early days of the infection when the risk of transmission is the highest, and negative results do not rule out acute/recent SARS-CoV-2 infection. In general IgM suffers from false positivity more than other classes of antibodies,[9] and positive IgM results do not rule in acute/recent SARS-CoV-2 infection either. Grifoni et al. found SARS-CoV-2-reactive $CD4^+$ T cells in ~40%–60% of unexposed individuals, suggesting cross-reactive T cell recognition between circulating "common cold" coronaviruses (HCoV-OC43, HCoV-HKU1, HCoV-NL63, and HCoV-229E) and SARS-CoV-2,[10] and false positive results due to cross-reactivity with other coronaviruses are also possible. It is advised to check whether cross-reactivity with common cold coronaviruses has been validated or not prior to selection of antibody assays. It is also important to keep in mind that positive and negative predictive values of antibody assays depend on disease prevalence. When disease prevalence is low, false positivity rate is increased even with the excellent specificity.

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Disclosure

None reported. **MM**



Antimicrobial Stewardship by Leveraging Electronic Medical Records

by Sayo Weihs, PharmD

Antimicrobial stewardship programs (ASP) are no longer optional hospital programs, but a mandated program as a direct result of the growing antimicrobial resistant threat.



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Abstract

This paper describes how an antimicrobial stewardship program was successfully developed and integrated into a university medical center's electronic healthcare records and improved antibiotic selection.

Introduction

Antibiotics have transformed modern medicine. Swift initiation of antibiotics to treat infection reduces morbidity and mortality in cases like sepsis.[1] Antibiotic resistance and/or abuse are important clinical problems. Centers for Disease Control and Prevention (CDC) estimates that more than 2.8 million antibiotic resistant infections occur in the United States each year, and more than 35,000 people die as a result.[2] In addition, nearly 223,900 people in the US required hospital care for *C. difficile* and at least 12,800 people died in 2017.[3] Varying estimates have been published, but many reports estimate antibiotic misuse as around 30% of all antibiotic prescribed in the U.S.[2, 4] Rittman et al. reported that antibiotic resistance may cost the US up to $20 billion in healthcare costs and $35 billion in lost productivity annually.[5]

Antimicrobial Stewardship Programs Are Mandatory

Antimicrobial stewardship programs (ASP) are no longer optional hospital programs, but a mandated program as a direct result of the growing antimicrobial resistant threat. Missouri Department of Health and Senior Services RSMO 192.667.19 states "…each hospital shall establish an antimicrobial stewardship program for evaluating the judicious use of antimicrobials, especially antibiotics that are the last line of defense against resistant infections. The hospital's stewardship program and the results of the program shall be monitored and evaluated by hospital quality improvement departments and shall be available upon inspection to the department. At a minimum, the antimicrobial stewardship program shall

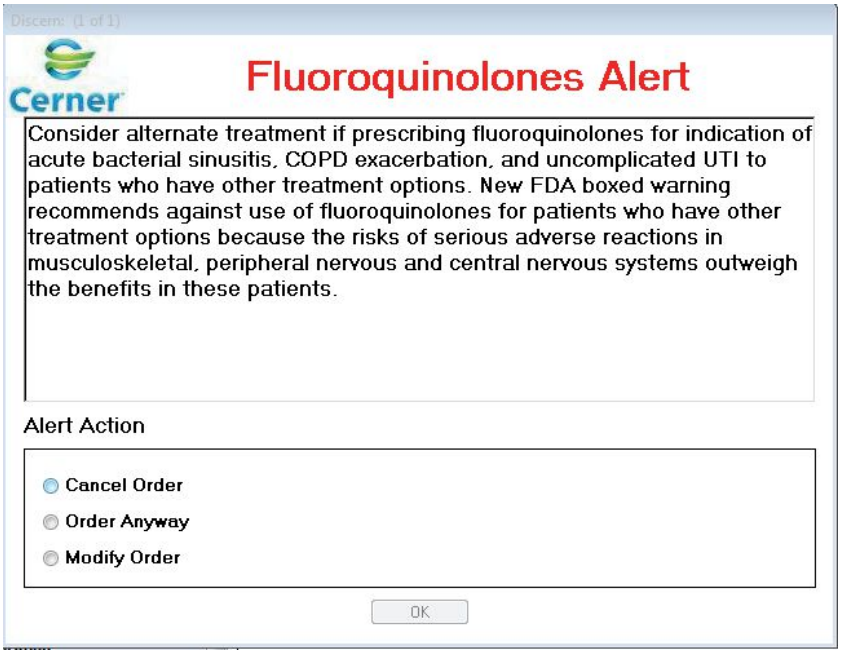


Figure 1. Pop-Up Alert Fluoroquinolones Source: Cerner

be designed to evaluate that hospitalized patients receive, in accordance with accepted medical standards of practice, the appropriate antimicrobial, at the appropriate dose, at the appropriate time, and for the appropriate duration." CDC updated its guideline in 2019 highlighting the seven core elements of ASP including hospital leadership commitment, accountability, pharmacy expertise, action, tracking, reporting and education.[2]

At Truman Medical Centers (TMC), we implemented an antimicrobial stewardship program in 2009. In our 10 years of experience, we have started our effort with interventions such as prospective review and feedback, antibiotic restriction policy, education, clinical pathways and site-specific guideline for optimal antibiotic use. Since then, we have had opportunity to elevate our antimicrobial stewardship effort with the advances in information technology.

Given the advancement in electronic medical records, TMC partnered and implemented such programs as live Antimicrobial Stewardship (AMS) worklist through our electronic health records (EHR) vendor (Cerner). These EHR activities are collectively called clinical decision support system (CDSS). CDSS is defined as utilizing individual patient data coupled with population statistics and computerized clinical guidance to provide patient-specific management recommendations either on clinician request or at the point of care.[6] Live alerts in the EHRs changed how the antimicrobial stewardship activities were conducted from daily reports and collecting patient information by hand on those who are on targeted broad spectrum antibiotic for prospective audit to instantly identifying those patients who needs antimicrobial stewardship review. AMS worklist also identifies patients who has de-escalation opportunity, positive culture but no antibiotic, rapid diagnostics results availability, drug-bug mismatch and more. These are all identified by the AMS worklist alert system through rules built to identify patients with potential AMS opportunity. This has enabled our AMS to review more patients any time, any day. We have also published our site-specific antimicrobial guide in an app form, providing easy access for all providers with up to date information on their website or their handheld device. This online/app platform has increased use of the antimicrobial stewardship guidance, as well as enabled us to send push-notification for any updated site-specific guideline. This has been useful to keep our providers up to date on their knowledge and resources.

ASP Prospective Audit and Feedback

Prospective audit and feedback are accomplished through review of lists of patients on antibiotics and alerts for combinations of specific antimicrobials and clinical or microbiology results. These prospective audits are generally done after the antibiotic has already been ordered and often

after the first dose has been administered. In ambulatory care areas, prospective audit and feedback are difficult to perform as prescriptions are generated and sent into the outpatient pharmacy before any of the ASP can be performed. In order to solve this problem, we investigated functions of CDSS to help with the dilemma.

We theorized that the CDSS warning alert for the prescribers based on indication and medication could steer prescribers away from ordering inappropriate antibiotics. At TMC, we did a retrospective chart review to evaluate the impact of a computer-based decision warning pop-up sign using CDSS to see if prescribers are appropriately avoiding ordering levofloxacin for indications such as chronic obstructive pulmonary disease, uncomplicated urinary tract infection or sinusitis based on the 2016 FDA warning for fluoroquinolone use in uncomplicated indications. Any time a provider ordered levofloxacin for the above inappropriate indications, a warning (Figure 1) would pop up alerting the provider to avoid levofloxacin. There was substantial effort made so that the pop-up alert would only fire in violation of well-defined indications/contraindications. This in order to reduce warning fatigue.

Timelines of October 2015 through March 2016 before CDSS and October 2016 through March 2017 after CDSS were compared. There were 1,404 orders of levofloxacin for any indications before CDSS and there were 113 (8.5%) orders of levofloxacin for inappropriate indications. After CDSS, there were 1,142 orders for levofloxacin for any indications and 45 (3.9%) orders for Levaquin for inappropriate indications. This is a statistically significant difference of $p<0.0001$. There was a reduction in levofloxacin use/1,000 patient days from 41.6 to 33.4 as well as decreased average duration of levofloxacin use from 3.3 days to 1.3 days.

Our results showed less levofloxacin orders for inappropriate indications after the implementation of CDSS. With these results, we extrapolated that this targeted CDSS intervention was beneficial at our particular institution. CDSS may be able to impact inappropriate antibiotic use to help promote improved prescribing habits. At TMC, we are currently working on utilizing indication and medication based targeted CDSS expansion to outpatient antimicrobial stewardship. This should assist providers to prescribe appropriate antibiotics selections real-time, at the point of prescribing based on best-practices medication and indication. This allows prospective rather than retrospective evaluation of prescribing appropriateness.

Conclusion

CDSS is a robust tool that can improve the AMS programs. CDSS can be active or passive as described above at TMC. In other clinical and institutional settings, CDSS can be appropriately designed and personalized. An important learning point we emphasize: CDSS is dependent on provider acceptance of the CDSS interventions. It is critical to educate provider-subscribers the function of CDSS, its use and how it can improve patient care and outcomes.

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Disclosure

None reported.

MM



Staphylococcus aureus Bacteremia: Contemporary Management

by Leny Abraham, MD & David M. Bamberger, MD

All patients with uncomplicated *Staphylococcus aureus* bacteremia are recommended to receive at least two weeks of intravenous antibiotic therapy; for complicated cases, four to six weeks has been the standard practice.



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Abstract

***Staphylococcus aureus* bacteremia (SAB) is a serious cause of bloodstream infection associated with significant morbidity and mortality. Complications include deep-seated foci of infection including infective endocarditis, device-associated infection, osteoarticular metastases, pleuropulmonary involvement, and recurrent infection. With the 30-day all-cause mortality being around 20%, a collaborative effort of early Infectious Diseases (ID) consultation and Antimicrobial Stewardship Program (ASP) involvement will show improved SAB outcomes and therapy optimization.[1]**

Introduction

Staphylococcus aureus bacteremia (SAB) continues to be a major cause of community and healthcare-acquired bacteremia. While the exact incidence of SAB is difficult to determine, surveillance data from the U.S. shows incidence rates of 20 to 50/100,000.[2] Rates elsewhere in the industrialized world are reported to be 10 to 30/100,000.[3] These discrepancies may be due to the differences in infection control practices, health care systems, accessibility, and adequacy of surveillance data.

In the United States, rates of healthcare-associated methicillin-resistant *Staphylococcus aureus* (MRSA) decreased by 17.1% from 2005-2012. The rate of decline later slowed from 2013-2016. Community-acquired methicillin susceptible *Staphylococcus aureus* infections (MSSA) conversely, have slightly increased from 2012 to 2017.[4] Given these data points, institutions are striving to improve their standards on infection control and infection prevention of SAB.

Classification of SAB

Initially, SAB was differentiated into two categories which were healthcare-associated and community-acquired. With differentiation by molecular means and health care exposure with community onset of SAB, the classification of health care-associated community onset was created.[5] Now SAB is classified into three categories with those being: 1) community-acquired, 2) healthcare-associated community-onset, and 3) healthcare-associated hospital-onset.[6]

Community-acquired SAB generally refers to those individuals with no previous contact with the health care system. They include injection drug users and spontaneous osteoarticular infections such as vertebral osteomyelitis or epidural abscess. Those with community-

acquired SAB are more likely to have greater than one complication such as endocarditis with acute renal failure, shock, acute respiratory distress or disseminated intravascular coagulation on presentation.[7]

Healthcare-associated, community-onset SAB includes those individuals who have constant contact with the healthcare system. These patients include individuals hospitalized in the past 90 days, those receiving intravenous therapy, wound care, or skilled nursing care at home, residence in a long-term acute care facility or nursing home, and those receiving dialysis or chemotherapy.[6]

Healthcare-associated, hospital-onset SAB refers to those acquired in the hospital and include central-line associated bloodstream infections, ventilator-associated pneumonia, and surgical site infections.[8] Hospital-acquired SAB is more likely to be due to methicillin-resistant strains and is a leading cause of nosocomial bloodstream infection. With the increasing use of intravascular catheters such as port-a-catheters, hemodialysis lines, and peripherally-inserted central catheters, there has been a rising incidence of catheter-associated SAB.

Risk Factors for SAB

Risk factors for SAB include age, underlying medical conditions, injection drug use, presence of intravascular catheters or prosthetic devices and need to be recognized when initially assessing patients.

There have been numerous studies demonstrating age as a determinant of increased SAB incidence. High rates of incidence are seen in the first year of life which decreases in young adulthood but slowly rises with advancing age. The incidence of SAB is 100 per 100,000 person-years among subjects 70 years of age but is only 4.7 per 100,000 person-years in younger, healthier U.S. military personnel.[3]

The incidence of SAB is also associated with certain underlying medical conditions. In a 21-year longitudinal study done at Duke University from 1995-2015, individuals with diabetes, renal disease dependent on dialysis, rheumatoid arthritis, malignancy history, corticosteroid use, transplant history, and HIV were among the most likely to acquire SAB.[9] Specifically for the HIV-infected population, lower CD4 count (<100) accounted for an independent risk factor for SAB and among those, injection drug users had the highest burden of SAB.[10]

Injection drug users have been found to have a high rate of nasal colonization. Studies have shown those with *S. aureus* nasal carriage have higher rates of SAB with their colonizing strains.[11]

Any prosthetic device or indwelling catheter remains a foreign body and possible nidus for infection. The Duke University longitudinal study revealed more than half of the enrolled patients had an implantable device such as a central vascular catheter, pacemaker/defibrillator, prosthetic valve, endovascular prosthesis, or arthroplasty, which served as their source of SAB.[9] Intravascular catheter is the most common cause of hospital-acquired SAB.

Complicated SAB

SAB is notorious for having varied sources of causation. Common sources include catheter-related, pleuropulmonary, osteoarticular, and heart valve. SAB may be further classified as complicated or uncomplicated. The Infectious Diseases Society of American (IDSA) has defined uncomplicated SAB as those in which there is: exclusion of endocarditis, no implanted prostheses, negative follow-up blood cultures drawn two to four days after the initial set, defervescence within 72 hours after initiating appropriate antibiotic therapy, and no evidence of metastatic infection.[12] In a prospective, observational cohort study done in the late 1990s, patients were followed up to 12 weeks after an initial positive blood culture result. Complications included central nervous system involvement, embolic phenomena, metastatic site of infection or recurrent infection within 12 weeks. Predictors of complicated SAB were community acquisition, persistent positive blood cultures at 48 to 96 hours, persistent fever at 72 hours, and skin findings suggestive of systemic infection.[13]

Diagnostic Evaluation of SAB

In general, blood cultures returning positive for *Staphylococcus aureus* should initiate prompt clinical evaluation and initiation of empiric antibiotic therapy. A thorough history and physical are essential in providing information on the source of bacteremia and evidence of any suggestion of metastatic infection.

Imaging for metastatic disease should be tailored according to symptoms. Assessing for back pain indicating possible vertebral osteomyelitis or discitis, abdominal pain indicating possible renal or splenic infarct, headaches or vision changes for metastatic CNS manifestations are just a few examples of evaluating the extent of disease.[14]

Most patients with positive blood cultures for SAB undergo transthoracic echocardiogram (TTE)



Intravascular catheter is the most common cause of hospital acquired Staph aureus bacteremia.

to investigate for potential endocarditis if the risk is high and the source is not apparent. The use of routine transesophageal echocardiogram (TEE) is more controversial. While it has increased sensitivity, the costs, risks and availability should be considered. Generally, if a patient is considered to have low risk of endocarditis on the basis of a negative TTE, nosocomial acquisition of SAB, clearance of bacteremia ≤72 hours, absence of intracardiac device or prosthetic valves, absence of hemodialysis dependence, and no clinical signs of metastatic disease or endocarditis, TEE may not be required.[15]

Management of SAB

All patients with uncomplicated SAB are recommended to receive at least two weeks of intravenous antibiotic therapy. For complicated SAB, therapy with intravenous antibiotics for four to six weeks has been the standard practice.[16] The selection of antibiotic is dependent on methicillin susceptibility. Agents used for treatment of MSSA include penicillinase-resistant semisynthetic penicillins, first-generation cephalosporins, vancomycin and daptomycin.[17] A beta-lactam is the preferred drug of choice for MSSA bacteremia. Anti-staphylococcal penicillins such as nafcillin are often utilized as first line agents. Concern with frequency of dosing and adverse effects of nephrotoxicity and neutropenia have led to interest in alternative beta-lactams. Cefazolin is a first-generation cephalosporin with a favorable pharmacokinetic profile and less frequent dosing. *In vitro* data suggests an inoculum effect can occur resulting in high rates of antibiotic failure for treatment of MSSA infection with high bacterial inoculum.[18] Despite this *in vitro* data, the impact of the inoculum effect in the clinical scenario is controversial.[19] There have been several retrospective cohort studies comparing anti-staphylococcal penicillins to cefazolin treatment. In a large retrospective cohort study done in Australia

from January 2007 to September 2013, mortality was compared in patients with MSSA bacteremia treated with flucloxacillin to those treated with cefazolin. It found there was no difference in 30-day mortality. It suggested cefazolin is equivalent or superior to anti-staphylococcal penicillins but that randomized controlled trial data are lacking.[20]

In the case of MRSA bacteremia, vancomycin or daptomycin monotherapy is recommended as first line agents.[12] Vancomycin is a glycopeptide that inhibits cell wall synthesis. It has been questioned on its efficacy profile and adverse effects. There have been concerns of poor tissue penetration, slow bactericidal activity, resistance issues, inability to achieve adequate drug levels, and nephrotoxicity.[21] Daptomycin is a cyclic lipopeptide that causes depolarization of the bacterial cell membrane. It was seen to have similar efficacy to standard therapy for both MSSA and MRSA bacteremia.[22] Adverse effects of myopathy, eosinophilic pneumonia and the lack of efficacy in MRSA pneumonia preclude its use in certain clinical situations.

Treatment failure defined as persistent MRSA bacteremia for seven days or more is of concern and should prompt evaluation of whether a change in therapy is required. IDSA guidelines recommend an assessment for foci of infection that may need surgical attention and/or consideration of high dose daptomycin in combination with another agent such as gentamicin, rifampin, linezolid, or a beta-lactam antibiotic.[12] Combination therapy with vancomycin and gentamicin or rifampin has been associated with adverse effects such as nephrotoxicity and drug interactions. In a recently published randomized clinical trial, combination therapy with beta-lactams also showed no significant improvement in mortality.[23] Patients were randomized to standard therapy (vancomycin or daptomycin) plus an anti-staphylococcal beta-lactam (flucloxacillin, cloxacillin, or cefazolin) for seven days or standard therapy alone. The study was stopped early as there was a high incidence of acute kidney injury with combination therapy. It demonstrated the addition of anti-staphylococcal beta-lactam to vancomycin or daptomycin did not result in improvement in the end point of 90-day mortality, persistent bacteremia, relapse or treatment failure.[23]

Ceftaroline, a beta-lactam that has activity against MRSA has been studied in a preliminary manner in combination with daptomycin with a suggestion of better efficacy when compared to vancomycin monotherapy.[24] Similarly, in a retrospective matched cohort design study, those who received a combination of daptomycin and ceftaroline were compared to monotherapy with vancomycin.[25] Mortality rates were similar in the two groups even though patients on combination therapy had higher rates of persistent bacteremia at study entry, and questioned whether receiving combination therapy at the start of therapy could be beneficial. Blinded, randomized controlled studies are needed to study combination therapies.

