# Missouri Medicine

The Journal of the Missouri State Medical Association www.msma.org/missouri-medicine July/August 2019



School of Medicine
*University of Missouri Health*

# Optimal Care of the Hospitalized Patient

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**On the Brink: Losing Measles Elimination Status**
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# Missouri Medicine

*The Journal of the Missouri State Medical Association - Since 1904*

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**GUEST EDITORIAL**

On the Brink: Why the U.S. is in Danger of Losing Measles Elimination Status
by Mary Anne Jackson, MD & Christopher Harrison, MD ..... 260



**PERSPECTIVE**

Law Enforcement Problems Associated with Medical Marijuana Legalization: A Missouri Perspective
by Jeff Lofton ..... 265

Medical Marijuana: The Australian Experience
by David J. Castle, MD, Nigel Straus, MD, Amanda Norman, BA & Yvonne Bonomo, MD ..... 270

**MEDICAL | LEGAL**

Mandatory Blood Testing
by Wakaba Tessier, JD & Wendy Keegan, JD ..... 274

**AMA REPORT**

Physician Advocacy: The AMA Annual Meeting 2019
by the Missouri Delegation to the AMA and compiled by **Charles Van Way, III, MD** ..... 279

**PRESIDENT'S FORUM**

MSMA: Let Us Help You
by **James DiRenna, DO** ..... 282

**SCIENCE PERSPECTIVE**

Groundhog Day: My Constant Headache Due to Spontaneous Cerebrospinal Fluid Leak
by Alisha Wright, DO & Cindy Schmidt, PhD ..... 287

**MEDICAL SCHOOL PERSPECTIVE**

Strengthening Our Collaborations
by Steven Zweig, MD ..... 289

**SCIENCE OF MEDICINE | FEATURE SERIES**

*Presented by the University of Missouri - Columbia School of Medicine: Optimal Care of the Hospitalized Patient*

A Quality Improvement Initiative: Developing a Multi-Disciplinary Team for Infective Endocarditis
by Hariharan Regunath, MD, Archana Vasudevan, MD, Kapil Vyas, DO, Chen Li-Chien, MD, Sachin Patil, MD, Jane Terhune, MD & Stevan P. Whitt, MD ..... 291

TIGER Team: Rapid Response at the University of Missouri
by Catherine Messick Jones, MD, Kelly J. Butler, LPC & Karen R. Cox, RN ..... 297

Update on Dual Antiplatelet Therapy for Secondary Stroke Prevention
by Alexandria Stringberg, PharmD, Ryan Camden, PharmD, Kathryn Qualls, PharmD & Syed H. Naqvi, MD ..... 303

Hepatic Encephalopathy in the Hospitalized Patient: A Review for Hospitalists
by Harleen Kaur Chela, MD, Nishchayjit Basra, DO & S. Hasan Naqvi, MD ..... 308

Approach to Positive Blood Cultures in the Hospitalized Patient: A Review
by Harleen Kaur Chela, MD, Archana Vasudevan, MD, Christian Rojas-Moreno, MD & S. Hasan Naqvi, MD ..... 313

**SCIENCE OF MEDICINE**




Opioid Use Disorder Assessment Tools and Drug Screening
by James Ducharme, MD & Sean Moore, MD ..... 318

Factors in Accessing Routine Health Care: Mental Health and Postpartum Mothers
by Patricia J. Norton, MD, Mary Mosley, MA, David G. McBride, PhD & Venkata Garikapaty, PhD ..... 325

External Intensivists Versus In-House Intensivists: Analysis of Outcomes of Nighttime Coverage of ICUs by External On-Call and In-House On-Call Intensivists
by Madhuri Ramakrishnan, MD, Siva Sagar Taduru, MD, Parth Patel, MD, Mustafa Younis, MD & Majdi Hamarshi, MD ..... 331

Correlation of Nutrition with Immune Status in Human Immunodeficiency Virus Outpatients
by Rashmi Thimmapuram, Sree Lanka, Anthony Esswein & Lawrence Dall, MD ..... 336

**FROM YOUR ASSOCIATION**

1 Picture = 1,000 Words ..... 277
Correspondence ..... 284
Missouri Medicine in the News ..... 286
Member Services Directory ..... 340

**ON THE COVER**

MSMA announces the formation of the Women Physicians Section. Details at www.msma.org/women-physicians-section.