Guidelines emphasize empiric treatment, repeating blood cultures to document clearance of bacteremia and narrowing to appropriate therapy once cultures have finalized. Recent studies have demonstrated the concern for inappropriate therapy selection, delayed response time in choosing appropriate therapy, and failure in recognizing associated complications may lead to increased detrimental outcomes.[26,27] Infectious Diseases consultations (IDC) improve SAB outcomes including a reduction in mortality, complication rates, and relapse. In a study done at Dartmouth-Hitchcock Medical Center, 240 patients with SAB were selected to be evaluated.[26] Of those, 122 patients received IDC. The observed characteristics between both groups were similar. Those who received IDC were advanced in age and more likely to have health care-associated SAB. Those who received Infectious Disease consultation had more appropriate antimicrobial selection and monitoring of positive blood cultures, intravascular catheter/device removal (if needed), and lower mortality. Another study done at Barnes-Jewish Hospital between 2005-2007 evaluated the 28-day all-cause mortality and 365 day all-cause mortality to assess the efficacy of IDC for SAB.[27] IDC was associated with 56% reduction in all-cause mortality in SAB patients within 28 days of the positive blood culture. Those who had IDC were more likely to have received appropriate antibiotic therapy, evaluation by TEE, and appropriate planned duration of antimicrobial therapy.[27]

In addition to IDC, clinical guidance by Antimicrobial Stewardship Programs are well positioned to influence SAB outcomes. Collectively, joint efforts between IDC and ASP can improve care and outcomes. In one study, lack of ASP intervention was associated with suboptimal management in 20% of cases, including use of vancomycin for MSSA bacteremia, inappropriate use of oral antimicrobial therapy, and absence of any antimicrobial therapy.[28] ASPs have shown benefit by closely monitor microbiologic data and decreasing the time between effective and de-escalated therapy. The clinical course of SAB prior to

and post implementation of rapid polymerase chain reaction (rPCR) testing for *Staphylococcus aureus* and methicillin resistance with ASP involvement was compared in a study at the Ohio State University Medical Center.[29] A pharmacist from the ASP was contacted with the result of the rPCR and immediately recommended IDC and appropriate antibiotics. rPCR testing with ASP was associated with earlier appropriate antimicrobial usage, a lower mean length of stay and lower hospital costs.

Conclusion

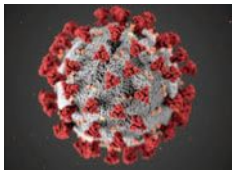
SAB continues to be a major cause of bloodstream infection worldwide. Incidence rates of community-onset MSSA bacteremia have increased. Appropriate use of IDC and ASP may improve selection of antimicrobial therapy, response time, and management and recognition of complications of SAB that may improve outcomes.

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Disclosure

None reported. **MM**

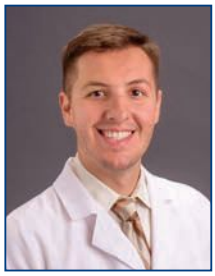


EXPEDITED PUBLICATION

Increased Incidence, Morbidity, and Mortality in Human Coronavirus NL63 Associated with ACE Inhibitor Therapy and Implication in SARS-CoV-2 (COVID-19)

by Armin Krvavac, MD, Tarang P. Patel, MD, Ethan M. Karle, DO, Nicholas B. Epstein, MD, Elizabeth A. Reznikov, DO, Lancer G. Gates, DO & Zachary M. Holliday, MD

Clinical trials on methylene blue as a therapeutic and anti-viral agent in SARS-CoV-2 would be well supported by the literature and offers a promising mechanism by which to block the inflammatory response seen in SARS-CoV-2.



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Abstract

Background

The endemic human coronavirus NL63 strain (HCoV-NL63) employs angiotensin-converting enzyme 2 (ACE-2) receptors on cell surfaces to infect hosts in the same manner as SARS-CoV and the novel SARS-CoV-2. It has been proposed that patients on angiotensin-converting enzyme inhibitor (ACE-I) and angiotensin receptor blockers (ARB) therapy infected with SARS-CoV-2 have a higher mortality rate due to over-expression of ACE-2 receptors.

Aim

We sought to evaluate the impact of ACE-I/ARB on infectivity of various endemic coronavirus strains, hypothesizing that rates of ACE-I use among patients with HCoV-NL63 would be higher compared to other endemic coronavirus strains that do not utilize the ACE-2 receptor.

Design/Methods

A retrospective cohort study was designed to evaluate a total 466 subjects with a positive respiratory pathogens panel for one of the endemic coronavirus strains. Rate of ACE-I/ARB use among each coronavirus strain and clinical outcomes from the 88 HCoV-NL63 positive subjects was collected.

Results

Analysis revealed a higher rate of ACE-I (p=0.006) use among the HCoV-NL63 positives compared to the other three endemic coronavirus strains. The rate of invasive mechanical ventilation (p=0.007) and 90-day mortality (p=0.045) among HCoV-NL63 positives on ACE-I therapy was higher compared to those HCoV-NL63 positives not on ACE-I therapy.

Conclusion

Concurrent therapy with an ACE-I was associated with an increased rate and severity of infection with the HCoV-NL63. This association was not found in infected patients on concurrent ARB therapy. These findings support the importance of further evaluation in patients on these therapies who are infected with the novel coronavirus SARS-CoV-2.

Introduction

Coronaviruses were first identified in the mid-1960s and named for the crown-like spikes that protrude from their envelope (corona – in Latin means crown). Four endemic human coronavirus strains (HCoV-229E, HCoV-HKU1, HCoV-NL63, and HCoV-OC43) represent the majority of disease and are frequently referred to as "common cold" viruses.[1,2] Emerging epidemiologic evidence reveals a broad range of clinical outcomes including severe lower respiratory tract infections among immunocompromised patients.[2-4] Additionally, the last two decades have brought on the emergence of three new human coronaviruses (SARS-CoV, MERS-CoV, and SARS-CoV-2) that have resulted in severe disease with high morbidity and mortality.[1,5]

The protruding spikes on the viral envelope contain the receptor binding domain (RBD), which plays a vital role in the binding interaction between the virus and its host receptor.[6] Furthermore, the coronavirus RBD contains neutralizing epitopes that induce most of the immune response.[7-9] This makes the differences and similarities between RBDs on different coronavirus strains an important area of study in future treatment and vaccine development. More importantly, the novel coronavirus (SARS-CoV-2, also referred to as COVID-19) which is responsible for the current pandemic, shares the same host receptors as one of the endemic coronaviruses (HCoV-NL63) and SARS-CoV.[10,11]

HCoV-NL63 utilizes angiotensin-converting enzyme 2 (ACE-2) receptors on cell surfaces as a binding domain to enter and infect the cells.[11-13] The SARS-coronavirus (SARS-CoV) and novel coronavirus (SARS-CoV-2) also utilize the same ACE-2 receptor for binding.[10,14-17] Conversely, the other three endemic coronaviruses (HCoV-229E, HCoV-HKU1, and HCoV-OC43) do not share this binding domain. HCoV-229E binds to aminopeptidase-N (APN),[18,19] while HCoV-HKU1 and HCoV-OC43 bind to sialic acid (N-acety-9-0-acetylneuraminic acid) to gain cellular entry.[20-23]

Current epidemiological data suggests that patients with heart disease, chronic kidney disease, hypertension, and diabetes are at the highest risk for poor outcomes and infection with the novel coronavirus.[24,25] Several editorials have suggested that this increased morbidity and mortality in patients infected with SARS-CoV-2 is related to angiotensin-converting enzyme inhibitors (ACE-I). Postulating that these poor outcomes may be related to over-expression of ACE-2 receptors on cell membranes as a result of chronic therapy with ACE-I and angiotensin receptor blockers (ARB).[26-29]

We sought to evaluate the role of ACE-I and ARB to the infectivity of coronaviruses that utilize the ACE-2 receptor to gain cellular entry. As the prevalence of SARS-CoV and SARS-CoV-2 in our study population is low, we opted to use the surrogate HCoV-NL63 as it uses the same ACE-2 receptor. We hypothesized that rates of ACE-I use among patients with HCoV-NL63 would be higher compared to other endemic coronavirus strains that do not utilize ACE-2 receptor.

Methods

We designed a retrospective cohort study to evaluate patients with a positive respiratory pathogens panel (multiplex polymerase chain reaction) for one of the four endemic coronavirus strains between the years 2015 and 2020. Approval was obtained from the Institutional Review Board (IRB approval #2021063) and a database was aggregated using electronic medical record query. De-identified patient information was collected via chart review.

Baseline demographic data was collected for each patient including age, gender, BMI, and chronic medical comorbidities at the time of the positive respiratory pathogens panel (RPP). Medical comorbidities of interest that were collected included a history of hypertension (HTN), chronic kidney disease (CKD), coronary artery disease (CAD), congestive heart failure (CHF), diabetes mellitus (DM), and chronic lung disease (COPD, asthma, and cystic fibrosis). Additional chart review was performed to identify the endemic strain of coronavirus that was positive on RPP along with history of ACE-I or ARB use and dose within 30 days of the positive RPP. Furthermore, subjects who tested positive for the HCoV-NL63 strain had clinical outcome data collected. These data points included need for hospitalization within 30 days of the positive test, hospital length of stay, admission to the intensive care unit (ICU), need for invasive mechanical ventilation, and 90-day mortality.

The study was performed at a single academic tertiary care center and included both inpatient and outpatient visits. Inclusion criteria included all adults over the age of 18 with a respiratory pathogen panel

Table 1. Baseline Characteristics

Baseline Characteristics					
		229E n=66	**HKU1** n=96	**NL63** n=88	**OC43** n=221
Age (avg)		55.8	52.9	58.5	61.2
BMI (avg)		31.3	32.1	31.7	31.6
Gender	% Male	45%	41%	42%	45%
	% Female	55%	59%	58%	55%
HTN	n (%)	34 (51.5%)	49 (51%)	51 (58%)	136 (61.5%)
CKD	n (%)	9 (13.6%)	10 (10.4%)	10 (19.3%)	33 (14.9%)
CAD	n (%)	12 (18.2%)	16 (16.7%)	17 (19.3%)	48 (21.7%)
CHF	n (%)	16 (23.2%)	20 (20.8%)	16 (18.2%)	58 (26.2%)
DM	n (%)	18 (27.3%)	29 (30.2%)	47 (53.4%)	67 (30.3%)
COPD	n (%)	24 (36.4%)	34 (35.4%)	27 (30.7%)	127 (57.5%)
Asthma	n (%)	6 (9.1%)	18 (18.8%)	10 (11.4%)	12 (5.4%)
Cystic Fibrosis	n (%)	1 (1.5%)	2 (2.1%)	3 (3.4%)	3 (1.4%)

Abbreviations: 229E (Human coronavirus 229E), NL63 (Human coronavirus NL63), HKU1 (Human coronavirus HKU1), OC43 (Human coronavirus OC43), BMI (Body Mass Index), HTN (Hypertension), CKD (Chronic Kidney Disease), CAD (Coronary Artery Disease), CHF (Congestive Heart Failure), DM (Diabetes Mellitus), COPD (Chronic Obstructive Lung Disease).

test positive for one of the four endemic coronavirus strains (HCoV-229E, HCoV-HKU1, HCoV-NL63, and HCoV-OC43). Exclusion criteria included adolescents below 18 years of age. The primary outcome of this retrospective analysis was to assess the rate of ACE-I and ARB use amongst each endemic coronavirus strain. Secondary outcome measures focused on clinical outcomes among those with HCoV-NL63 positive subjects. Collected data was analyzed using GraphPad Prism 8; Chi-square and p values calculated with two tails.

Results

A total of 470 positive results for one of the four endemic coronavirus strains was queried in our electronic medical system between the years of 2015 and 2020. Among these, four duplicate results were excluded from the final analysis. The remaining 466 underwent complete chart review as detailed in the methods. There were 66 positive for HCoV-229E, 96 positive for HCoV-HKU1, 88 positive for HCoV-NL63, and 221 positive for HCoV-OC43. A total of five subjects were identified to be double positive (positive for two strains of endemic coronavirus on the same RPP). Of those who were, double positive, two subjects were positive for both HCoV-NL63 and HCoV-229E, one subject was positive for HCoV-NL63 and HCoV-OC43, and one subject was positive for HCoV-HKU1 and HCoV-OC43. Basic patient demographics and comparison of the cohort groups are included in Table 1.

The rate of ACE-I and ARB use among each cohort is reported in Figure 1. There was a higher rate of ACE-I use among HCoV-NL63 positive subjects (36.4%) compared to HCoV-229E (15.2%), p-value = 0.014. Furthermore, the rate of ACE-I use among HCoV-NL63 positives was higher compared to the combined rate amongst the three other endemic strains, p-value = 0.006. The use of ARBs was not different among the four endemic coronavirus strains.

The clinical outcomes among HCoV-NL63 positive subjects on ACE-I versus HCoV-NL63 positive subjects not on ACE-I is reported in Figure 2. There was a higher rate of (28.1% versus 7.1%, p-value = 0.007) invasive mechanical ventilation and (21.9% versus 7.1%, p-value = 0.045) mortality respectively among HCoV-NL63 positive patients that were on ACE-I therapy. Clinical outcomes with HCoV-NL63 positive patients who use ARBs versus those who do not use ARBs did not demonstrate statistically significant differences. Nevertheless, of those who

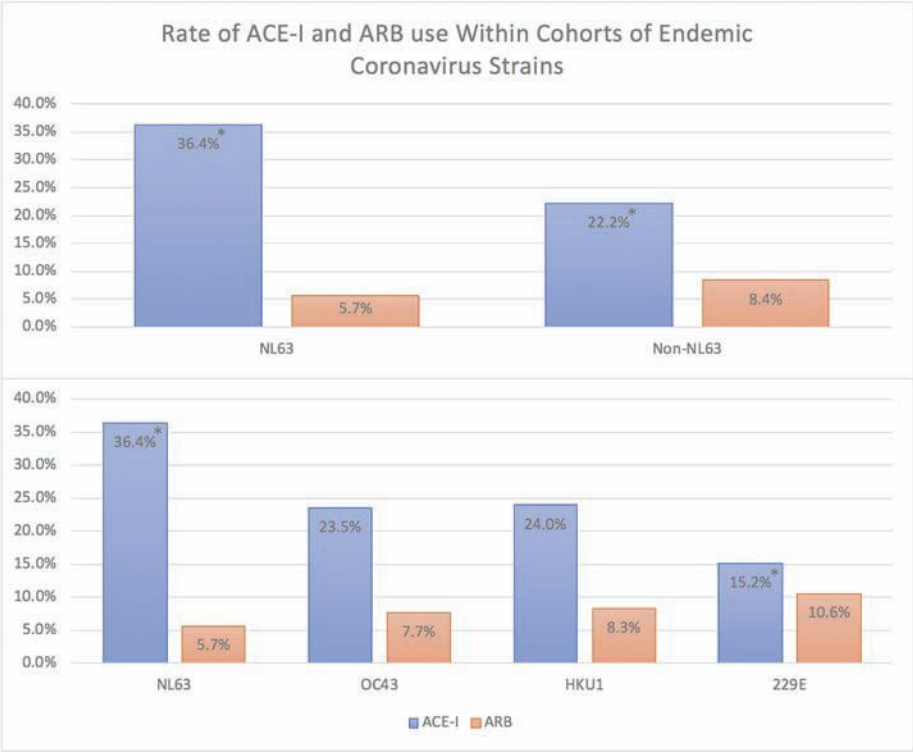


Figure 1. Rate of ACE-I and ARB use Within Cohorts of Endemic Coronavirus Strains.

Top Panel: Comparing rate of ACE-I and ARB use among NL63 positive patients versus pooled data of non-NL63 endemic coronavirus strains. P-values comparing human coronavirus NL63 on ACE-I versus combination of other three human coronavirus strains (p-value = 0.006).

Bottom Panel: Comparing rate of ACE-I and ARB use among NL63 positives versus other endemic coronavirus strains. P-values comparing human coronavirus NL63 on ACE-I to other endemic coronavirus strains (p-value = 0.014 comparing to human coronavirus 229E; p-value = 0.267 comparing to human coronavirus HKU1; and p-value = 0.085 comparing to human coronavirus OC43).
(* denotes significant p-value)

Abbreviations: ACE-I (Angiotensin-Converting Enzyme Inhibitor), ARB (Angiotensin Receptor Blocker), 229E (Human coronavirus 229E), NL63 (Human coronavirus NL63), HKU1 (Human coronavirus HKU1), OC43 (Human coronavirus OC43).

were HCoV-NL63 positive and on an ARB required ICU admission less often compared to HCoV-NL63 positives not on ARB therapy. Furthermore, none of the five HCoV-NL63 positives subjects on ARB required invasive mechanical ventilation or contributed to 90-day mortality rate. P-values for clinical outcomes are reported in Table 2.

Discussion

The renin-angiotensin system (RAS) represents one of the most crucial systems in the regulation of various vasoactive components within the neural, pulmonary, renal, and cardiovascular systems. As such, multiple pharmacologic interventions target various steps of the RAS to effect cardiovascular and renal function. In the case of ACE-I and ARB, this is via blockage of angiotensin converting enzyme-1 (ACE-1) and angiotensin II type-1 receptors (AT1R), respectively.[30] ACE-1 is involved in the formation of angiotensin II and is responsible for degradation of bradykinin (BK). On the other side of the pathway, ACE-2 acts to counter RAS activation through degradation of angiotensin II, the final product of this pathway known for its vasoconstrictive, proliferative, and pro-inflammatory effects via the AT1R.[31] RAS becomes a topic of discussion in the midst of the SARS-CoV-2 pandemic as studies have demonstrated that both SARS-CoV and SARS-CoV-2 use host ACE-2 receptors to gain cellular entry.[10,14-17] It is postulated that this leads to downregulation of ACE-2 expression resulting in overstimulation of RAS due to increase angiotensin II production. The use of the ACE-2 receptor is not unique to SARS-CoV or SARS-CoV-2, as it is also used by the endemic strain HCoV-NL63.[11-13]

Within our cohort there was a higher rate of ACE-I use among HCoV-NL63 positive subjects compared to other endemic coronavirus strains (36.4% vs 22.2%, p-value = 0.006). These findings suggest that patients on ACE-I therapy may be at higher risk of infection with coronavirus strains that utilize the ACE-2 receptor. The severity of illness seen in our study among those infected with HCoV-NL63 and on ACE-I therapy may be explained by several mechanisms. Inhibition of ACE-1 by ACE-I and angiotensin

Table 2: Clinical Outcomes of HCoV-NL63 Positive Cohort

Clinical Outcomes of HCoV-NL63 Positive Cohort				
	Hospital Admission	**ICU Admission**	**Invasive Mechanical Ventilation**	**90-day Mortality**
All HCoV-NL63 Positive (n=88)	78 (88.6%)	24 (27.3%)	13 (14.8%)	11 (12.5%)
On ACE-I (n=32)	32 (100%)	11 (34.4%)	9 (28.1%)	7 (21.9%)
	p = 0.011	p = 0.258	**p = 0.007**	**p = 0.045**
Not on ACE-I (n=56)	46 (82.1%)	13 (23.2%)	4 (7.1%)	4 (7.1%)
On ARB (n=5)	5 (100%)	1 (20%)	0 (0%)	0 (0%)
	p = 0.410	p = 0.707	p = 0.338	p = 0.334
Not on ARB (n=83)	73 (88%)	23 (27.7%)	13 (15.7%)	11 (13.3%)

Abbreviations: HCoV-NL63 (Human Coronavirus NL63), ICU (Intensive Care Unit), ACE-I (Angiotensin-Converting Enzyme Inhibitor), ARB (Angiotensin Receptor Blocker)

receptors by ARBs have been shown in animal models to significantly upregulate the expression of ACE-2 and ACE-2 receptors.[32-35] This upregulation of ACE-2 receptors on host cells could theoretically increase the chance of binding with the viral RBD and ultimately lead to infection. However, if that were the case, we would expect similar up-regulation of ACE-2 and ACE-2 receptors by ACE-I and ARBs; that in turn should lead to similar infection rates and severity of illness among those patients. However, it should be noted that the HCoV-NL63 positive subjects in our study had a lower rate of ARB use. Furthermore, the few HCoV-NL63 positive subjects on ARB therapy had much better clinical outcomes then the remainder of the HCoV-NL63 cohort. This suggests a possible protective and opposite effect from ACE-2 utilizing coronavirus strains with ARB therapy compared with ACE-I.

Almost all mention of the role of ACE-I and ARB in regard to coronavirus strains that use the ACE-2 receptor have been speculation and conjecture with a lack of scientific evidence and clinical data to support discontinuing ACE-I and ARB therapy in SARS-CoV-2 patients.[26-29,36-38] Two retrospective studies from China showed an association with hypertension and increased morbidity and mortality from SARS-CoV-2. In these studies, HTN had a hazard ratio of 1.70 for death in 201 SARS-CoV-2 positive patients, and 3.05 for in-hospital mortality in 191 SARS-CoV-2 positive patients.[24,25] Neither study specifically evaluated the role of ACE-I or ARB in outcomes and was unable to derive if a separate confounding factor contributed to the observed hazard ratios. However, it should be noted that the described conditions with higher hazard ratios for poor outcomes (HTN, DM, CAD) are all routinely treated with ACE-I or ARB, and use of these medications may be a confounding factor contributing to the observed hazard ratios.

In our study, we saw a significant difference in ACE-I use among HCoV-NL63 positive subjects, and those subjects had a higher need for invasive mechanical ventilation (p-value = 0.007) and higher 90-day mortality rate (p-value = 0.045). While the association between ACE-I use and increased morbidity with SARS-CoV-2 infection has not been fully elicited, current data suggests the interface of the RBD on the protruding spikes of the viral envelope with ACE-2 receptors plays a pivotal role. The beneficial role of ACE-1 inhibitors in the context of HTN, CKD, CAD, CHF, and DM is well established. Whereas the role of ACE-2 has yet to be fully understood, and is still under investigation. In humans, ACE-2 is primarily produced by type II alveolar epithelial cells and Clara cells in the lungs.[39] Interestingly, the destruction of alveolar

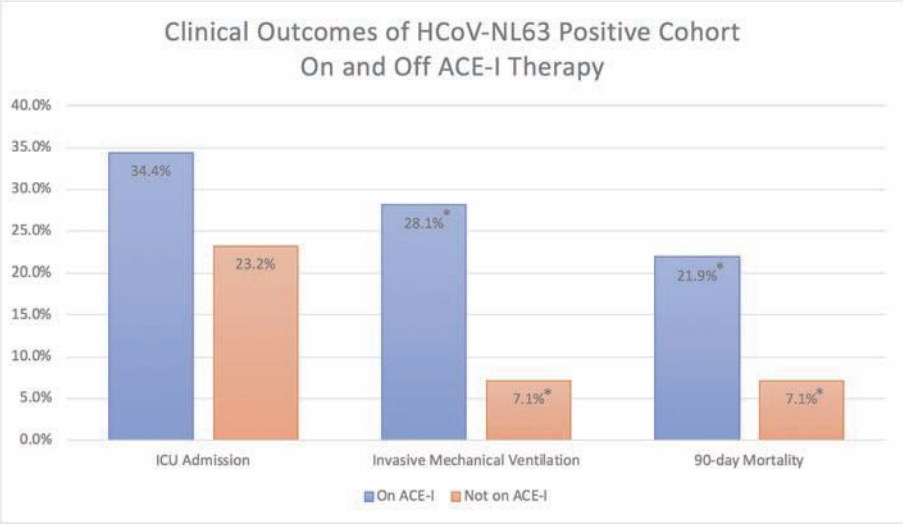


Figure 2. Clinical Outcomes of HCoV-NL63 Positive Cohorts on ACE-I Therapy versus Those Not on ACE-I Therapy.

P-values comparing clinical outcomes among NL63 positive patients on ACE-I therapy versus those not on ACE-I therapy. (* denotes significant p-value)

Abbreviations: HCoV-NL63 (Human Coronavirus NL63), ICU (Intensive Care Unit), ACE-I (Angiotensin-Converting Enzyme Inhibitor).

epithelial cells represents a crucial step in the proposed mechanism for acute respiratory distress syndrome (ARDS) due to ACE-2 utilizing coronavirus strains (SARS-CoV and SARS-CoV-2).[40] The combination of upregulation of ACE-2 in animal models by ACE-I/ARB and the knowledge that SARS-CoV, SARS-CoV-2, and HCoV-NL63 utilizes the ACE-2 receptor to propagate host infectivity has led to the premise that use of ACE-I in the setting of these infections may result in worse clinical outcomes. Although it should be noted that this remains merely an association with many possible confounding factors; a cause-effect relationship cannot be established without a randomized control trial.

One possible mechanism to explain the differences seen in our study related to ACE-I versus ARB is related to the kinin-kallikrein-bradykinin system (KKBS) pathway (Figure 3). As mentioned earlier, SARS-CoV, SARS-CoV-2, and endemic strain HCoV-NL63 utilize the same ACE-2 receptor to gain cellular entry. This results in the attenuation of the ACE-2-angiotensin II-mas receptor axis, with amplification of the ACE-1-angiotensin II-AT1R axis.[41] In summation, this leads to decreased ACE-2 and increased angiotensin II due to its decreased breakdown by ACE-2. Further, ACE-2 within the KKBS pathway is able to hydrolyze the active bradykinin metabolite desArg^{9}-bradykinin (DABK). When ACE-2 is depleted, there is increased signaling of DABK through Bradykinin B1 receptors (BKB1R). Receptors that are present in inflamed states, and lead to tissue inflammation and ARDS, a concerning sequela of SARS-CoV-2 leading to morbidity and mortality.[41-43]

We expect a negative feedback loop to be initiated by the SARS-CoV-2 when binding with ACE-2 receptors on type II pneumocytes.[44-45] Elevated levels of angiotensin II, due to impaired degradation from a decrease in ACE-2 as described above, result in increased binding with AT1R that leads to activation of inflammatory pathways.[46] We anticipate patients on ACE-I therapy to have elevated angiotensin II and ACE receptor expression at baseline from chronic ACE-1 suppression. This results in increased activation of inflammatory pathways in patients infected with HCoV-NL63 on ACE-I therapy; that may partly explain the worse outcomes seen among those patients in our study. Conversely, we speculate the trend towards improved outcomes in those infected by HCoV-NL63 on ARB therapy are likely related to receptor blockade. *In vitro* studies show ATR1 blockade has an anti-inflammatory effect.[47] Of note, SARS-CoV-2 infected patients from China had markedly elevated angiotensin II serum levels which were associated linearly with viral load and lung injury.[48] In rat models, high angiotensin II levels were shown to decrease the production of ACE mRNA in the lung and decrease pulmonary ACE activity.[49] The decreased degradation of BK in the context of decreased ACE facilitates downstream release of tumor necrosis factor alpha (TNF-alpha) and interleukin 1 (IL-1), which leads to the characteristic fatal cytokine storm and vasodilatory shock seen in SARS-CoV-2.[50-54]

Given the physiological set-up in patient's on ACE-I, we postulate that BK antagonism could at least

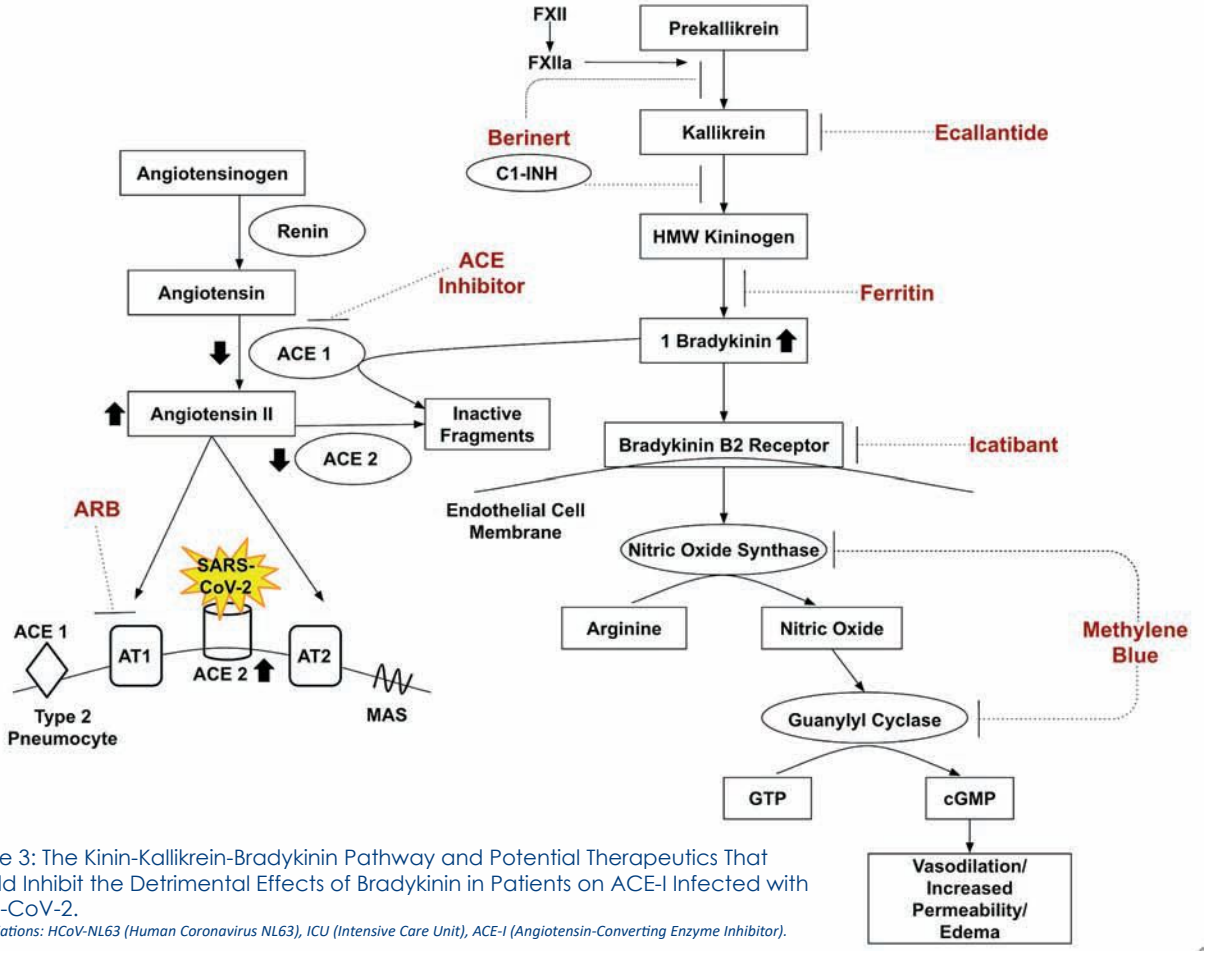


Figure 3: The Kinin-Kallikrein-Bradykinin Pathway and Potential Therapeutics That Would Inhibit the Detrimental Effects of Bradykinin in Patients on ACE-I Infected with SARS-CoV-2.

Abbreviations: HCoV-NL63 (Human Coronavirus NL63), ICU (Intensive Care Unit), ACE-I (Angiotensin-Converting Enzyme Inhibitor).

in part reduce morbidity and mortality in patients specifically on ACE-I therapy with SARS-CoV-2. This potential mechanism has been suggested by others with no study to date in SARS-CoV-2 patients. Dr. Gulistan Bahat in a letter dated March 18, 2020, to the editor of the *British Medical Journal* recommended that BK antagonism be considered as a future therapeutic option for COVID-19 infection.[55] While the negative effects of BK can potentially be antagonized by several medications along the KKBS pathway (Figure 3), most promising and feasible would be the use of methylene blue (MB).

MB is both a strong inhibitor of nitric oxide synthase and a weak inhibitor of guanylate cyclase, which together decrease the production of cyclic guanosine monophosphate (cGMP); blocking BK's ability to cause vasodilation, increased permeability, and edema.[56] MB has shown efficacy in an animal study, in vasoplegic syndrome, and in two previous case reports which demonstrated improved oxygenation and liberation from mechanical ventilation.[57-60] Currently there is only one active clinical trial evaluating the role of MB in the treatment of COVID-19 (NCT04370288 - "Clinical Application of Methylene Blue for Treatment of COVID-19 Patients").

MB also has the potential to prevent SARS-CoV-2 infection, and has been shown to clear the virus from blood products. An observational study from France reported that a cohort of 2,500 cancer patients who had already been on treatment with MB prior to emergence of SARS-CoV-2 pandemic did not develop flu-like illness.[61] This is thought to be related to antiviral and anti-inflammatory properties of MB. Another study evaluating safety of convalescent plasma transfusion, utilized MB to treat blood products from SARS-CoV-2 patients, and found that MB successfully eliminated the virus, further supporting its role as an anti-viral agent.[62]

Aside from our retrospective analysis, at this time there has been no formal study of the role of ACE-I or ARB in outcomes associated with ACE-2 receptor utilizing coronavirus strains. Further, there have been

contradictory hypotheses suggesting in some cases ACE-I or ARB may be beneficial or harmful in SARS-CoV-2 patients and there is currently a lack of scientific evidence to support the discontinuation of these medications. Conditions with higher hazard ratios for poor outcomes in SARS-CoV-2, such as HTN, DM, and CAD, are all routinely treated with ACE-I or ARB and use of these medications may be a confounding factor. With everything taken together, our study suggests that ACE-I therapy may be detrimental while ARB therapy may be beneficial. As of the writing of this manuscript, there are over a dozen clinical trials in the process of initiating enrollment to examine the role of ARB therapy in hospitalized and non-hospitalized patients diagnosed with SARS-CoV-2. We propose the deleterious inflammatory effects related to SARS-CoV-2 infection is related to upregulation of ACE-2 receptor leading to downregulation of ACE-2 enzyme production and increased Angiotensin II levels which then act on the AT1R. The potential difference seen between ACE-I and ARB is most likely related to a baseline deficient of ACE-1 in patients on ACE-I therapy which sets them up for an over-activation of the KKBS pathway in addition to an ACE-2 deficiency which also contributes to activation of the KKBS pathway. On the other side, ARB therapy would block AT1R, and thus improve upon the deleterious effects seen from an overabundance of angiotensin II leading to an inflammatory response. The potential use of MB as both an anti-viral and anti-inflammatory agent in the treatment of SARS-CoV-2 patients offers a promising new therapeutic and preventative therapy in SARS-CoV-2. Meanwhile, continuation of ARB therapy or transitioning those patients from ACEI to ARB therapy may in fact be beneficial via AT1R blockade.

Limitations

This retrospective study focused on the association between ACE-I and ARB therapy with endemic coronavirus strains. Though the results show higher rates of ACE-I therapy among the HCoV-NL63 positive cohort and worse clinical outcomes, it should be emphasized that these are merely associations that do not account for potential confounding factors. The results may also have limited external validity as all of the data is collected from a single academic center. Future multicenter randomized control trials are needed to evaluate the true impact of both ACE-I and ARB on endemic human coronavirus strains and the novel SARS-CoV-2. Lastly, we did not aggregate the data of the duration that patients were on ACE-I or ARB therapy prior to infection with HCoV-NL63.

Conclusions

In conclusion, concurrent therapy with an ACE-I was associated with an increased rate, as well as, increased severity of infection with the HCoV-NL63 strain. This association was not found in patients on ARB therapy and in fact, there is decreased incidence and severity of HCoV-NL63 infection in those on ARB therapy in our study population. This paradox may suggest an effect by ACE-I on the KKBS pathway which is independent of the expected up regulation of ACE-2 receptors secondary to virus binding and consequent ACE-2 depletion. Furthermore, ARB therapy would block AT1R which we suspect is protective via amelioration of the inflammatory response. These findings support the importance of further evaluation in patients on these therapies who are infected with the novel coronavirus SARS-CoV-2. Clinical trials on MB as a therapeutic and anti-viral agent in SARS-CoV-2 would be well supported by the literature and offers a promising mechanism by which to block the inflammatory response seen in SARS-CoV-2.

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Disclosure

None reported.

MM

Training for Longevity: The Reverse J-Curve for Exercise

by Evan L. O'Keefe, MD, Noel Torres-Acosta, MD, James H. O'Keefe, MD & Carl J, Lavie, MD

If one's goal is to decrease the risk of CV events and improve life expectancy, a regular regimen of moderate activity is adequate.

Abstract

A wealth of scientific literature backs the unique therapeutic benefits of exercise for quality of life, cardiovascular (CV) health, and longevity. Consequently, many have assumed that more exercise is always better. However, chronic excessive endurance exercise might adversely impact CV health. Ultra-endurance races can inflict acute myocardial damage, as evidenced by elevations in troponin and brain natriuretic peptide. Moreover, sudden cardiac arrest occurs more often in marathons and triathlons than in shorter races. Veteran endurance athletes often show abnormal cardiac remodeling with increased risk for myocardial fibrosis and coronary calcification. Chronic excessive exercise has been consistently associated with increased risks of atrial fibrillation (AF), and along with some attenuation of longevity benefits. The optimal dose of exercise remains unknown and probably differs among individuals. Current studies suggest that 2.5 to 5 hours/week of moderate or vigorous physical activity will confer maximal benefits; >10 hours/week may reduce these health benefits.