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# On the Brink: Why the U.S. is in Danger of Losing Measles Elimination Status

*by Mary Anne Jackson, MD & Christopher Harrison, MD*

**As clinicians we need to make strong recommendations for maintaining on-time (if not accelerated) vaccine schedules.**



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In 2019, the twenty-two U.S. states have reported outbreaks. This means that a measles outbreak is not just a plane ride away but also could be just a bus ride or car trip away.

In the pre-vaccine era in the U.S., nearly all who were susceptible—up to 3-4 million individuals—developed measles each year, and in the early 1900s an average of 6,000 deaths occurred. In the 1950s and early 1960s, measles peaks, commonly noted during late winter and spring, were still associated with an increased risk for death (1 in 10,000 cases), especially in malnourished children.

Routine measles vaccination of infants at one year of age was introduced in 1967; however, because outbreaks continued, the Centers for Disease Control & Prevention (CDC) Advisory Committee on Immunization Practices in 1989 recommended a second dose of measles, mumps,

and rubella (MMR) vaccine before school entry. A significant drop in confirmed cases between 1993 and 2001 prompted a declaration that endemic measles had been eradicated in the U.S. in the year 2000.

In the next decade, spikes in the number of cases occurred sporadically, mostly linked to importation of disease in international travelers or to outbreaks in U.S. communities with large pockets of unimmunized. Outbreaks attracting particular media attention included the 2015 California Disneyland outbreak that resulted in multi-state spread as well as the 2017 Minnesota outbreak that occurred in Somalian Americans.

What makes the current statistics most concerning is that as of May 24, 2019, we now have 26 states (Arizona, California, Colorado, Connecticut, Florida, Georgia, Illinois, Indiana, Iowa, Kentucky, Maine, Maryland, Massachusetts, Michigan, Missouri, New Mexico, Nevada, New Hampshire, New Jersey, New York, Oklahoma, Oregon, Pennsylvania, Texas, Tennessee, and Washington) that have reported confirmed measles cases.[1] There have been seven states with ongoing outbreaks in the first four months of 2019—resulting in the largest number of measles cases in the last 25 years (Figure 1).

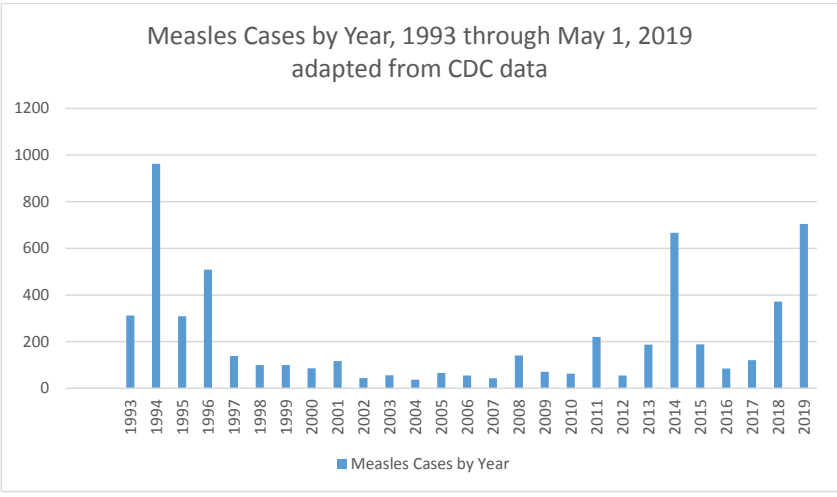



Figure 1. Measles Cases by Year

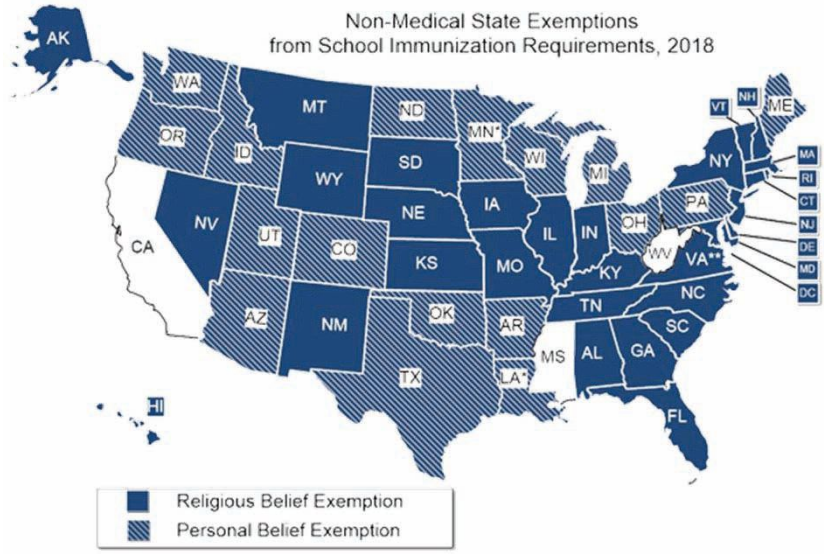



Figure 2. States Allowing Non Medical Exemptions

There are five likely reasons to explain why the 2019 outbreak is occurring and has been difficult to contain:

1. Disease is just a plane ride away given that multiple countries have substantial measles burden.
2. While national MMR adherence rates are at or near the herd immunity threshold of 93%, there are pockets of under-immunized or unimmunized.
3. Personal vaccine exemptions are allowed in 18 states and "hotspot" metropolitan communities have been identified (Figure 2).
4. Measles is highly contagious and spreads easily to susceptible individuals.
5. Measles is difficult to recognize in the prodromal stage.

## Not Just a Plane Ride Away

To flourish, measles needs introduction into the "fertile ground" of persons not immune to measles. Lack

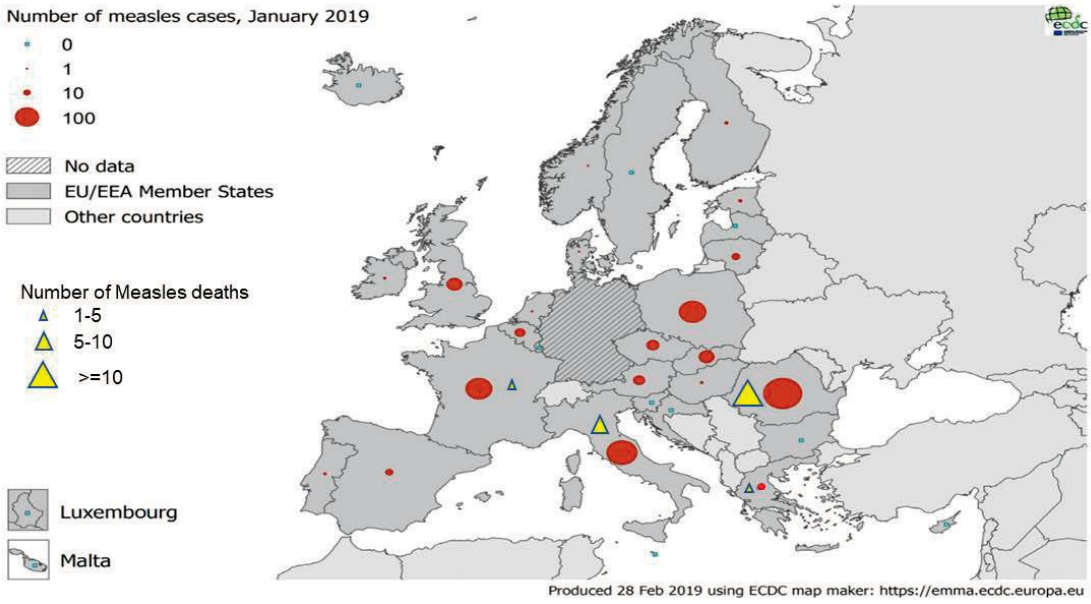



Figure 3. Measles Cases and Deaths in Europe from January 2018 – January 2019.
*https://ecdc.europa.eu/sites/portal/files/documents/measles-monthly-report-march-2019.pdf*