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Introduction

Physical inactivity and obesity are among the leading causes of death and disability, with myriad adverse effects, especially for the cardiovascular (CV) system. Today in the United States (U.S.) about half of all adults have some form of CV disease (CVD).[1] Thus, physical activity and exercise training have become among our most powerful tools for the prevention and treatment of noncommunicable disease—CVD in particular.[2] Physical activity and an improved cardiorespiratory fitness lessen the incidence and burden of coronary artery disease (CAD) and reduces risk of major adverse CVD events (MACE). Each metabolic equivalent (MET) gain in fitness confers a 30% reduction in all-cause mortality in unfit individuals (those with an initial < 5 MET exercise capacity).[3] The most physically active cohort in middle age has a predicted life expectancy eight years longer than a sedentary cohort; and for patients with established CVD, undertaking cardiac rehabilitation consistently improves prognosis and quality of life.[4]

Exercise positively affects virtually every aspect of the body and brain, and its unique ability to improve physical and mental wellbeing has convinced the general public that staying physically active is one of the best ways to stay healthy and enhance longevity. In fact, maintaining a high level of CV fitness (aerobic and muscular fitness) improves prognosis independently of other therapies, and plausible arguments can be made that exercise/fitness is the most potent medical

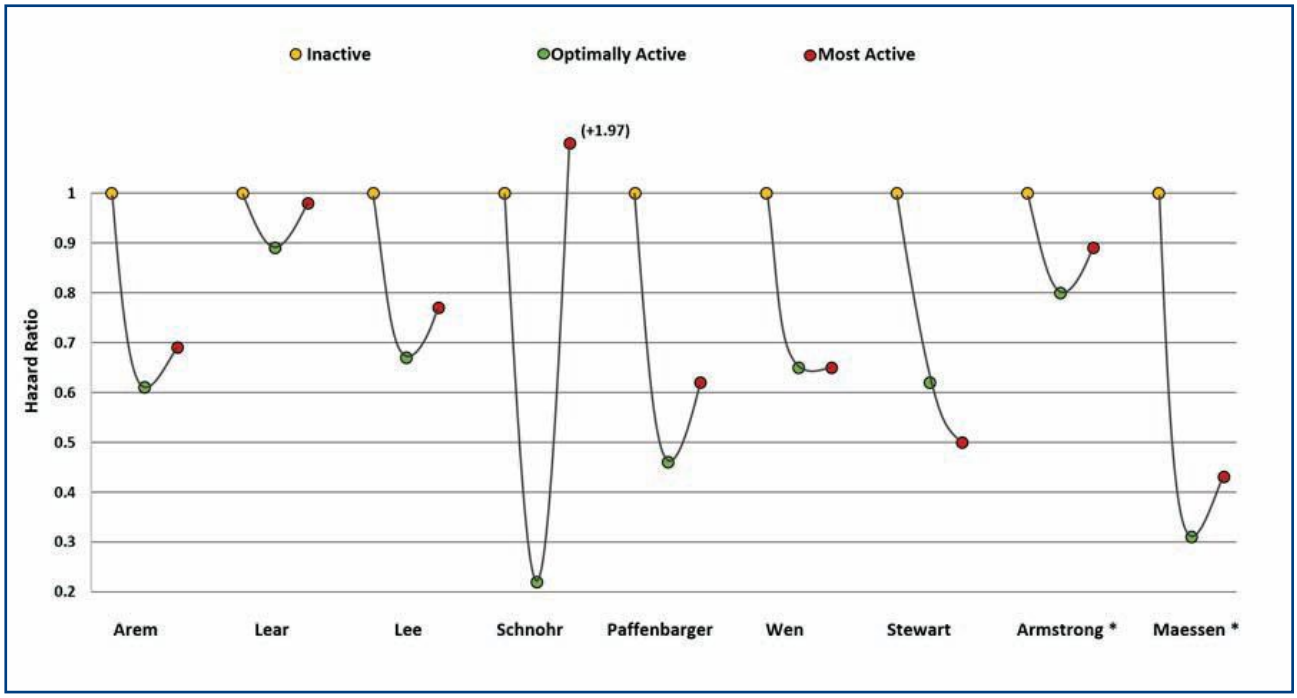


Figure 1. All-cause mortality and incident cardiovascular diseases from epidemiological studies. Overview of curvilinear dose-response association between physical activity volume and cardiovascular health outcomes. Adapted from Franklin et al., Paffenbarger et al., Stewart et al.[15,16,52]
*Indicates incident cardiovascular disease as outcome.

therapy we have in the battle against CVD.[5] Although the ideal dose of exercise remains unknown; it is clear that at least half of Americans are not meeting the physical activity guidelines recommendations of > 150 minutes/week of moderate exercise. Importantly, significant longevity benefits are conferred by even just 15 minutes/day of light or moderate physical activity, which is about half the recommended minimum dose of daily exercise, with the steepest risk reductions seen in the cohort going from completely sedentary to just mildly active.[6] At the other end of the spectrum, about 2.5% of U.S. adults may be overdoing exercise, thereby exposing themselves to potential deleterious health outcomes.[7]

The ideal dose of exercise for conferring robust health and optimal longevity is being hotly debated in the scientific literature. The aim of this article is to clarify this issue, focusing on the cumulative data.[8-14]

Reverse J-Curves of Exercise

The optimal dose of physical activity for maximizing health benefits is unknown,[15] and even 2,500 years ago, Hippocrates taught: "if we could give every individual the right amount of nourishment and exercise—not too little and not too much—we would have found the safest way to health."[7] This suggests that there might be a dose range of physical activity that is optimal for improving wellbeing and life expectancy, with attenuation of these benefits when the amount of exercise is above or below this ideal range. Indeed, Paffenbarger back in 1986 reported a reverse J-shaped association between exercise (walking, stair climbing, and sports play) and all-cause mortality. That prospective study followed 16,936 male Harvard alumni for 16 years and found that death rates declined inversely as energy expended on physical activity increased from < 500 to 3,500 kcal/week.[16] However, the 18% of men exercising > 3,500 kcal/week had attenuation of the age-adjusted reduction in risk of death, showing a 38% reduction compared to a 54% mortality reduction for those doing 3,000 to 3,500 kcal/week.[16]

Since then multiple large observational studies, together comprising over three million individuals, have reported similar results suggesting there is likely an upper threshold for the benefit of exercise whereby very high doses of strenuous physical activities appear to be associated with loss of some of the longevity

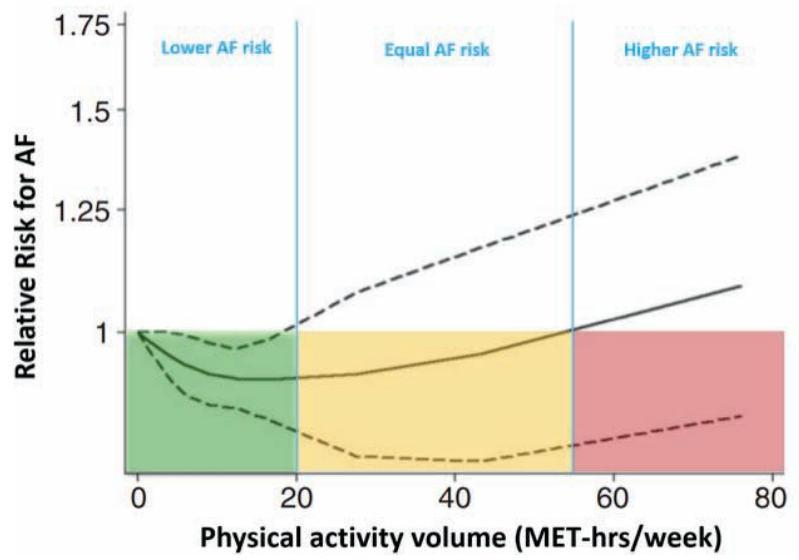


Figure 2. Dose–response association between physical activity volume and AF risk. Individuals performing physical activity for 5 to 20 MET-h/wk demonstrate a significant risk reduction for AF, whereas higher exercise volumes do not appear to attenuate AF risk. A trend toward increased AF risk is apparent among individuals reporting >55 MET-h/wk. AF = Atrial fibrillation; MET-hrs/week = metabolic equivalents of task hours per week. Adapted from Franklin et al.[15]

benefits conferred by less extreme doses of vigorous exercise. As depicted in Figure 1, nearly all of the large observational studies reproduce this reverse J-curve. In this relationship, the risks of CVD and premature mortality go down in dose dependent fashion, until a threshold of exercise is exceeded, at which point the benefits are attenuated compared to less extreme doses of physical activity. In many studies the drop-off in risk reduction noted with very high dose exercise did not reach statistical significance due to the small number of individuals in the upper extreme cohort. Yet, this reverse-J pattern is recurring theme, and in very large studies the attenuation of health benefits noted with extremely high doses of exercise does meet statistical significance.[8]

Arrhythmias

Physical exercise has been associated with a number of CV adaptations, both structural and electrical, including enlargement of all chambers of the heart, improved function, increased cardiac and arterial compliance, sinus bradycardia, and in some individuals increased PR interval and right bundle branch block.[17,18] The increased incidence of atrial fibrillation (AF) seen in endurance athletes is one of the best documented cardiac maladaptations and is thought to be one of the hallmark characteristics of cardiac overuse syndrome. In 1998 Karajalainen et al. examined 300 veteran endurance athletes and reported a five-fold greater incidence of AF as compared to a sedentary control cohort.[19] AF since then has been associated with higher intensity exercise regimens, faster competitive finishing times and absolute number of endurance races completed.[20] Long-term endurance exercise— ≥ 2,000 hours and/or ≥ 20 years of training—displays a strong correlation with AF even in individuals without CV risk factors.[21,22] While individual studies have reported that chronic endurance sports participation increases risk of AF anywhere between two- and ten-fold, a recent meta-analyses quantified an odds ratio for overall risk of AF at just above five-fold.[23]

Similar to many other health outcomes, moderate doses of physical activity are effective in preventing AF, whereas both low and high volumes of exercise are associated with increased risk of AF. As compared to more fit subjects, those with < 6 METs exercise capacity showed elevated incident rates of AF, and after adjustment each 1 MET gain in fitness was associated with a 7% lower risk of incident AF (hazard ratio 0.93, 95% confidence interval 0.92-0.94, P<0.001).[24] In regards to weekly dose of physical activity, even small doses of exercise, such beginning with 5 MET-hours/week appear to reduce risk of AF, with maximal benefits seen at 20 MET-hours/week (Figure 2).[25] Above 55 MET-hours/week, which is approximates to 10 hours of vigorous exercise/week, the risk of developing AF begins to exceed that of the sedentary cohort, displaying a J-curve relationship.[25]

Atrial flutter and/or AF were noted in a significant cohort of former Swiss professional cyclists.[26] Following the successful ablation of atrial flutter, previous endurance sport participation and an ongoing practice of high level exercise increased the risk of recurrent AF.[27] Furthermore, a group of former professional cyclists had a five-fold increased prevalence of

ventricular tachycardia as compared to 309 male senior leisure time golfers (15% vs. 3%, P=0.05).[26] Although complex ventricular tachyarrhythmias are sometimes seen in competitive athletes, and have been included as one manifestation of the "athlete's heart syndrome," it is unclear whether this constitutes a benign or high-risk cardiac condition.[28,29] Some authors argue that the adverse structural changes in the ventricles and atria induced by chronic strenuous endurance exercise produces the substrate for a development and progression of a proarrhythmogenic state.[30] Other potential contributors to arrhythmias in veteran endurance athletes include: excessive sympathetic activity/catecholamine overload, increased oxidative stress, myocardial fibrosis, electrolyte abnormalities.

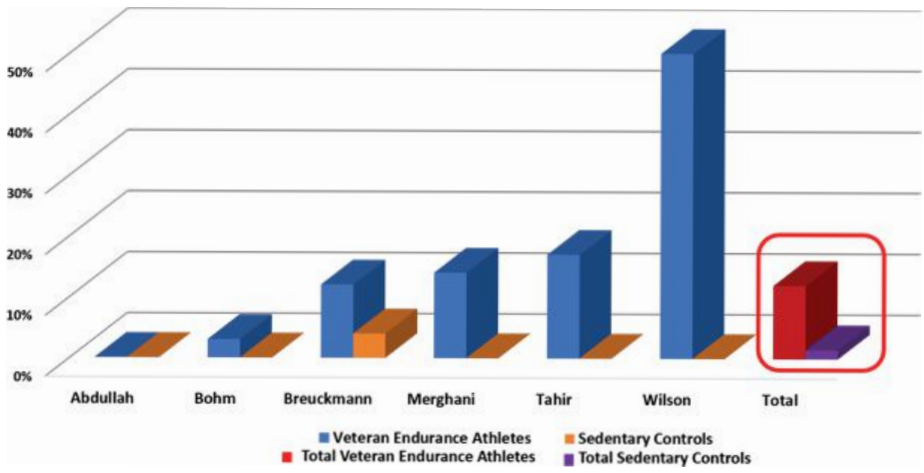


Figure 3. Overview of studies comparing prevalence of LGE between male athletes and control subjects. LGE = Late gadolinium enhancement Adapted from Franklin et al.[15]

Myocardial Fibrosis

Myocardial fibrosis is a nonspecific response to a variety of cardiac injuries such as: acute myocardial infarction (MI), myocarditis, uncontrolled hypertensionand valvular dysfunction. This pathological fibrosis in the heart predisposes to myocardial stiffness, arrhythmias and adverse cardiac outcomes.[31] Myocardial fibrosis is best visualized with cardiac magnetic resonance imaging (MRI), specifically demonstrated by late gadolinium enhancement (LGE).

Chronic endurance sport training/racing has been shown to increase risk of showing LGE, and this has been documented in otherwise healthy, asymptomatic lifelong endurance athletes.[31-33] Moreover, LGE is significantly and directly correlated with the number of years spent training, and the number of marathons and other ultra-endurance competitions completed.[32,34] During times of strenuous exercise cardiac output increases approximately five-fold above resting values, rising from 5 L/min to 25 L/min or more, leading to disproportionately distributed strain on the heart with increases in wall stress of 125% vs. 4% on the right and left ventricles, respectively.[35] These physical strains in conjunction with sustained elevations in catecholamines and reactive oxygen species likely cause cumulative injuries in the myocardium—ultimately leading to scarring as demonstrated by LGE.

The evidence regarding the clinical relevance of this resultant myocardial fibrosis is lacking. One small study of four veteran athletes with LGE reported wall motion abnormalities corresponding to the fibrosed myocardial segments.[36] Additionally, during two years of follow-up, MACE and coronary revascularization occurred more commonly among endurance athletes with myocardial LGE compared to veteran athletes without fibrosis, suggesting that this myocardial damage may play a prognostic role.[33] Interestingly, not only number of ultra-endurance races completed, but also the severity of coronary artery calcification (CAC) independently predicted presence of LGE.[34] The cumulative data on cardiac MRI shows a 12% prevalence of LGE in veteran endurance athletes, which is eight-fold higher than the 1.5% prevalence among the control group of individuals who were doing not more than the minimum dose of daily physical activity recommended by the World Health Organization (Figure 3).[15]

Coronary Artery Calcification

The evidence in regards to CAC in veteran endurance athletes is complicated. A large and consistent body of data shows that the amount of calcium in the coronary arteries is an accurate predictor of risk for MACE.[37] Paradoxically, although exercise

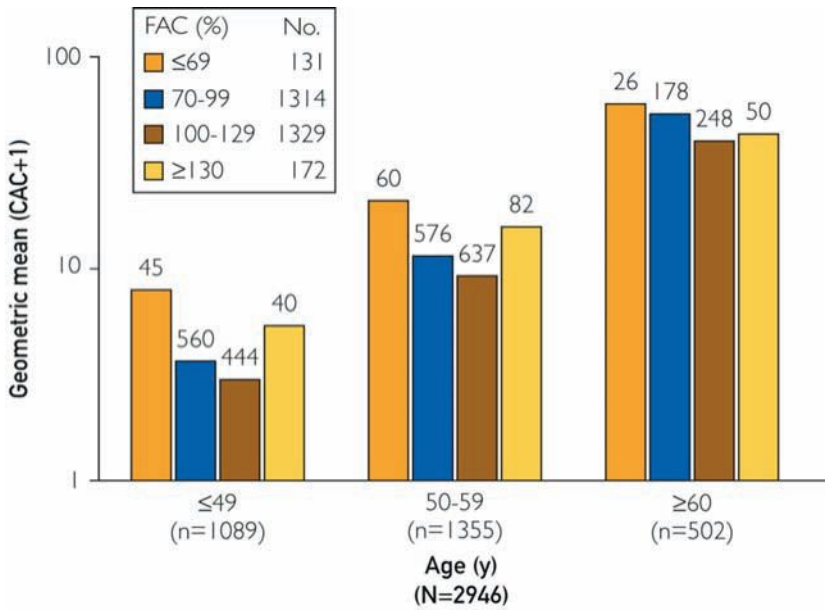


Figure 4. Association of fitness levels with CAC burden. CAC = coronary artery calcium; FAC = functional aerobic capacity. Adapted from Kermott et al. [38]

decreases CAD risk, high volume endurance training appears to substantially increase the CAC burden with Kermott and colleagues demonstrating the presence of the familiar reverse J-curve (Figure 4).[38] Merghani et al. reported that masters athletes 54±8 years of age were approximately twice as likely to have atherosclerotic plaque as compared to healthy controls, and these endurance athletes were more likely to show CAC scores ≥ 300 (11.3%) and luminal stenosis ≥ 50% (7.5%).[39]

Generally, studies have confirmed that veteran endurance athletes have increased coronary calcification compared to sedentary controls, but they tend to be less likely to have high-risk volatile plaques of mixed calcific and lipid laden morphology.[39-41] An observational study of 21,758 individuals found that those with at least 3,000 MET-min/wk had a higher CAC burden compared to less active cohort. Even so, those same highly active individuals showed a nonsignificant trend towards a decrease in mortality (HR 0.77, 95% CI 0.52-1.15) as compared to the less active cohort.[40] Another study reported that very-vigorous-intensity exercise was the most strongly predictive of CAC, but was also associated with reduced prevalence of mixed plaques.[41] Thus, the veteran athletes doing the highest volumes exercise will often have more coronary calcification, but they also tend to have a more stable and benign plaque composition.[41,42]

Taken together, these data suggest that very high doses of strenuous physical activity are associated with increased risk of coronary calcification but are not associated with dangerous plaque composition or increased risk of all-cause or CVD mortality, even among veteran athletes with high CAC scores. Much like the evidence for exercise-induced myocardial fibrosis, it is difficult to conclude that CAC and other cardiac maladaptations are completely benign. However, currently the functional relevance of such findings is of undetermined significance and this issue will require more study with larger patient populations of veteran endurance athletes.

Acute Risk Associated with Vigorous Exercise

Up to 90% of all exercise-related sudden cardiac deaths (SCD) occur in recreational athletes rather than competitive athletes, with an estimated incidence raging from 1:22,000 -1:69,000 in adult recreational athletes, versus 1:50,000 in young competitive athletes.[43,44] The riskiest period for SCD is during and shortly after exercise.[15] In the U.S. Physician study, the risk of SCD was transiently elevated 17-fold during and 30 minutes after vigorous physical activity. This risk was much higher in individuals who were the least active when compared to subjects who exercised more often (relative risk 74 vs 11).[15] Similarly, another study found that the most sedentary cohort had a 25-fold increase risk of SCD compared to those who were at least moderately active.[15] In athletes aged > 35 years, over 80% of the SCDs are cause by CAD; whereas among younger athletes (< 35 years) congenital abnormalities of the heart muscle, coronaries and conduction system are the most common cause of SCD.[45]

Longer and more physically demanding races

appear to pose a higher risk for SCD. Data from almost 11 million long distance race participants showed a higher incidence of SCD in marathons (1.01/100,000) compared to half marathons (0.27/100,000); only 29% of victims survived the cardiac arrest.[46] Of note, the death rate of males was more than double of the female race participants (0.98 vs 0.41/100,000).[47] This gender difference has been seen with respect to many aspects of the cardiac overuse syndrome, whereby women appear to be less susceptible than men to adverse cardiac effects of chronic high-dose endurance exercise.

The rate of SCD in triathlon athletes has been reported to be higher than marathon races. In a case series of 4.7 million triathlon participants the incidence of SCD was estimated to be 1.74/100,000 participants.[48] Similar to marathons, males had three times higher risk when compared to females (2.40 vs 0.74/100,000). Also, there was a three-fold higher risk in men > 40 years when compared to younger participants.[48]

Acute MI also occurs at an increased rate during or soon after vigorous exercise. Several studies have demonstrated a two- to ten-fold increased risk for MI within one hour of physical activity.[15] Endurance events including marathons and ultra-marathons have been associated with derangements in cardiac biomarkers. In marathon runners, significant post-race troponin elevations have been detected in direct correlation with exercise intensity.[49] A rise in brain natriuretic peptide levels was also seen in the marathon runners, but these elevations bore no relationship to exercise intensity.[49]

In addition to biochemical changes, functional changes are also present following intense exercise. One study of 40 athletes competing in endurance races (marathon, endurance triathlon, alpine cycling) found that the post-race right ventricle (RV) ejection fraction (EF) decreased by nine percentage points, with no change in left ventricular (LV) EF. The greatest reduction in RVEF was seen in the athletes who completed the longest event (ultra-triathlon).[50] Moreover, LGE on MRI was seen at the site of the RV attachment to the interventricular septum in 13% of the endurance athletes and commonly was seen in conjunction with pulmonary hypertension in these same individuals. Interestingly those athletes who had been competing for more years (20 years vs eight years) had significantly lower resting RVEF.[50] Repeated insults to the RV as seen during protracted strenuous exercise could cause myocardial necrosis ultimately leading to scarring and irreversible RV remodeling, creating the substrate for arrhythmias. The approximate amount of exercise required for this effect is speculated to be about > 20 hours/week for > 20 yrs.[43]

Conclusion

If one's goal is to decrease the risk of CV events, and improve life expectancy, a regular regimen of moderate activity is adequate. Very high doses of strenuous exercise may attenuate some of the benefits bestowed by less extreme efforts. The best forms of exercise for improving mental health and longevity appear to be social sports such as tennis, golf, badminton, soccer, basketball, volleyball, and group exercise, which not only improves fitness, but also promote interpersonal bonding and tend to reduce stress.[51] The current body of data is not strong enough to recommend that recreational athletes reduce their exercise dose, especially if this is something that improves their quality of life, or is needed to optimize performance in competitions, as the risks appear to be modest and somewhat uncertain yet. Even so, we should emphasize that the maximal benefit for CVD risk reduction occurs at much lower, safer and more moderate exercise doses.

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Disclosures

None reported.