of immunity can be by choice (vaccine declination due to personal, philosophical, or religious reasons) or due to true vaccine-contraindication (e.g. immune-compromised hosts or those too young to be eligible for vaccine). Measles virus exposure of a cluster of non-immune persons creates a bigger ripple effect than if there is only an occasional non-immune person. Think of an exposure within a non-immune cluster as multiple stones causing multiple overlapping secondary ripples when skipped across a pond. In contrast, an exposure in a mostly immune population with herd immunity (>93% of exposed are immunized) is like a single stone dropped in a pond causing one small concentric set of ripples.

Measles introductions have classically been via a person who is in the incubation period traveling to the U.S. by airplane from a country already having an outbreak. Years ago, outbreak countries were mostly in the developing world. Not all of the top 10 countries for measles cases during the last eighteen months per the World Health Organization have been in developing countries; top ten measles countries include Madagascar, Ukraine, India, Nigeria, Kazakhstan, Chad, Myanmar, Thailand, Philippines, and Republic of Congo.[2]

Europe has also been a not uncommon measles source over the past ten years, with France, Italy, Romania, Greece, Macedonia, and Serbia having the highest European rates; and the UK and Turkey are not far behind (Figure 3).

## MMR Adherence is Not Uniform

But now in 2019, the 22 U.S. states (Figure 1) having reported outbreaks confirm that most, if not all, states have measles-non-immune clusters. This means that a measles outbreak is not just a plane ride away but also could be just a bus ride or car trip away. CDC reports of vaccine adherence show that MMR coverage varies by state.[3-5] Twenty-four states and the District of Columbia (DC) had 2017 MMR adherence rates below 93% at kindergarten age. [4] The lowest rates were in D.C. (~83%), Colorado, Kansas, Washington, Minnesota, Alaska, and Indiana.

Another recent report of a model predicting measles outbreaks used the number of international flights from endemic countries together with apparent clusters of under-immunized persons within states and even among zip codes within cities[6] to project Chicago, New York, Miami, Los Angeles, Washington state and mid-Texas as likely near-future measles epicenters (likely hotspots) (Figure 4).

## Nonmedical Exemptions Are Allowed in Most States

While all 50 states have measles vaccine

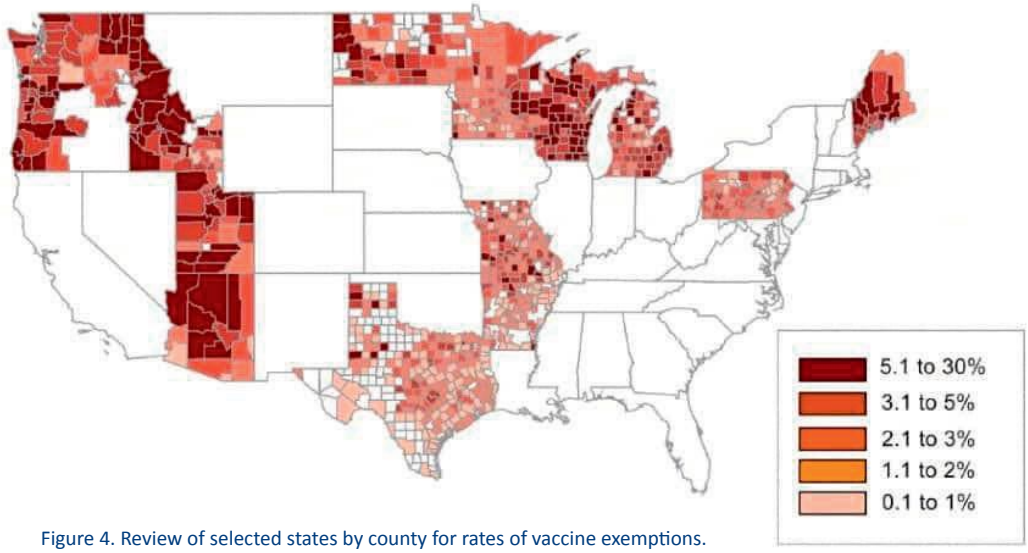



Figure 4. Review of selected states by county for rates of vaccine exemptions.

mandates for school attendance, almost all allow for religious exemptions and eighteen states allow for philosophical or personal exemptions.[7] The reported "hotspot" metropolitan locales where large numbers of kindergarteners have not received MMR vaccine have been linked to the increase in overall state nonmedical exemption (NME) rates. Cities with increased NMEs include Seattle and Spokane in Washington; Portland, Oregon; Phoenix, Arizona; Salt Lake City and Provo, Utah; Houston, Fort Worth, Plano, and Austin, Texas; Troy, Warren and Detroit, Michigan; Kansas City, Missouri; and Pittsburgh, Pennsylvania.[6] Data also demonstrate that areas with the highest NME rates were in rural counties, e.g. in the state of Idaho. It's critical to know that children with NME for MMR vaccine are 35 times as likely to develop measles as a child who has been immunized. Those children who develop measles and recover, still run the risk, estimated at 1:609 for those who are infected at age ≤12 months and 1:1367 <5 years, to develop a fatal, late stage complication of measles, namely, subacute sclerosing panencephalitis (SSPE) years later. Based on data from the CDC and California Encephalitis Project, such cases occurred in children with a median age of 12 years, but as young as 3 years and as old as 35 years.[8]

The median coverage for the two-dose schedule for MMR vaccine is 94.3% in the U.S.—but was below the herd immunity threshold of 93% in Alaska, Arkansas, Colorado, DC, Idaho, Indiana, Kansas, Kentucky, Minnesota, Ohio, Wisconsin, and Washington. Also remember that even in states with 93% coverage, clusters of non-immunized children can exist. [9]

## Measles is Highly Contagious

In addition to strengthening the emphasis on removing NME options, the national response to this outbreak depends on practitioners to promote MMR vaccine and expand access, and community campaigns to increase awareness. Awareness is critical for both the general public and medical providers because measles is one of the top three most contagious infections in the world, two to three times as contagious as mumps, rubella, smallpox, diphtheria, or polio. And unlike most other infections, it is spread airborne, meaning that spread doesn't require direct contact with an infectious person or fomite. Merely inhaling air in the same area as an infected person will transmit measles to a non-immune person, hence the extreme measures needed for infection control and quarantine practices.

## Measles Prodrome is Nonspecific

Another factor in potentially rapid and extensive spread is that there are typically 8-12 days of incubation, so a person can acquire measles from an exposure and travel long distances and across many

areas before prodromal symptoms begin. Diagnosing the prodromal symptoms as measles is also difficult because the fever, headache, and myalgia mimic many other infections. This results in a contagious timeframe of 5-21 days after exposure (patients can be contagious even before symptom onset), although contagion usually recedes four days after onset of rash in immune competent patients.

The good news is that we have a proven tool for treating measles now, e.g. Vitamin A supplementation. And, nutrition is generally better than in the early 19th century when measles deaths were more common. With over 800 cases and counting in the U.S. at the time of writing this article (mid-May 2019), this will be the biggest outbreak since the 1990s.