MM

Missouri's Fentanyl Problem: The China Connection

by William V. Stoecker, MD, K. Taylor Bosworth & Fred Rottnek, MD

The social conditions that correlate with the increased used of illegal drugs and risk of overdoses from illicit fentanyl: poverty-both rural and urban, unemployment, and homelessness are expected to persist and may get worse in the current pandemic. China is the primary source of illegally imported fentanyl.



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Abstract

Recently, Missouri has followed an overall upward trend in opioid overdose deaths. In 2018, Missouri was the state with the largest absolute and percentage increase in opioid-related overdose fatality rates per capita over the previous year (18.3% and 3.1/100,000). This increase occurred despite an overall decrease in U.S. opioid-related death rates in the same period. This report identifies illicitly manufactured fentanyl (IMF) (and analogues) as the drug most responsible for this rise in opioid deaths in Missouri, with stimulant overdoses (primarily from methamphetamine) in second place.

Within Missouri, we find the areas where opioid deaths are highest: St. Louis and the city's fringe areas, following the national trend for high rates in fringe areas. Based on reports from CDC Wonder data, county medical examiners, law enforcement agencies, and drug addiction prevention agencies, we conclude that IMF and related synthetic opioids arriving from China are primarily responsible for fatal narcotic overdoses in Missouri. Despite the COVID-19 disruption of fentanyl manufacturing and distribution centers in and around Wuhan, China early in the pandemic, preliminary 2020 data from medical examiners' offices show an upswing in opioid deaths, an indicator that Chinese fentanyl producers have restored the supply chain.

Missourians are Dying of Fentanyl Overdoses

Case Report 1, March 2020

The 25-year-old man was found dead in a motel in St. James, Missouri, still wearing pajamas and a hospital armband from his stay at Phelps Health Hospital, where he left against medical advice. Drug paraphernalia found in the room included a heroin cooking apparatus: an upside-down Coke can with a cutout in the side to insert his butane lighter, which he favored over cooking with a spoon. His prescription bottle of alprazolam had only two tablets remaining from the 30 tablets he was prescribed at discharge. Police and the coroner speculated that he sold some of the tablets to afford the final high. Police found five used naloxone (Narcan®) packages in the man's car—these signaled a history of successful opioid reversals. The toxicology report showed alprazolam, heroin, and

the drug that likely killed him: fentanyl. His mother, a nurse, told police that she had little contact with him recently; she knew only that he used drugs and favored heroin. In his car, police and the coroner found completed papers for drug rehabilitation filled out nine days earlier—a missed opportunity that could have prevented his death. [1]

Case Report 2, December 2019

A 22-month-old girl was found unresponsive in her parents' home in Rolla; she could not be revived. Her mother told police that she and her daughter had fallen asleep on the couch. A criminal investigation found fentanyl on a nearby coffee table, the probable source of the fentanyl identified in the girl's toxicology results. Before she fell asleep, the girl was eating fish crackers at the table her parents used to cut drugs. The couple faces murder charges. [1,2]

Fentanyl and the Power to Kill

Fentanyl is a potent opioid and 50-100 times as potent as morphine. [3, 4] It takes 2 mg (or less) of fentanyl, about the weight of 3 grains of sugar, (Figure 1), to kill an adult who is not opioid-tolerant; less to kill a child, and still less for some highly potent fentanyl analogues. Carfentanil, approximately 100 times as potent as fentanyl, has the potency to tranquilize an elephant with a single carfentanil dart.[5,6] The potency of fentanyl and its analogues, together with low cost, makes fentanyl very attractive to drug dealers to add to a drug such as heroin or even totally replace heroin, which is relatively expensive. Drug dealers are now adding fentanyl to other drugs, including cocaine, methamphetamines, and counterfeit opioid pills.[7, 8, 9]

Illicitly manufactured fentanyl (IMF) is fentanyl manufactured outside of the controlled conditions of pharmaceutical laboratories. IMF can possess several forms, for example in the form of powder or pressed pills, or in gel capsules. It is most commonly found combined with other drugs, especially heroin. It is increasingly found in other illicit substances including cocaine and counterfeit pills. The DEA has reported a large increase, from 5,483 reports (2014) to 15,179 reports (2015), in law enforcement seizures of drugs containing IMF.[8] Because many experts refer to IMF as fentanyl, we use the terms 'fentanyl'or 'illegal fentanyl' in this report. We clarify that the



Figure 1. A lethal dose of fentanyl (2 mg) and penny.[10]

synthetic opioids responsible for fatal narcotic overdoses are illicitly manufactured and not diverted from the legal prescription supply.

To understand Missouri's fentanyl problem and how it relates to national trends, we used national toxicology lab data, interviews with Drug Enforcement Agency (DEA) personnel and online government data, reports gathered from CDC Wonder data, other federal reports, and the book F*entanyl, Inc.: How Rogue Chemists Are Creating the Deadliest Wave of the Opioid Epidemic* by Ben Westhoff (Atlantic Monthly Press, 2019). Data for the state of Missouri was obtained from the Missouri Department of Health and Human Services (DHHS) statistics and interviews with Evan Mobley and Andrew Hunter of Missouri DHHS. We begin by looking at the national problem of opioid overdoses.

Fentanyl is Driving the U.S. Overdose Pattern

Drug overdose rates in the U.S. are driven by opioids: 69.5% of drug overdose deaths in 2018 involved an opioid. [12] Since 2015, most of these deaths involve synthetic opioids, primarily fentanyl (Figure 2). From 2017 to 2018, the U.S. experienced a decline of 2% in deaths from all opioids.[12] There was a decline of 13.5% in deaths from prescription opioids and a decline of 4.1% from deaths due to heroin; however, there was a 10% increase in deaths due to synthetic opioids, primarily fentanyl.[12]

Fatal drug overdose statistics are taken from ICD-10 coding for drug overdose deaths on death

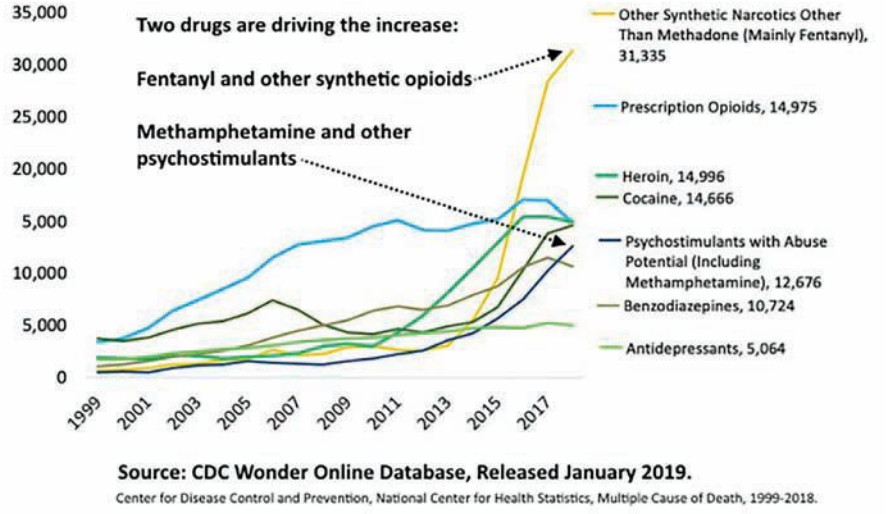


Figure 2. Drug overdose deaths, 1999-2018. Center for Disease Control and Prevention[11]

certificates. The drug overdose code for fentanyl and related synthetic narcotics is T40.4: "death from synthetic opioids other than methadone." This category includes not only fentanyl and fentanyl analogues but also other synthetic narcotics such as U-47700, a street drug known as "pink," "pinky" or "U4" and associated with an increasing number of fatal opioid overdoses.[13-16]

These data have limitations, as Nora Volkow, MD, of the National Institute on Drug Abuse (NIDA) stated, "Unfortunately, comprehensive toxicological testing is not performed in many cases, or the results are not recorded on death certificates, so the reported numbers of fatal opioid overdoses and overdoses due to fentanyl might not capture the full scope of the epidemic."[17] Novel fentanyl analogues often cannot be identified by many toxicology laboratories and consequently are underreported.[13, 18]

How Illegal Synthetic Opioids Including Fentanyl Arrive in the United States

Figure 3 shows two means of entry of illegal synthetic opioids into the U.S.: a route into the U.S. by the postal service, and routes into the U.S. used by drug traffickers. In both cases, Chinese chemical factories are the source of these synthetic opioids arriving in the U.S.[19, 20, 21] Clandestine laboratories in Mexico convert Chinese fentanyl precursors to fentanyl and combine IMF with heroin.[21, 22] The Mexican cartels "tend to use crude methods" to make it and "they just take the fentanyl and stir it with a spoon," said Doug Coleman of the DEA.[23] Illegal fentanyl is then trafficked into the U.S. market, already combined with heroin and other drugs. The U.S. General Accountability Office has determined that Canada, as well as Mexico, is a supply route for drug traffickers.[19]

American drug dealers can order fentanyl and analogues to be sent by mail from China, often diverted through another country.[24] One Chinese drug dealer who operates openly on the Chinese social media WeChat said that sending drugs through the Chinese mail to the U.S. is easy: "We have our people in the postal companies." [24] Chinese sources can be found on the Internet that will ship fentanyl analogues that are still legal in China.[24] Chinese dealers can also provide fentanyl and analogues that are now illegal in China, using underground sites on the dark web and accepting payment for the drugs with underground currency such as Bitcoin.[25] Shipment within the U.S. for all these drugs is illegal, so packages are misleadingly labeled and often shipped via other countries, to avoid seizure by U.S. authorities. Unfortunately, most packages arrive to the U.S. drug dealer or consumer intact.

New Fentanyl Analogues from Chinese Factories

One reason for the proliferation of fentanyl analogues is that many of these variants are still legal in China. Despite ongoing negotiations with the U.S. the Chinese government chooses not to regulate the entire class of fentanyl drugs but instead regulates fentanyl itself and a subset of fentanyl

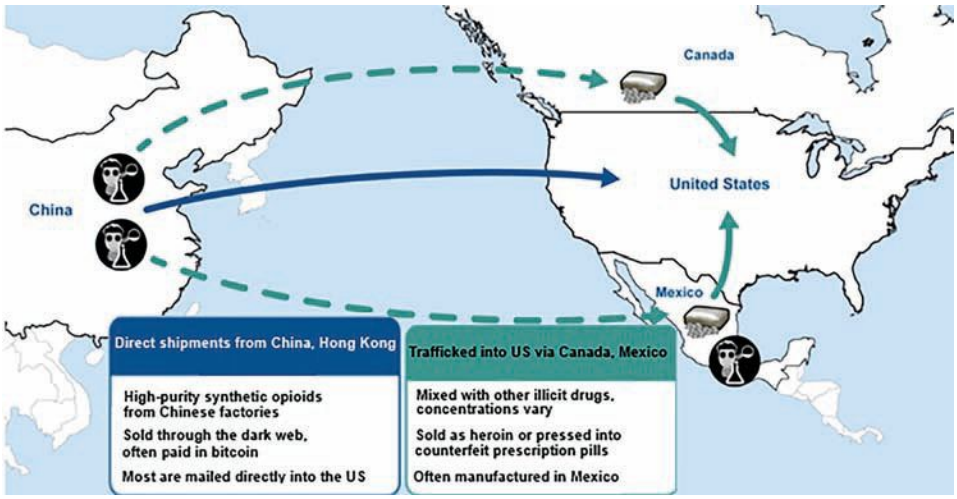


Figure 3. Illicit synthetic opioid flows from China. Fentanyl and analogues arrive in the US either directly via mail or trafficked by narcotic distributors. Modified from GAO-18-205. [19]

analogues, which it schedules one at a time, if it chooses to schedule them at all.[26] A New York Times article describes the Chinese chemical industry as "vast, and poorly supervised, with between 160,000 and 400,000 chemical companies operating legally, illegally, or somewhere in between." [27] Besides fentanyl and analogues, the industry produces large quantities of inexpensive generic drugs and pharmaceutical ingredients used by more advanced pharmaceutical companies to synthesize more profitable medicines.[27]

Chinese chemists are adept at developing new analogues not yet regulated in China or other countries, and their companies can sell these legally on the Internet without penalties in China, staying a step ahead of the Chinese government.[26] In this way, Chinese chemical factories can follow Chinese regulations and continue to sell fentanyl analogues and precursors on the open Internet. Local authorities favor industrial growth, which is substantial for the thousands of successful Chinese chemical companies.[28]

There are many ways to modify fentanyl and retain activity; thus dozens of new compounds continue to be created.[21] Fentanyl is modified by replacement of its propionyl chain or by replacement of its ethylphenyl moiety. The resulting analogues are further modified by substitution with fluoro-, chloro-, or methoxy- groups at the N-phenyl ring, to create analogues such as isobutyryl fentanyl-alpha-methylfentanyl butanamide.[21, 29] Toxicology reports from overdose victims increasingly demonstrate a number of fentanyl analogues such as acryl fentanyl. [21]

Wuhan, China is Headquarters for Chinese Fentanyl and Fentanyl Precursor Production

"The bulk of them (fentanyl precursors) seemed to come from a single corporation,"[30] run by Ye Chuan Fe, purportedly "once the richest man in Wuhan."[31] Ye controls Yuancheng Group, a legal conglomerate that includes many chemical manufacturers that produce a wide array of chemicals from food additives to pharmaceuticals. Yuancheng's success has been repeatedly praised by Communist Party officials.[32] Another chemical company based in Wuhan selling fentanyl and analogs is 5A Pharmatech, led by Yan Xiaobing, who was placed on the Justice Department's list of international drug traffickers.[33]

Chinese chemical and pharmaceutical companies "continue to operate with little oversight," concluded a 2017 report about fentanyl from the U.S.-China Economic and Security Review Commission.[34] Conditions in these labs vary—some labs are clean and up to U.S. pharmaceutical standards. However retired DEA agent Dennis Wichern, said, "Some of the pictures of these Chinese labs are sickening. It reminds me of the old meth-lab days when I worked in Missouri."[34]

A newsletter in 2020 from Ben Westhoff stated that disruption in the supply chain of fentanyl from China resulted in a shortage of opioids available from dealers. This, in addition to social distancing measures and fears regarding COVID-19, resulted in increased difficulty in obtaining drugs. Very preliminary data demonstrated a transient decrease in opioid-related deaths in the St. Louis area. Dr. Rachel Winograd, Associate Professor at UMSL's Missouri Institute of Mental Health and founder of MOHOPE.org and NOMODEATHS.org

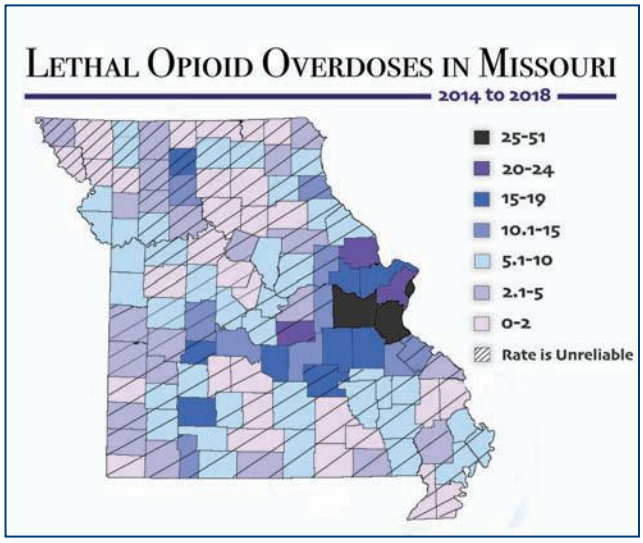


Figure 4. Lethal opioid overdoses in Missouri, 2014-2018, statistics from MO DHHS [40]

heard from partners on the ground who noticed an increase in people who use drugs who say, in effect, it is "impossible to find my drug of choice. I'm ready to talk about treatment."[35] Police in Jefferson County and Phelps County confirmed that prices for narcotics on the street rose somewhat.[36, 37]

Missouri Recently Topped the Nation in Growth Rate for Overdose Deaths

Missouri reflects the national trends, with most drug overdose fatalities related to opioids.[12] Recent trends nationally show an overall decrease in death rates from opioids, including prescription opioids and heroin. Missouri deviated from this trend recently and for a brief time was the state with the largest absolute and percentage per year increase in opioid-related overdose fatality rates. Rates per capita rose in 2018 over the previous year (18.3% and 3.1/100,000).[12] This increase occurred despite an overall national decrease in U.S. opioid-related death rates in the same period.

When the data is disaggregated among counties, a clearer picture emerges. If St. Louis City and County numbers are excluded from Missouri, overdose deaths decreased about 6%—better than the national average. However, in St. Louis City and County, overdose deaths increased by 27%. The majority of these overdoses occurred in black males, with 90% of these deaths associated with fentanyl—compared to 78% of overdose deaths in 2017.[38, 39] While the disparity is not surprising, the magnitude of the disparity is. The black community is North St. Louis City and County face well-documented long-standing problems in access to care, health resources, and trust of health care messaging. These results can guide future funding in more equitable and effective prevention, harm reduction, and treatment.

The map in Figure 4 shows the crude opioid death rate per capita for each county in Missouri. St. Louis city has the highest opioid death rate in the state, followed by Jefferson and Franklin Counties, which belong to the urban fringe areas that demonstrate the highest opioid mortality rates nationally.[40, 41] Jackson County, which includes Kansas City, has lower opioid death rates than some rural areas, much lower than found in St. Louis. Brandon Costerison, of the St. Louis chapter of the National Council on Alcoholism and Drug Abuse (NCADA), states St. Louis is one of the top five urban regions in the country for opioid-related deaths. [9] In explaining St. Louis' high overdose rate, DEA's National Drug Threat Assessment, December 2019, found that Chicago-based street gangs in St. Louis, with ties to the national Crips gang, are the main source of the area's heroin.[7] Costerison cites second-hand sources that identify Omaha and Dallas as the main suppliers for Kansas City, with entirely different sources for their heroin.[9] These five-year rates obscure some recent changes, especially the rise of deaths in rural areas. The number of opioid deaths rose 50% (from 12 to 24) in Boone County from 2017 to 2018.[40] Stacy Huck, a staff member in the Boone-Callaway County medical examiner's office, found most overdoses were either fentanyl or methamphetamine ("meth") related.[42] Boone County Police Sgt. Brian Leer said, "Meth [sic] used to be the drug we battled here. Meth labs dropped off when Mexican labs began producing methamphetamines. It's fentanyl in heroin that is driving the overdoses now. Boone County has a problem with 'Gray Death' [the street name for the gray-colored mix of heroin and varying amounts of fentanyl, fentanyl analogues and U-47700]. The route is Chicago to St. Louis and then across Missouri. The stigma of heroin has gone away—it's more accepted in the user world."[43] Bill Callahan, head of St. Louis Division DEA, said, "Meth is still a big problem in western Missouri. We have some instances of meth with fentanyl contamination."[44] In fact, the street

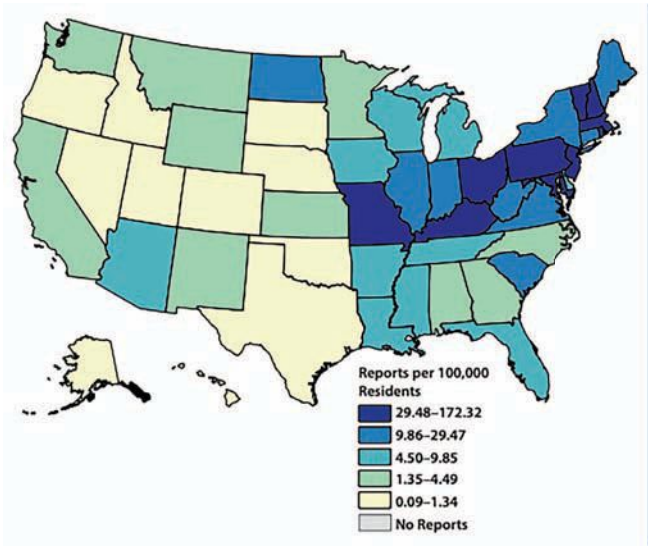


Figure 5a. Fentanyl toxicology reports, per capita.