Hopefully, we will not see a measles death in the U.S. this year – or ever. But if the U.S. national outbreak is not controlled, deaths may occur as have been reported in Europe (33 deaths in the past 12 months)[10] (Figure 3). And by 2029, we could again start seeing the late and devastating complication of measles disease, subacute sclerosing panencephalitis (SSPE), a progressive and fatal dementia. We can only hope that the public health interventions added to individual clinicians doubling down on administering MMR per the recommended schedule (including catch up dosing) will curb this outbreak's momentum and prevent such tragedies.

One aspect of outbreak control may come down to accelerating MMR schedules (immunizing infants 6-12 months old and giving second MMR doses before 4-6 years of age) if public health officials deem it necessary at hotspots or for children traveling to U.S. hotspots. Accelerated MMR dosing of 6-12-month olds produces an immune response but such doses are not "valid" for school attendance in most areas. So reimmunization at 12-15 months of age is usually needed. A repeat dose is also a potential issue for patients receiving a second MMR before 4 years of age (also not valid for most school districts), given recent experience with waning protection against mumps developing five years after the most recent MMR.[11]

Of note, longtime measles expert, James Cherry, MD, has long been a champion of a second MMR at 1-3 months after the 12-15 month MMR dose to catch up the 5% or so primary failures, and this is an option per current Advisory Committee on Immunization Practices (ACIP) schedules. Regardless, we need to keep track of children getting accelerated MMR dosing to ensure the repeat doses at a future date do not fall between the cracks.

## Summary

As clinicians we need to make strong recommendations for maintaining on-time (if not accelerated) vaccine schedules. Most people listen to us when we are firm in our recommendations. And it is important now to ask the extra question to decide if an accelerated schedule is needed – "Any travel in the near future?" – but with a twist, i.e. it is not just foreign now, even a domestic travel can be to an outbreak area.

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# Law Enforcement Problems Associated with Medical Marijuana Legalization: A Missouri Perspective

*by Jeff Lofton*

**It is unrealistic to think that Missouri will enact medical marijuana without the myriad of law enforcement, educational, medical, judicial, social and motor vehicle problems occurring in other states that passed similar legislation the past.**

Following a majority vote on Amendment 2 in the November 2018 election, the state of Missouri embarked on what will likely be a perilous medicinal marijuana journey. Implementation of the law began in 2019. In other states passage of medical marijuana laws has created unique problems for law enforcement. As a Missouri Police Chief, I will address them in this article.

## Medical Marijuana in Missouri

The Missouri Division of Health and Senior Services will be overseeing the implementation of Amendment 2, which allows the dispensary, manufacturing and cultivating licenses to be awarded to qualified applicants. The legalization of prescription marijuana for purported health purposes will allow individuals to visit and attain the now-legal-item from one of 192 dispensaries throughout Missouri. Stemming from this legislation, several Missouri House bills have been submitted covering a wide range of topics including: giving priority to women and minorities who submit dispensary applications; changes to criminal penalties involving various narcotics, such as fentanyl and cannabidiol (CBD); allowing individuals to sell and transport up to two ounces of cannabis; and the act of expunging historical marijuana-related offenses once an individual gets approved for a patient identification card. With the passing of Amendment 2, the ripple effect of the marijuana bills waiting for discussion and vote, it appears Jefferson City, indeed all the Show-Me State, is looking 'green' for the foreseeable future.

CBD and hemp are not involved in this process and have been placed under the Missouri Department of Agriculture. The law enforcement perspective is not exactly clear, and adaptation is necessary. In other states law enforcement officers report far more problems with medical marijuana, even more problems with recreational marijuana and few problems with CBD and hemp.