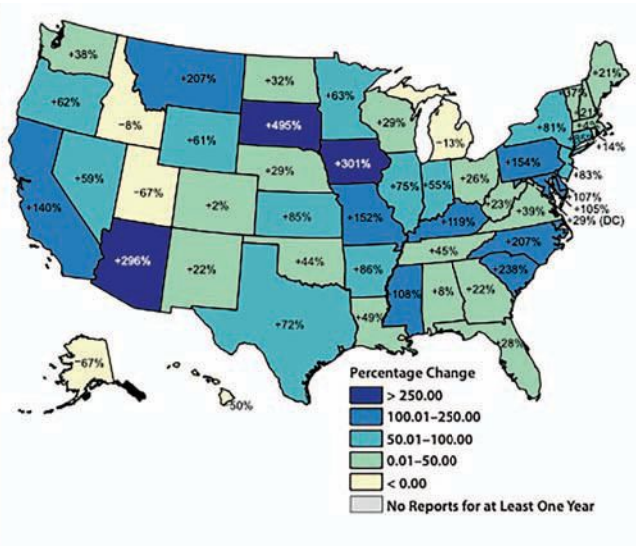


Figure 5b. Fentanyl toxicology reports, rate of change.[49]

slang term 'goofball' now refers to a combination of methamphetamine and either heroin or fentanyl.[45]

Accounting for Opioid Deaths: Missouri is a "Street drug" State, and Not a "Prescription Overdose" State

In 2018, Missouri providers wrote 63.4 opioid (fentanyl included) prescriptions per 100 persons, somewhat more than the national average rate of 51.4 per 100.[46] There are a few outlier Missouri counties, including Dunklin, Butler, St. Francois, and Howell, with opioid prescription rates from 2017 data over two-and-a-half times the national average. Dunklin County ranks the highest with 148.6 opioid prescriptions per 100 people.[47] Only St. Francois County of the four counties listed above ranks within the top quarter of opioid overdose counties in the state, and Dunklin County has one of the lowest opioid overdose fatality rates in the state: 0.66 persons per 100,000 (one person died 2014-2018).[39] St. Louis City, with the highest rate of opioid deaths, ranks below the national average for opioid prescriptions: 42.5 per 100 persons.[47] Evan Mobley of the Missouri DHHS advised caution about citing numbers of prescriptions written as the sole measure of controlled substance prescribing habits, without considering the duration of the prescription.[48] Careful prescribing practices remain the best approach for providers.

Fentanyl and Fentanyl Analogues in America: Fentanyl is Moving West

Toxicology laboratory reports gathered by the CDC demonstrate an increasing national rate of fentanyl overdoses (Figure 5). Toxicology laboratory reports show fentanyl death rates are highest in the eastern part of the country. Missouri is one of only nine states with a high rate (29 or more per 100,000 persons aged 15 or older in 2017) of fentanyl toxicology reports.[49] All these states except Missouri are east of the Mississippi River (Figure 5a). However the highest growth rates in fentanyl reports are from toxicology labs further west. Missouri was one of eight states that had a growth rate in reports of 150% or more. All these states except three are west of the Mississippi River (Figure 5b). Fentanyl analogue reports demonstrate a similar westward movement.

Missouri was one of 14 states to have more than 200 reports of the non-fentanyl synthetic opioid U-47700 in 2017, and had the fourth highest rate of growth in U-47700 (pink) reports: 854% increase from 2016 to 2017, behind only South Carolina, Illinois, and Michigan.[49]

One reason for the east-to-west gradient in fentanyl-related overdose rates is the regional monopolies that control access to heroin, which offer only the type of heroin their distributor can supply.[50] Powder heroin, available in Eastern states, is relatively easy to combine with fentanyl.[51,52] "Black tar" heroin, a dark, sticky opium-like substance predominant

in western states, is difficult to mix with fentanyl. Keven Wandler, MD, Chief Medical Officer at Advanced Recovery Systems, stated, "I have not yet heard stories of people lacing black tar heroin with fentanyl.[53] But the market is changing: toxicology lab reports demonstrate that fentanyl is increasingly found in more western states. This march westward is now playing out in Missouri.

Conclusion

Missouri's At-Risk Demographic

One of the major driving forces for the use of fentanyl, both knowingly and unknowingly, is the heroin market in the U.S. In several ways, the opioid crisis is founded on economic distress within communities across Missouri. Without any adulteration, the average retail price of pure heroin has significantly increased. Synthetic opioids, both fentanyl and analogues, are available at a far cheaper price than street heroin as they are cheaper to manufacture.[6] By adding cheap synthetic opioids, the price per milligram of the final product has almost halved from 2010 to 2014.[6, 51] The decrease in prices for fentanyl-adulterated heroin and the increased opioid potency, which can vary significantly among opioid batches, equate to more users, more demand and more danger for each user. In recent years, the heroin market has expanded from the inner-city domain to towns and rural locations, which puts most of Missouri at risk.[6, 51]

The social conditions that correlate with the increased use of illegal drugs: poverty–both rural and urban, unemployment, and homelessness are expected to persist and may get worse in the current pandemic. Economic constraints may reduce access to addiction treatment, which is of primary importance in reducing opioid deaths.

One new and unknown factor in Missouri is the new medical marijuana law 19 CSR 30-95 passed in 2018. Bill Callahan, head of DEA's St. Louis District, said, "Marijuana is not necessarily a gateway drug, but it is a gateway to a culture shift because you're running with a different group of people." [44] Speaking of teenagers' ability to make decisions, Callahan said, "The brain is not fully developed."[44] Thus as Callahan sees it, there may be more exposure to different drugs once a young person becomes acquainted with a new group of people who will expose them to new and dangerous drugs, including fentanyl and analogues.

Epilogue

Preliminary Data Show Opioid Deaths Continue to Rise in Missouri

In early 2020, when the Chinese government shut down activity in and around Wuhan due to the COVID-19 virus, the illicit opioid supply chain was disrupted. Yet the communists acted quickly to promote economic recovery. A South Central Drug Task Force officer found that "heroin/fentanyl continue to be available in the area for roughly the same prices." The officer noted unusually high numbers of Narcan use in some rural Missouri counties.[54]

We queried two county medical examiner offices who noted a year-on-year increase in opioid-related deaths. The St. Louis County Medical Examiner's Office reports preliminary opioid-related deaths for the first five months in 2020 were up 17% from the year before (112 deaths in 2019 and 131 in 2020). Because of short-staffing (and an increase in overdose cases), it is difficult keep current with data entry and these preliminary 2020 totals are expected to rise.[55]

Outstate areas are also on track to equal or exceed overdoses totals of previous years. The Boone County Medical Examiner's office which performs examinations for Boone and Callaway counties has preliminary data showing opioid deaths are increasing. Boone and Callaway counties have already had respectively nine and three cases of known opioid deaths for the first half of 2020, with a further 34 and 11 cases pending final assignment of cause of death.[56] Boone and Callaway are on track to outpace the 2014-2018 annual averages of 13 and 4 fatalities, respectively.

Brandon Costerison of NCADA has summarized the situation for the illicit drug user in Missouri: "The drug supply is in chaos. Due to social distancing, those users may be using alone at home, and people don't know to check on them." [57] In the era of COVID, narcotic addicts who overdose are dying alone at home.

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Disclosures

None reported. **MM**

Youth Suicide: A Population Crying for Help? A System Overloaded? Who Can Help?

by Ravi Shankar, MD, Rasha El Kady, MD & Arpit Aggarwal, MD

Abstract

Suicide is the second leading cause of death in young adults (15-24 years old). There continues to be limited access to mental health services for many patients who are in mental health crisis because of shortage of trained psychiatrist and mental health providers. Patients identified with high risk factors should get a full comprehensive psychiatric evaluation. Management should focus on preventative strategies, early identification as well as treatment with appropriate psychopharmacology and psychotherapy.

Introduction

Suicide has been one of the leading causes of death in youth. It was identified as the second leading cause of death in young adults (15-24 years old) from 2011-2015.[1] According to the National Vital Statistics Reports, suicide was the second leading cause of death in younger age group of 10–24 years of age accounting for 16.8% of deaths. It was also the fourth leading cause of death for ages 25–44 accounting for 11.2% of deaths.[2] It is interesting to note, that even though suicide was among the top 10 leading causes of death in 45-64 age group it had dropped to the eighth leading cause of death.[2] In looking at the data it is clear that youth is clearly an extremely vulnerable population for suicide. What is even more alarming is there continues to be a concern for a national shortage of child and adolescent psychiatrists. This shortage led the American Academy of Child and Adolescent Psychiatry to start a work force initiative in 2002 to address this. The American Medical Association estimated 8,000 child and adolescent psychiatrists in the United States in 2013.[3] The U.S. Bureau of Health Professions estimated a need for approximately 12,600 by 2020 to meet the mental health needs of the country.[4]

According to American Foundation for Suicide Prevention suicide is the tenth leading cause of death in Missouri ranking it eighteenth compared to the other states. In breaking down the suicide by age groups it is the second leading cause of death of 15-24 years, third leading cause of death of 25-34 years, fourth leading cause of death of 35-54 years, eighth leading cause of death of 55-74 years, and seventeenth leading cause of death in individuals above the age of 65. According to this report "on average one person dies by suicide every eight hours in the state." A brief report in April 2015 by Missouri Suicide Prevention Project, the suicide rates in Missouri have remained stable but, have been higher than the national average. Seventy-five percent in 2013 were white males between the ages of 18-24 with 49% using firearms.[5]

Many mental health problems in adults have origins in adolescence who lack access to services during this time.[6] Three national surveys showed that of the children between the ages of 6-17 who were screened for mental health services only one-fifth actually received the services.[7, 8] It is also interesting to note that one-third of individuals 16 years or older presented to emergency departments in the preceding year of completing the suicide.[9]



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Risk Factors

The assessment of suicide risk factors should include a comprehensive psychiatric evaluation of the youth including collateral information from parents, other family members, teachers, caregivers and friends. Psychopathology,[10] substance misuse,[11] and a history of suicide attempt[12] are considered strongest predictors of future suicidal behaviors in youth. Major depressive disorder carries the greatest risk for suicide attempts and a higher severity of depressive symptoms is associated with a greater likelihood of attempting suicide.[10,11] In numerous studies, a history of previous suicide attempt has been associated with increased future suicide attempts.[13-15] A family history of suicide attempt seems to convey a greater risk of suicide attempts in youth as shown by monozygotic twin studies.[16]

A history of interpersonal violence or maltreatment (e.g. being a victim of bullying or physical/sexual abuse) increases the risk for completed suicide. According to a study, adolescents with a history of cyberbullying were 11.5 times more likely to report suicidal ideation compared to adolescents without any bullying experiences.[17] A recently published study found that increased weekend screen time was associated with higher child-reported suicidality while increased parental supervision and positive school involvement were found to be associated with a decrease in child reported suicidality.[18] Conflicts and dysfunction in families are also associated with an increase in the risk of suicidal behaviors in youth.[18] Other risk factors include a history of adoption,[19] male gender, and a history of physical or sexual abuse.[20]

Adolescence is also the time when many youth may experiment with substances which may be mood-altering. In a systematic review and meta-analysis published in February 2019 that involved 23,317 adolescents and 11 studies, use of cannabis in adolescence did have an increased risk having depression and suicidal concerns even later in life.[21] Rates of cannabis use in individuals aged 18-29 years have almost doubled between 2001-2002 to 2012-2013 from 10.5%-21.2%.[22] In August 2019, the U.S. Surgeon General also put out a Health Advisory on "Marijuana Use and Developing Brain" stressing importance of need for protecting youth and pregnant women.[23] Educating teenagers about the risks of cannabis and providing resources for youth to teach them skills to resist peer pressure and getting them access to other prevention programs should be a key component in program implementation. These findings should be considered in developing public health policy and prevention programs.

Treatment and Management

For management of suicide in youth, prevention is the key. In public health there are three major categories of prevention: primary, secondary, and tertiary prevention.

In primary prevention the main target is the general population of youth before developing suicidal thoughts, gestures, or actions. This can include a wide range of interventions, one of which is legislative policies restricting access to firearms. [24] Adolescent suicide by firearm kills more than 1,000 10-19 years old children and adolescents annually in the U.S.[25] This article is not necessarily against the second amendment constitutional right to "keep in bear arms." Citizens of Missouri have the right to protect themselves and many Missouri families enjoy hunting. However, it is a crucial for caregivers of youth to know that the mere presence of firearms in a household increases the suicide risk to all children at home.[26] Caregivers must appreciate their responsibility in preventing gun access to children,[27] since suicide in youth is generally more impulsive and with lower intent level compared to adults.[28] Another crucial intervention is educating youth against substance use and resisting peer pressure. Studies have shown adolescent cannabis consumption was associated with increased risk of developing depression and suicidal behavior even in the absence of a premorbid condition.[29]

Other primary preventative interventions include construction barriers to where suicide could be committed by jumping, detoxification of domestic gas, restriction of pesticides, use of lower toxicity antidepressants, restricting sales of lethal hypnotics.[30] In general, children and adolescents need to be educated about the seriousness of suicide, making suicidal statements, the seriousness of bullying and cyber bullying.

In secondary prevention, the main goal is early identification of children and adolescents at risk for suicide and then referring them for assessment and treatment.[24] Please refer to list of resources for the state of Missouri at the end of this article. Thus, training individuals who could have contact with high risk children and adolescents is imperative.[31] For example, school teachers, school counselors, parents, foster

Suicide Facts & Figures: Missouri 2019*



On average, one person dies by suicide every eight hours in the state.

Over four times as many people die by suicide in Missouri in 2017 than in alcohol related motor vehicle accidents.

The total deaths to suicide reflect a total of 24,161 years of potential life lost (YPLL) before age 65.

Suicide cost Missouri a total of **$1,016,985,000** combined lifetime medical and work loss cost in 2010, or an average of **$1,188,066 per suicide death**.

*Based on most recent 2017 data from CDC. Learn more at afsp.org/statistics.

10th leading cause of death in Missouri

2nd leading cause of death for ages 15-24

3rd leading cause of death for ages 25-34

4th leading cause of death for ages 35-54

8th leading cause of death for ages 55-64

17th leading cause of death for ages 65 & older

Suicide Death Rates

	Number of Deaths by Suicide	Rate per 100,000 Population	State Rank
Missouri	**1,151**	**18.49**	**18**
Nationally	47,173	14.00	

afsp.org/StateFacts

American Foundation for Suicide Prevention

parents, staff in residential facilities, staff in the juvenile system, pediatricians, ER providers, etc., are trained to recognize at-risk youth. They are encouraged to ask them directly about suicidal thoughts and intentions [32] and then refer them to mental health providers.

In tertiary prevention, the goal is to prevent suicidal actions. This typically occurs after youth have been identified as a high-risk individual and have been referred to mental health. Numerous randomized clinical trials showed that cognitive behavioral therapy (CBT) and other psychotherapies are effective in reducing suicidal ideations and attempts.[33] CBT is a form of talk therapy that works on changing cognitive distortions which are negative perceptions of reality. Dialectical behavioral therapy (DBT) is a subtype of CBT. It is an evidence-based therapy that has also been proven to reduce suicide attempts in adolescents.[34,35] DBT adds emphasis on emotional regulation, grounding techniques and interpersonal relationships.

The combination of psychopharmacology (medication management) with psychotherapy shows improvement of depression and suicidality scales which was found to be similar to those observed in non-suicidal children.[36] Another tertiary preventative strategy is developing a safety plan with the patient. It is a written list of coping strategies and support resources that the patient can use when endorsing suicidal thoughts.[37]

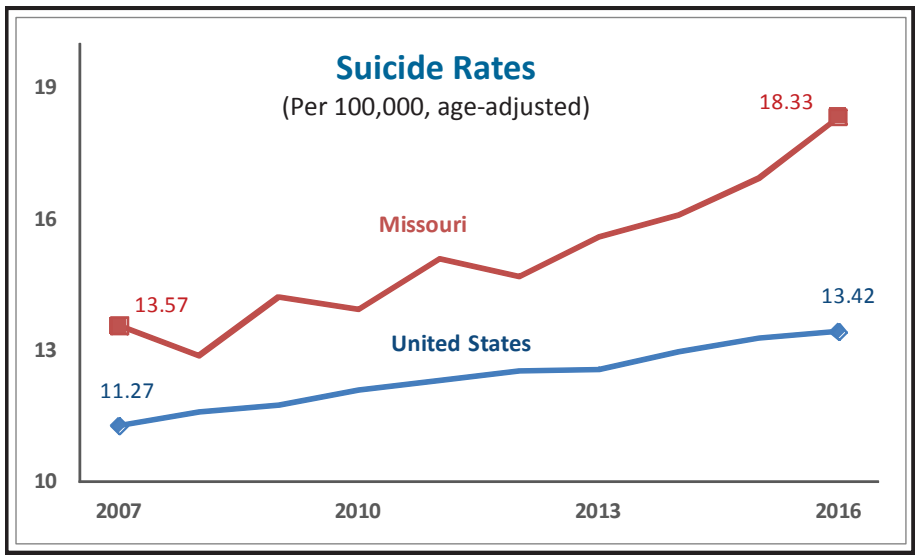
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MISSOURI INSTITUTE OF MENTAL HEALTH AUGUST 2018

Suicide in Missouri: Where We Stand

- **Missouri is ranked 14th highest** in the nation with a rate of 18.33 (per 100,000, age-adjusted). The national rate is 13.42.
- **Over 1,000** Missourians died by suicide in 2016.*
- On average, **1 person dies by suicide every 8 hours** in Missouri.
- **Suicide is the 10th leading cause of death** in Missouri and nationally:
  - **2nd** leading cause of death among 10-34 year-olds
  - **4th** leading cause of death among 35-54 year-olds
- Rates have **increased by over 30%** since 1999.
- In 2016, **76%** of those who died by suicide were **male** and **92%** were **Caucasian.**
- **57%** of all suicides in 2016 involved **firearms**, followed by suffocation (24%) and poisoning (14%).**



UMSL MIMH Missouri Institute of Mental Health

Resources in Missouri

Crisis Text Line
Text HELLO to 741741 and speak anonymously to a crisis counselor. FREE, 24/7 support

National Suicide Prevention Lifeline
800-273-8255

TLC (Talk, Listen Care) Warmline
4-10 pm 7/365
Local: 573-651-3642
Toll Free: 877-626-0638

Mental Health Association of the Heartland Compassionate Ear Warmline
Local: 913-281-2251
Toll-free: 866-927-6327
English: 4–10 pm 365
Spanish: 5–8 pm M-F

Depressive, Manic-Depressive Association of St. Louis Friendship Line
Toll-free: 866-525-1442
Local: 314-652-6105

Central Missouri Crisis Hotline
Toll-free: 800-833-3915

National Alliance on Mental Illness Missouri Warmline
Local: 573-624-7727
Toll Free: 800-374-2138
Hours: 9 am–9 pm M–F

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Disclosure

None reported.

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Lung Cancer in Non-Smokers

by Sarah Dubin, MD & Daniel Griffin, DO

Lung cancer in non-smokers is almost exclusively non-small cell lung cancer, with adenocarcinoma being the most common type.



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Abstract

Lung cancer is the leading cause of cancer death worldwide and the third most common cancer following breast and prostate.[1] As expected, the primary factor leading to lung cancer is tobacco smoke, and as smoking rates have declined, we have also seen an overall decline in lung cancer rates.[2] Despite the general reduction in lung cancer rates, the rate of lung cancer in non-smokers has been noted to be increasing.[3-8]

Introduction

With the overall rates of lung cancer and tobacco smoking declining, the evaluation of lung cancer in non-smokers has become of clinical interest. Several studies have suggested that lung cancer in non-smokers is different from both a biologic and epidemiologic perspective such that it should be looked at as a completely distinct entity.[9] When discussing lung cancer in non-smokers, the term "non-smoker" or "never smoker" classically refers to individuals who have smoked less than 100 cigarettes in their lives. In terms of the type of cancer, non-smokers are mainly afflicted with non-small cell lung cancer, predominantly adenocarcinoma. Due to the exceedingly low rates of small cell lung cancer in non-smokers, this will not be addressed further here.[10] In this article we will review the epidemiology, risk factors and treatments for lung cancer in non-smokers.