## Challenges of Law Enforcement with Medical Marijuana

According to the Constitution of the United States of America, "The right of the people to be secure in their persons, houses, papers and effects, against unreasonable searches and seizures, shall not be violated, and no warrants shall issue, but upon probable cause, supported by oath or affirmation, and particularly describing the place to be searched, and the persons or things to be seized." In considering the Fourth Amendment, it should be understood that an exception exists called the Plain View Doctrine. If a law enforcement officer observes any potential evidence or contraband in plain view during a lawful contact or interaction, the officer will normally move directly to securing the item(s) and then deal with the issues at hand. A common occurrence of this exception is a traffic stop contact where the operator of a motor vehicle has committed a violation of motor vehicle law (ex: exceeded posted speed limit, failed to signal, equipment failures,



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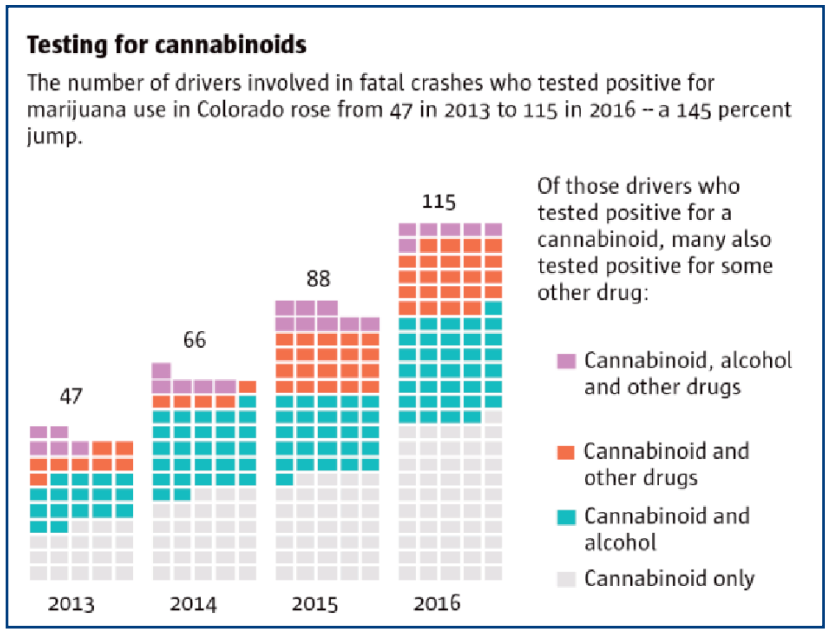

Illegal growing and sales of marijuana to avoid taxes are a problem for law enforcement.
*Source: Getty images*

etc.) and contact is made by the law enforcement officer at the driver-side window of the vehicle. Then, while making contact with the operator, to investigate the observed violation, the law enforcement officer notices in plain view an open metal grinder and a small clear bag partially filled with what appears to be a green leafy substance. At that point, in layman terms, the officer temporarily 'owns' the car. If the items are not visibly seen, but an odor of burnt or fresh marijuana is detected by the officer from his/her position next to the vehicle, this too would qualify under the Plain View Doctrine.

Amendment 2 creates further troublesome gray areas for law enforcement to wade through. Will some new or seasoned officers now be reluctant to investigate what they observe in plain view, specifically through odor? If an individual who was removed from their vehicle, placed roadside for search of person and property based on plain view odor of a now-legal substance, and was found to possess the marijuana legally, now have platform for a winnable lawsuit? Will the reactive community policing agencies simply ignore any type of marijuana activity?

In contrast to the gray area of speculation and argument, there are items I believe are solidly in the 'You can bet your house' categories that will definitely increase. Will there be an increase in driving under the influence of marijuana incidents? Yes. There are liquor laws, yet people still consume alcohol and operate motor vehicles. There are also posted speed limits and littering laws, yet people still drive faster than they are allowed and toss plastic and paper products into the environment. People are people, and just because something is legal, doesn't mean it will be perfectly followed with adherence and a genuine concern for fellow citizens. It has not happened in the past; it is not happening now, and it is unlikely that it will happen in the future. Will there be an increase in dealing with individuals with co-occurring conditions, assaults, burglaries, and further graduation to harder substances? Yes. There are individuals existing in society everywhere who have an undiagnosed mental condition. Gaining access to marijuana could possibly lead to an even more complex condition with substance abuse and mental health disorders. My responses are based on my law enforcement experience, but also a review of other states further down the medical marijuana problem strewn roadway.