Epidemiology

Worldwide, 15-20 percent of men with lung cancer are non-smokers while over 50 percent of women with lung cancer are non-smokers.[11] This demographic has some significant geographic differences as lung cancer in non-smoking women in Asia comprises approximately 60-80 percent of the cases of lung cancer.[12] In a study performed in the United States, roughly 19 percent of women with lung cancer were non-smokers, and only 9 percent of men with lung cancer were non-smokers.[13] As this data has shown, lung cancer in non-smokers tends to be more common in females (Table 1).

Along with this data, there have been several studies to suggest the rates of lung cancer in non-smokers is overall increasing.[3-8] The evidence on mortality rates among non-smokers versus smokers with lung cancer has been conflicting. Some studies have suggested lower mortality rates in the non-smoking population.[14] Despite this, other studies have indicated no significant difference or even a possible increase in mortality.[5] One finding that has been consistent is that despite non-smoking women more frequently being diagnosed with lung cancer, they do have an overall decreased mortality when compared to

men.[24] This data is similar in the smoking population as well, as women have been known to live longer than men with lung cancer.[15] The age at which lung cancer is diagnosed in non-smokers has classically been considered to be a younger population. Recent studies looking at the age of diagnosis have refuted this clam as the majority of non-smokers with lung cancer were diagnosed at an older age as compared to smokers.[16]

Table 1. Lung Cancer – Smokers vs Non-Smokers

Lung cancer		
	Smokers	**Non-Smokers**
Age at diagnosis	66 years	67 years
Sex predominance	Male	Female
Most common subtype	Adenocarcinoma (65%)	Adenocarcinoma (93%)
Time to seek medical care	2 months	3 months
EGFR mutations	8%	36%
ALK mutations	4%	26%
Stage IV at diagnosis	49%	62%

Data taken from:
Margarida Dias, Rita Linhas, Sérgio Campainha, Sara Conde & Ana Barroso(2017) Lung cancer in never-smokers – what are the differences?, Acta Oncologica, 56:7, 931-935

Risk Factors

There have been several suspected risk factors for lung cancer in non-smokers, but none are known to be directly causative at this time. Several of the proposed essential risk factors will be discussed.

Age

Age at diagnosis for lung cancer in non-smokers has classically been considered to be a younger person's disease. Several studies have refuted this claim, showing that increasing age is a common predisposing factor.[16-17] The increased risk with age is felt to be due to the duration of exposure to potential carcinogens throughout one's life (e.g., secondhand cigarette smoke, radon gas).

Secondhand Smoke

Secondhand smoke has been implicated in the development of lung cancer in non-smokers.[25] Multiple studies have suggested that 15-35 percent of lung cancer in non-smokers is due to secondhand smoke exposure.[18] Importantly, there is also an increased risk for those non-smokers that have a spouse that is a smoker. In a meta-analysis that included 55 studies, it was found that women who were married to a smoker had a 27% increase in risk of lung cancer.[19]

Environmental Exposures

Several studies have also linked environmental exposures to lung cancer — some known exposures including asbestos, chromium, and arsenic.[21] There have also been studies linking indoor and outdoor air pollution to the development of lung cancer.[20] Asbestos exposure that is complicated by intestinal fibrosis or asbestosis is noted to lead to increased lung cancer rates. In one study, it was noted that asbestos exposure alone lead to a six-fold increase in relative risk of developing lung cancer, while asbestos exposure and smoking lead to a 59-fold increase. [22]

In developing countries, chronic exposure to cooking fumes from burning wood or frying has been linked to an increased rate of lung cancer in non-smokers.[20] This problem is most evident in developing countries where women are primarily in charge of cooking duties and can spend hours each day cooking amongst open flames. This exposure is thought to be the cause of some of the disproportionate lung cancer rates within this population.[20] Additionally, animal dung/feces can be dried and used as fuel, which when inhaled can also lead to increased risk of cancer and reactive airway disease.

Radon

Another potential risk factor is radon. Radon is a decay product of uranium-238, as well as radium-226, and possesses the capability of damaging respiratory epithelium via emissions of alpha particles. Radon is known to be present in soil, rock, and groundwater and due to this, it can accumulate in homes. Although controversial, exposure to radon within homes may play a role in the development of lung cancer in non-smokers.[23] There is a known increased risk of lung cancer among uranium miners which is felt to be due

to radon exposure. The increased radon exposure in this group has more clearly linked the exposure to lung cancer.[24] In a meta-analysis of 13 studies, there was a reported a direct relationship between the level of radon detected in homes and the risk of developing lung cancer; based on this information the authors estimated that radon exposure might be responsible for up to 2 percent of lung cancer deaths in Europe.[25]

Genetic Factors

Lung cancer in non-smokers is felt to have a genetic predisposition as many studies have shown that those with a family history of lung cancer are at increased risk.[26] To further illustrate this importance, in one case-control study that looked at over 2,400 relatives of 316 cases of lung cancer in non-smokers, there was a 25 percent increased risk of any cancer among the first degree relatives. There was also an increased risk of early onset (age less than 50 years) lung cancer among the relatives who smoked.[27] While this study does not directly link a history of lung cancer in non-smokers to future generations developing lung cancer, it does show the importance of genetic factors leading to the development of cancer as well as the risk involved when genetically susceptible individuals partake in smoking. There are specific germline mutations that have been identified in families with high rates of lung cancer in non-smokers. The most prominent of these is the germline mutation in the epidermal growth factor receptor (EGFR).[28] The identification of this mutation has led to specific advances in targeted treatment for individuals with this mutation, which is seen mainly in non-smokers with lung cancer.[29]

Lung Disease

Another important risk factor for the development of lung cancer in non-smokers is underlying lung disease. Lung disease can be due to many different factors which range from pre-existing disease or from chemotherapy and radiation.[26] The extent of this risk is not truly known as the majority of lung disease is related to smoking. Also, when looking at pulmonary fibrosis, studies also suggest there is some increased risk related directly to the disease.[27]

Oncogenic Viruses

Several viruses have been implicated in the development of cancer. Some of these include Epstein-bar virus (EBV), human papillomavirus (HPV), and Hepatitis B and C. Of these, HPV has known associations with head and neck cancers as well as potential implications in lung cancer.[28] Despite these potential implications, a meta-analysis on the role of HPV and the development of lung cancer in non-smokers was inconclusive.[29]

Estrogens

It has been postulated that estrogens and other female hormones could be leading to the increased risk of lung cancer in non-smokers.[11] It has also been noted that many of the non-small cell lung cancers express an estrogen receptor, and expression of this receptor is more common in lung cancer seen in non-smokers as compared to smokers.[30]

Biologic Differences

There are several differences in lung cancer between smokers and non-smokers; some of these include pathologic differences as well as molecular differences.

Pathologic Differences

Non-small cell lung cancer, mainly adenocarcinoma, is more common in non-smokers and light smokers, as well as former smokers. For heavy smokers, squamous cell carcinoma and small cell lung cancer are seen more commonly.[31]

Molecular Differences

With advances in the understanding of the molecular biology of cancer there have been found substantial differences between lung cancer in smokers versus non-smokers. Several studies have suggested that lung cancer in non-smokers is different enough from a biologic and epidemiologic perspective to be looked at as a completely different entity.[9]

Many different mutations have been found. The most common include the epidermal growth factor receptor (EGFR), Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation and anaplastic lymphoma kinase (ALK) gene rearrangement. Due to these known mutations, there has been a significant effort in attempts to find "driver" mutations in non-small cell lung cancer. Driver mutations are those mutations that appear to be leading to or "driving" a particular cancer. The National Cancer Institute's lung cancer mutation consortium presented data at the American Society of Clinical Oncology annual meeting on the evaluation

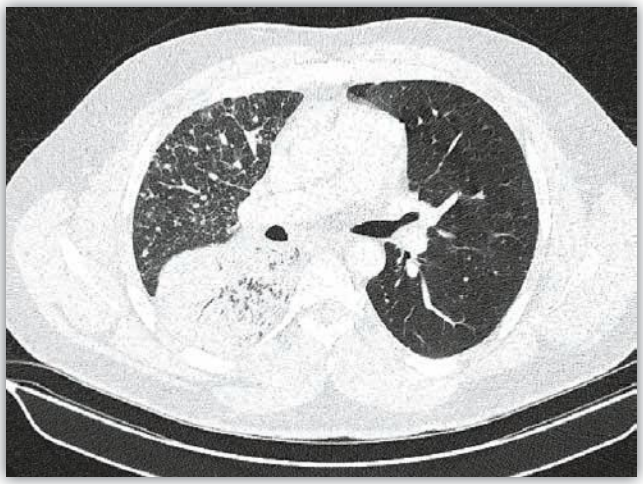


Figure 1. Atypical radiographic appearance of adenocarcinoma of the lung on CT imaging.

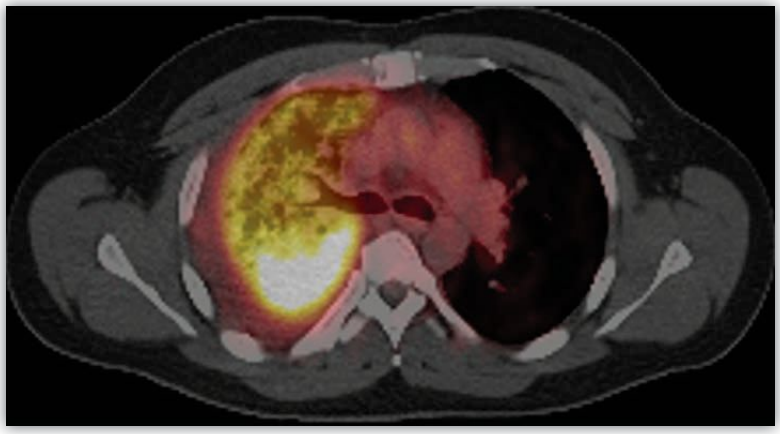


Figure 2. Atypical radiographic appearance of adenocarcinoma of the lung on PET imaging.

of 800 patients with non-small cell lung cancer and showed that 25 percent had KRAS mutations, 23 percent had EGFR mutations, and 6 percent had ALK rearrangements.[32]

Further data has shown that mutations in EGFR are more common in lung cancer of non-smokers compared to smokers.[33] Studies on the KRAS mutation have demonstrated that the mutation occurs at approximately the same rate in smokers as well as non-smokers with lung cancer, but the mutations are different with more transition mutations occurring in non-smokers compared to transversion mutations occurring is smokers.[34]

Lung Cancer Screening in Non-Smokers

Currently, there are no guidelines to recommend lung cancer screening in non-smokers. Symptoms of lung cancer are often nonspecific and include no symptoms to cough, dyspnea, weight loss, and loss of appetite. More specific symptoms do include chest pain and hemoptysis but these can be shared by many different diseases. Even in the setting of multiple symptoms there are still no guidelines to recommend screening for lung cancer in non-smokers. Current guidelines do recommend lung cancer screening in those 55-79 years of age with at least 30 pack year smoking, who are current smokers or have quit smoking in the past 15 years. In this setting, a screening low dose chest CT is appropriate. Despite there being no guidelines to recommend lung cancer screening in non-smokers, those with increased risk based on family history or other risk factors should be closely monitored for the development of symptoms that would warrant further testing (Figures 1 and 2).

Treatment

Non-smokers with lung cancer do not appear to respond better to standard treatment or have a better prognosis than smokers. Some studies have shown improved outcomes while others have not.[35] Despite this, there have been some newly developed targeted treatments that have shown promise in lung cancer due to specific genetic mutations. One such class is the EGFR tyrosine kinase inhibitors which include erlotinib, gefitinib, afatinib, and osimertinib. Studies involving these medications have suggested improved response rates and survival in non-smokers over smokers. The improved response rates are felt to be driven by the fact that this mutation is seen more commonly in non-smokers than smokers and that regardless of smoking status patients with these mutations have improved outcomes with these medications.[36]

Summary

Non-smokers are those who have smoked less than 100-lifetime cigarettes. Lung cancer in non-smokers is almost exclusively non-small cell lung cancer, with adenocarcinoma being the most common type. Non-smoking women are more likely to get lung cancer than non-smoking men. Regardless of smoking status, women with lung cancer tend to outlive men with lung cancer. It has classically been taught that lung

cancer in non-smokers occurs at a younger age, but current data does not seem to suggest this. There are several risk factors for the development of lung cancer in non-smokers and some of these include; age, secondhand smoke, cooking fumes, radon, environmental exposures, genetic factors, underlying lung disease, oncogenic viruses, and estrogens. There are many different genetic mutations seen in non-small cell lung cancer. Some of the most frequently occurring in non-smokers include EGFR mutations, KRAS mutations, and ALK rearrangements. With the discovery of specific genetic mutations, there has been the development of particular treatment targets to these mutations which have shown promise in the treatment of lung cancer.

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Disclosure

None reported. **MM**

Breast Implant-Associated Anaplastic Large Cell Lymphoma: What the Primary Care Physician Needs to Know

by Abigail Spaedy, MD, Daniel O'Toole, MD & Carol Ann Aylward, MD

BIA-ALCL is a rare malignancy associated with textured breast implants. It may occur with both saline and silicone implants, and it usually presents late with a seroma or mass.



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Abstract

This manuscript aims to outline the pertinent epidemiology, presentation, diagnosis, and treatment of patients who present with breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) as it pertains to primary care, such that the primary care physician (PCP) is able to appropriately care for patients with breast implants and counsel on risks of BIA-ALCL.

Introduction

Since 1997, the number of augmentation procedures in the United States has increased by 207%, according to the American Society for Aesthetic Plastic Surgery.[1] With growing popularity, there is more need for the PCP to have an understanding of potential complications, such that patients with breast implants may be appropriately managed and referred. Of late, there has been increasing media coverage reporting cases of anaplastic large cell lymphoma, a breast implant-associated lymphoma. Given the nature of the disease, it is most commonly diagnosed after symptoms develop, so all healthcare providers need to be alert to those clinical findings. This review aims to outline the pertinent epidemiology, presentation, diagnosis, and treatment of patients who present with breast-implant associated anaplastic large cell lymphoma (BIA-ALCL) as it pertains to healthcare providers, such that physicians are able to provide appropriate care for patients with breast implants, counsel on risks of BIA-ALCL, and ensure timely diagnosis.

Epidemiology

The first reported case of BIA-ALCL was in 1997, with approximately 293 recognized cases in the United States and 779 cases worldwide as of September 3, 2019, according to the American Society of Plastic Surgeons.[2] The incidence of BIA-ALCL in women with breast implants is estimated at 1 in 4,000-30,000.[3] It is important to note that both silicone and saline implants have been implicated in BIA-ALCL, but no cases have been documented prior to the advent of textured implants, suggesting a causal relationship between textured implants and BIA-ALCL (Figure 1).[3] Smooth implants have not been associated with BIA-ALCL. On July 24, 2019, at the request of the FDA - Allergan, one of the major

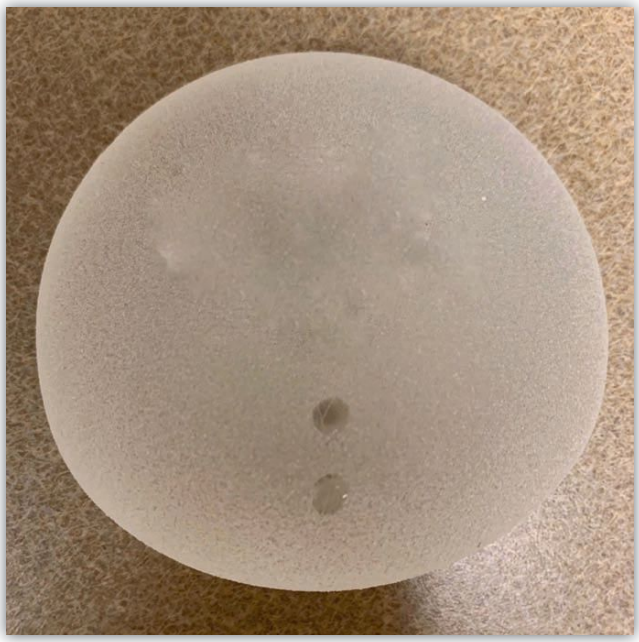


Figure 1. Photograph of textured breast implant.

breast implant manufacturers - withdrew its BIOCELL® Textured Implants. At the time of this FDA request, 481 of the 573 known cases were associated with these specific implants. Based on available data, the BIOCELL® Textured Implants have a six-times higher risk of BIA-ALCL than textured implants from other manufacturers.[4] The pathophysiology is currently unknown with multiple proposed hypotheses; several of these suggest a chronic inflammatory response involving CD4+ lymphocytes.[3]

Presentation

As patients frequently do not follow-up long-term with the plastic surgeon after breast augmentation or reconstructive procedures, it is important for the PCP and other healthcare professionals to be aware of the association between breast implants and anaplastic large cell lymphoma. Physicians other than plastic and reconstructive surgeons will likely be the first to encounter patients with BIA-ALCL, which may lead to a delay in diagnosis.[3] A basic knowledge of the presentation and management of BIA-ALCL by the PCP will minimize this delay.

When following a patient with breast implants, it is important to obtain a specific history regarding the implants, including initial and subsequent surgeries, the location of placement (subpectoral or subglandular), and the type of implant. For BIA-ALCL, onset of symptoms typically occurs greater than one year after implant placement, with the mean time to symptom onset being ten years following placement.[3] The majority of patients with BIA-ALCL present with a late-onset (>1 year after placement) seroma that manifests as swelling of the affected breast.[5] Additionally, on physical exam it is necessary to determine if the implants have changed in texture or firmness, which may be indicative of pathology. One systematic review showed that 66% of patients presented with seroma; 8% with a mass; 7% with both; and 18% with other symptoms, including capsular contracture, axillary lymphadenopathy, skin lesions, and B symptoms.[3] Upon presentation, the physician should perform a detailed physical exam, examining the breast for swelling, capsular contracture, cutaneous changes, and regional lymphadenopathy.[5] Any abnormal findings should prompt further workup and referral to the patient's plastic surgeon.

Diagnosis

Diagnosis of BIA-ALCL starts with ultrasound, as it has been found to be the most sensitive and specific screening tool in these patients.[5] If fluid is seen on imaging, the patient should be encouraged to follow-up with their plastic or breast surgeon for further workup, which may include aspiration of fluid and fluid analysis with immunohistochemistry, and flow cytometry to establish the diagnosis of BIA-ALCL.[1] It is important to note that mammogram is not the preferred diagnostic modality, as its sensitivity for identifying BIA-ALCL-associated effusion and mass has been shown inferior to ultrasound.[6] However, for any change within the breast, particularly with intact breast tissue (augmentation as opposed to reconstruction after mastectomy), it would be encouraged to also obtain a mammogram, particularly if greater than three months has passed since last imaging, so as not to miss the more common diagnosis of breast cancer. Further workup may include excisional biopsies of suspicious lymph nodes, [5] and PET/CT may be used for staging to assess for systemic disease.[3]

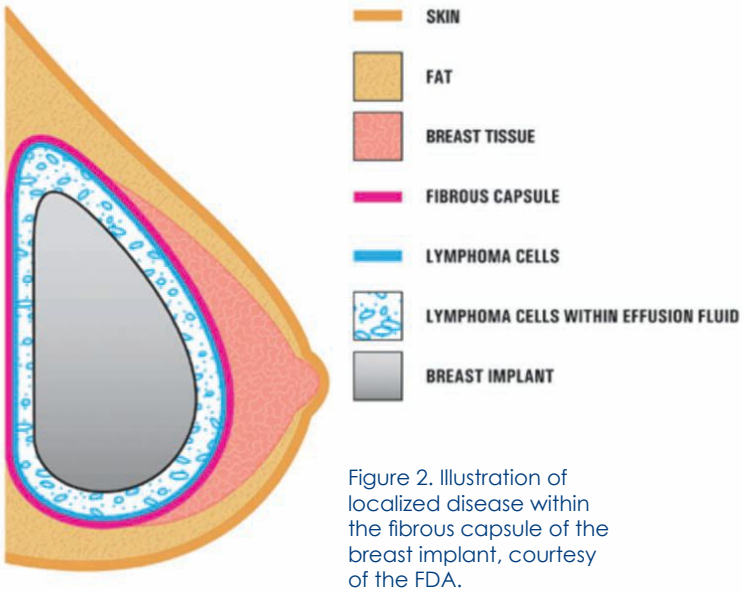


Figure 2. Illustration of localized disease within the fibrous capsule of the breast implant, courtesy of the FDA.

Once a cytologic diagnosis of BIA-ALCL is made, the patient should be referred to an oncologist and rported to the PROFILE registry.[3] A non-diagnostic workup with high clinical concern should be referred to a specialist to consider additional diagnostic options.

Treatment

Reported to date, BIA-ALCL generally has an indolent course and confers a favorable prognosis. The disease is usually localized to the scar capsule of the implant, and for localized disease, capsulectomy with implant removal is the treatment of choice (Figure 2).[3] Additionally, adjuvant radiotherapy may be used for localized disease; whereas, patients with systemic or extensive disease will require chemotherapy and radiotherapy.[3] Patients can be counseled that systemic or extensive disease is exceedingly rare with reported incidence of 1 in 250,000.[6] It is believed that the majority of cases can be managed with surgical excision of implant and capsule alone, while chemotherapy and radiotherapy are reserved for patients with recurrent or more extensive metastatic disease.[5] At this point in time, chemotherapy has not been found to significantly improve overall survival. As knowledge of this disease is incomplete, a multi-disciplinary, individualized approach should be taken in every case. Following treatment, patients require close follow up with exams every three to six months and imaging every six months for the first two years.[3]

Conclusion

At this time, the FDA does not recommend prophylactic screening or implant removal for asymptomatic patients, including those with Allergan BIOCELL® Textured Implants, due to the low risk of developing BIA-ALCL.[4] Further, asymptomatic women without breast changes do not require more than routine breast exams. Despite this, it remains important to discuss the patient's implants and be able to appropriately care for patients with breast implants. While the PCP is not expected to be an expert on BIA-ALCL, they will likely receive questions from concerned patients with implants. Knowing the basics about BIA-ALCL will allow the PCP to quell many of their patient's concerns and better care for patients with implants. BIA-ALCL is a rare malignancy associated with textured breast implants. It may occur with both saline and silicone implants, and it usually presents late with a seroma or mass. BIA-ALCL is usually localized and has a favorable prognosis. Most importantly, the patient can always be encouraged to follow up with their plastic surgeon for a more detailed discussion regarding complications of breast implants, as well as for diagnosis and management of BIA-ALCL.

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Disclosure

None reported.

MM

Part Three of Three-Part Series

Colorectal Surgery Review for Primary Care Providers

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

Improving screening rates among underserved populations can reduce the colorectal cancer burden in the United States.



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Abstract

Malignant colon and rectal disorders must be identified and treated. Timing and indication for diagnostic and screening colonoscopy are extremely important. A high index of suspicion to exclude malignancy is imperative. This paper will focus on the screening for and treatment of colorectal and anal cancers.

Screening for Colorectal Cancer

Colorectal cancer is common and deadly, ranking as the third most common cancer in both men and women. Fortunately, the implementation of widespread screening has directly led to a steady and ongoing decrease in incidence. A well-defined polyp to cancer progression, true for most colorectal cancers, allows detection and treatment of "pre-malignant" adenomatous polyps and early cancers before they become symptomatic and later stage.[1]

"Screening" is testing asymptomatic patients to detect a disease before it becomes clinically apparent to allow intervention and prevent disease progression. Patients are classified as either average or high-risk. Average risk for colorectal cancer is defined as individuals 50 years or older without a personal or family history of colorectal polyps or cancer, and no at-risk diseases such as ulcerative colitis or Crohn's disease.[2]

Primary care providers are vital to the success of any screening program. It is important to discuss with all patients that screening for colorectal cancer drastically reduces the chance of dying from colorectal cancer but a perfect test does not exist.

Summary of Recommendations and Considerations

1. Providers should begin screening for colorectal cancer at age 50 if no at-risk factors exist.

2. High-risk patients (personal or family history of polyps or colorectal cancer) should begin at age 40 years old or 10 years prior to the youngest first-degree affected relative.

3. Approved first-line screening should be either fecal testing or colonoscopy.

Colonoscopy

- Considered "best" but involves time off work, bowel prep, risks of procedural complications such as bleeding, bowel perforation[3] (4 in 10,000 endoscopies performed) or sedation issues, and costs more.
- However, colonoscopy remains the most reliable method to

Table 1. Colorectal Cancer Staging

Stage	Primary tumor[1]	Regional lymph nodes[2]	Distant metastasis[3]
I	T1/T2	N0	M0
II	T3/T4	N0	M0
III	Any T	N1	M0
IV	Any T	Any N	M1

[1]Primary tumor
T1: tumor invades lamina propria or submucosa;
T2: tumor invades muscularis propria;
T3: tumor invades through muscularis propria into the subserosa;
T4: tumor perforates the vascular peritoneum or directly invades other organs, including mesentery, abdominal wall, and pancreas.
[2]Regional lymph nodes
N0: no regional lymph nodes metastasis;
N1: regional lymph nodes metastasis.
[3]Distant metastasis
M0: no distant metastasis;
M1: distant metastasis.

prevent development of advanced polyps and cancers.

- Normal colonoscopy requires 10-year follow-up if the patient remains asymptomatic.[4]
- Abnormalities might require closer follow-up, ranging between three months to five years depending on the concern. This will be determined by the endoscopist.
- Fecal tests: FOBT, FIT or fecal DNA[5] ("Cologuard")
  - Less accurate: more false positives and false negatives.
  - Done more frequently (every two years at minimum).
  - Involves dietary or medication restrictions prior to test.
  - Compliance is also lower.
  - Abnormal results require follow-up colonoscopy.
  - Single digital exam in the office with FOBT cards is not adequate screening.
  - Fecal DNA test usage is likely to increase in the future, but it is currently hard to know their role.
  - Fecal tests are never appropriate for symptomatic patients, since a false test does not eliminate the need for colonoscopy to rule out an intermittently bleeding tumor.

4. All symptomatic and high-risk patients require diagnostic colonoscopy.

5. Incidence of colorectal cancer is increasing (for unknown reasons) in patients under the age of 50. All unexplained, persistent bowel symptoms require investigation (colonoscopy) regardless of age.

- Common symptoms to watch for: bleeding, bowel changes (more or less frequent, change in caliber, feeling of incomplete emptying, etc…), abdominal bloating, abdominal pain, unexplained or unintentional weight loss, among others.

6. The development of concerning symptoms between screening exams mandates further investigation as no test is perfect, and polyps or cancers can be "missed" or develop in the interim.

7. It is reasonable to not screen patients with significant medical comorbidity, advanced age or frailty, which reasonably decreases their life expectancy to less than 5-10 years. Otherwise, screening should continue (the risk for colorectal cancer rises as age increases) despite age over 75.

8. Other options in certain circumstances include digital rectal exams, flexible sigmoidoscopy, barium enema, and CT colonography. However, they are often adjuncts to the standard tests previously mentioned and generally used only if fecal tests or colonoscopy are contraindicated or not possible.[4]

9. The suspicion of hemorrhoids, or the finding of hemorrhoids on exam, does not rule out the presence of colorectal cancer unless a colonoscopy has been performed recently. Recurrent hematochezia requires endoscopic investigation even in patients younger than standard screening age. See Table 1.

Colon Cancer

Colon cancer affects approximately 107,000 new patients in the United States each year and is the third leading cause of cancer death. Despite significant improvements in prevention and treatment, 30,000 deaths are estimated to have been due to colon cancer.[6] Most patients will present with localized disease amenable to curative surgical resection, but approximately 20% of patients still present with distant metastasis.[5]

The cause of colorectal cancer is multifactorial. Risk factors include diet, smoking, alcohol, and genetic factors. Ulcerative colitis, Crohn's disease, familial adenomatous polyposis (FAP), hereditary non-polyposis colorectal cancer (HNPCC aka Lynch Syndrome) are common associated disease states.[21]

The evaluation of colon carcinoma includes colonoscopy; CT of the chest, abdomen, and pelvis with IV contrast; and labs including CBC and CEA.[9] The evaluation serves as the initial staging and preoperative planning. Genetic consultation in young patients and in patients with significant family history is important.

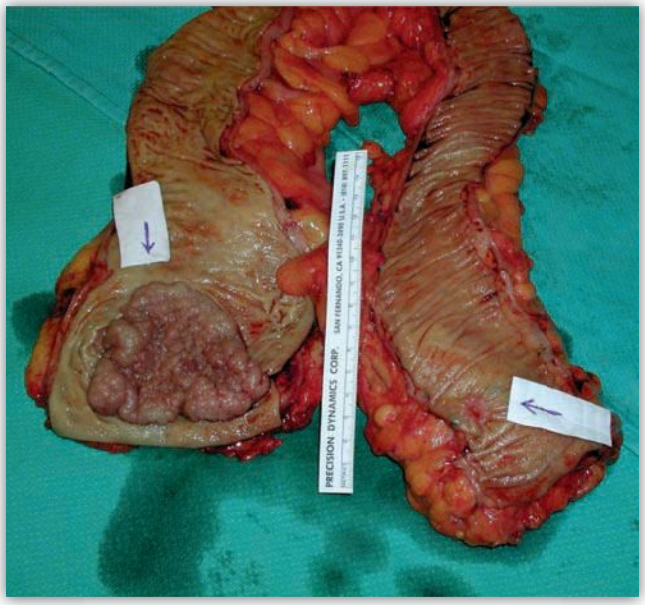


Figure 1. Colon Cancer.

The initial treatment for colon carcinoma is segmental colon resection which includes the draining lymph nodes. Patients are happy to learn that a colostomy should not be needed for an elective resection. In complicated, urgent settings (such as advanced colonic obstruction or perforation), a colostomy may be required. A minimally invasive approach, including laparoscopic or robotic technology, is considered standard of care, which minimizes complications in well-selected patients.[6] Extended resections may be required based on tumor location and in cases of FAP and HNPCC. Pathologic evaluation of the surgical specimen will confirm final stage and determine follow-up and further care (Figure 1).

Postoperatively the patient should be evaluated by an oncologist. In select stage II patients and stage III patients, chemotherapy may be recommended. Radiation is rarely indicated in the treatment of colon cancer.[7] Close postoperative surveillance with colonoscopy, labs and imaging is recommended to detect possible recurrence earlier than when it becomes symptomatic and less likely responsive to additional treatment.[8]

Many treatment options exist for Stage IV disease, occasionally including surgical treatment with curative intent. Long-term survival can be achieved for some patients with favorable tumor biology. A true multidisciplinary approach is required to prioritize goals and coordinate care among colorectal surgeons, hepatobiliary surgeons, medical and radiation oncologists, radiologists and pathologists.[10]

Rectal Cancer

Rectal cancer differs from colon cancer "only" in its anatomic location and is generally defined as adenocarcinoma in the distal 15 cm of the large intestine. However, this can complicate treatment significantly where careful consideration is needed for issues such as bowel function and control, involvement of adjacent organs like genitourinary structures, need for intestinal stoma (temporary or permanent), and pre and postoperative therapies such as radiation, among others. Rectal cancer is the disease around which many board-certified colon and rectal surgeons focus their expertise.

Fortunately, routine colorectal screening is quite effective in detecting polyps prior to malignant transformation or identifying cancers at an earlier stage. As a result, annual incidence has steadily decreased except in patients under 50, where it is increasing for unknown reasons. We have seen patients in their early 20s with no family history, risk factor or genetic mutation present with advanced disease. Additionally, rectal cancers are more likely to cause symptoms earlier, perhaps making early detection more likely compared to colon cancers in the right colon, for instance. Many can be detected on simple digital rectal exam. Rectal bleeding can be attributed to hemorrhoids only after a thorough investigation (Figure 2).[20]

Diagnosis of rectal cancer is confirmed by colonoscopy with biopsies of the concerning lesion/tumor. All rectal cancers require staging. CT of the chest, abdomen. and pelvis with IV contrast assesses for metastatic disease and possibly local invasion into nearby pelvic structures. MRI or trans-rectal ultrasound help determine the local stage (how deep into the wall

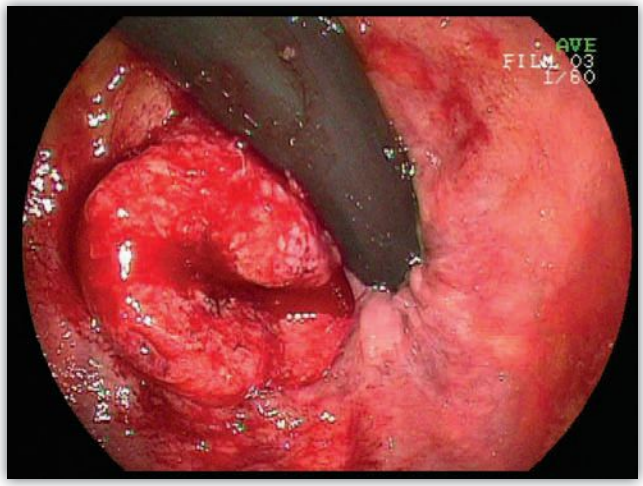


Figure 2. Rectal Cancer.



Figure 3. Anal Cancer

of the rectum the tumor grows or suggestion of adjacent lymph node spread). The CEA is sometimes elevated but can also be normal even in advanced disease.[11] If abnormal, it can be monitored over time to help detect possible recurrences prior to symptoms.

Similar to many other malignancies, the treatment of rectal cancer involves complete resection with negative margins and adequate lymph node resection. The two most common operations for rectal cancer are the low anterior resection (LAR) and abdominoperineal resection (APR, which necessarily includes a permanent colostomy.[12]) Minimally invasive surgery, either laparoscopy or robotic-assisted approaches have become standard of care among colon and rectal surgeons and help minimize complications.[14] Most colorectal surgeons offer sphincter preserving (ostomy avoiding) operations even in very low cancers, depending on tumor and patient factors. It is in cases with a very distal rectal cancer, at the level of the anal sphincters, where APR with permanent colostomy is expected. "Open" surgery still has a role in re-operative scenarios or other complicated pelvic situations. Recently, minimally invasive trans-anal approaches have grown in popularity for favorable early cancers or large polyps. Sometimes potentially complicated conventional rectal resection can be avoided.

Stage 2 and 3 diseases might benefit from preoperative chemo-radiation or stand-alone chemotherapy depending on location of tumor, patient factors and tumor factors. Stage 4 disease with spread to liver or lung or peritoneum is typically treated with systemic chemotherapy.[13] Other options such as liver directed embolization/chemotherapy/radiation are sometimes appropriate for certain metastatic tumors. Rectal cancer is also truly a multi-disciplinary cancer and colorectal surgeons should be involved in every case.

Long-term prognosis is directly related to stage of disease at the time of diagnosis. The most effective treatment remains prevention. Though a typical initial treatment plan can take up to a year, patients who present with Stage 2 and 3 diseases who undergo preoperative chemo-radiation, followed by operative resection, then adjuvant chemotherapy can many times achieve long-term disease free survival.

Anal Cancer

Anal cancer is defined as a malignant tumor originating from squamous cells of the perianal region (tumors within 5 cm of the anus) or anal canal (tumors incompletely visualized on simple inspection up into the distal rectum). Pathogenesis involves previous, occult Human Papilloma Virus infection in most cases. Approximately 1% of patients with HPV develop visible lesions such as condyloma. Fewer develop dysplastic lesions, which can then progress to invasive cancer. It is important to recognize that anoreceptive intercourse is not prerequisite for anal HPV/condyloma/dysplasia/malignancy as much personal and interpersonal grief may exist when this point is not clarified (Figure 3).

Fortunately, the incidence of anal cancer is around 5,000 cases annually. Virtually all tumors are found on simple visual and/or digital rectal exams. Many patients present for evaluation of their painful and "hemorrhoid" but their symptom onset is usually more insidious.[15] Biopsies, often obtained easily during office exam, confirm the diagnosis by histological exam. As with many cancers, staging exams are important and a CT chest, abdomen, and pelvis with IV contrast is standard. Size of tumor and degree of local invasion to adjacent structures is suggested during exam but can also be evaluated by trans-rectal ultrasound or contrasted pelvic MRI.[16]

Perianal tumors are generally treated with wide-local excision assuming a negative margin can be obtained without significant sphincter compromise. Larger tumors are more difficult to resect completely and are more likely to have lymph node spread. Chemo-radiation is recommended with very good results. Salvage radical operation (abdominoperineal resection with permanent colostomy) is reserved for those with persistent tumor after chemo-radiation and has less than ideal oncologic results when needed, usually indicating aggressive tumor biology.[17]

Anal canal tumors are rarely amenable to wide excision with negative margins due primarily to sphincter preservation concerns. Chemo-radiation is the mainstay of treatment. Chemotherapy includes 5-fluorouracil and mitomycin-C or cisplatin.[18] Results are excellent but radiation effects including incontinence and recto-vaginal fistula can occur. Radical surgery is again reserved for disease persistence and is associated with aggressive disease and a poor prognosis.

Patients treated with local excision or chemo-radiation require close office follow-up for five years including anoscopy every three to six months and periodic imaging. Recurrent post-treatment pain or bleeding that persists mandates evaluation.[19]

Conclusion

The United States has seen progress with colorectal cancer with both falling incidence and mortality rates. Factoring into this decline, the significance of early detection and removal of precancerous lesions through screening must be underscored. Screening participation is still suboptimal, among underserved populations. Improving screening rates among underserved populations can reduce the colorectal cancer burden in the United States.

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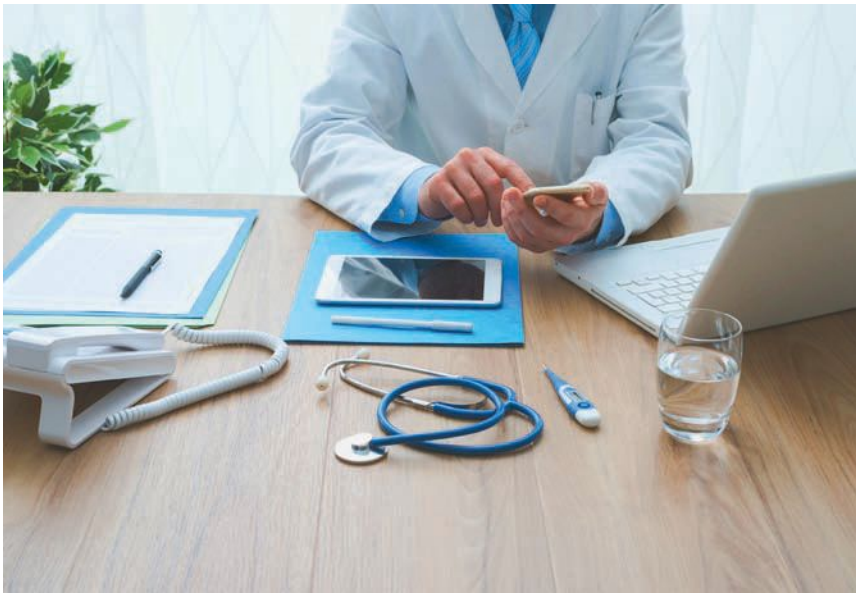
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None reported. **MM**





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