Personally, I have dealt with individuals who typically use a small amount of marijuana. A vast majority have been docile. The atypical, but not rare, marijuana user who may have a criminal record, be coming off a multi-drug high, have mental diseases, or is a carrier 'mule' for a criminal distribution ring are the types of individuals who will exhibit violent behavior. They often times attempt to flee from capture on foot or in a vehicle, and rarely are taken into custody without resistance. Missouri peace officers and the general public will be put at increased risk with the new medical marijuana law. Property crimes also increase in areas where narcotics are present, due to the need of abusers to steal items which can be sold or traded for drugs, food, or rent.




## Marijuana Law Enforcement Case

When some ill-informed people speak about marijuana being "nothing big to worry about," "it's just a plant," or "it's not any different or worse than cigarettes or alcohol," I immediately think of a male I've had recurring contact with over the past ten years. I'll refer to this individual by the name of Eric (not his real name), whom I first came in contact with when he was the age of 17. My agency was notified of a homeowner who requested a visit to his residence because he believed his son and nephews were involved in illegal activity. When I arrived, the gentleman invited me into his residence after explaining what he awoke to that morning. He informed me that he observed his son and two nephews asleep in the living room common area of the home, along with some odd clear glass bowls and a sweet type of smell. After entering the residence, I contacted all three males in the living room and upon identification I learned two were age 17 and the other was 15. All three had glass bongs with water and burnt marijuana residue present, along with a shoebox in the middle of the floor which contained more bongs and one-hitters, along with a small amount of fresh marijuana bud. This is where I met Eric for the first time, but it would definitely not be the last.

As we fast-forward through the last ten years since that incident, where I transported Eric to jail to be booked in as an adult for the first time, Eric has progressed from simply using personal amounts of marijuana, to selling small amounts to friends, to selling larger amounts to individuals who contacted him through his friends, to using methamphetamine, to then sell and use methamphetamine on a regular basis. Eric is not the only individual I, and other law enforcement officers, have observed escalate from marijuana to something else.

## Marijuana Is A Gateway Drug

Marijuana is most definitely a gateway drug. Regular marijuana users increase the risk of progressing to other more addicting, more dangerous and often illegal narcotics. Missouri held the top spot for all-things-methamphetamine for approximately a decade. Across the USA, meth was often called '417' as the slang term for the drug. This is the telephone area code for southwest Missouri which had the nation's highest meth arrests. Missouri still ranks anywhere from one to three for meth use and other narcotic problems as well. I have seen a spike in fentanyl and heroin use, and prescription medication abuse in my area of Southwest Missouri, but marijuana still gets collected as evidence more than of any other type of controlled substance. In specific areas throughout our jurisdiction, any of our law enforcement officers could stop ten cars and at least half of them would have some sort of narcotic on board. School districts in Christian County are also observing things never before witnessed: suicide threats on campus every week, liquid marijuana smoking devices (vapes, e-cigarettes,) where

detection is difficult, marijuana and meth sales on campus, threats of gun violence, and more.

## Law Enforcement Problems Created by Medical Marijuana

As a police officer, I've never been one to see a law enforcement problem, fight it, then all of a sudden sit back and just accept that so many people are involved in an illegal activity that we might as well legalize a portion of it so we can at least make some money off of them. Currently, law enforcement can attack certain situations with a task force, based on leads or probable cause attained by a trash rip, vehicle stops, confidential informant-controlled buys, etc., and through proactive patrol with the uniforms on the street who stop vehicles every day trying to locate narcotics. The problem we face is the fact we are outnumbered. Law enforcement is not the most desired career to embark upon at this time, and a lot of agencies are suffering from low employee numbers and difficulties with recruiting. The national average sits at around 17 to 18 law enforcement officers for every 10,000 citizens. Factoring in all the calls for service; past-burglaries, 911 emergencies, thefts, assaults, suspicious vehicles, child sex crimes, domestic violence issues, and so many more, the amount of total time available to focus on narcotic enforcement is very low. Even with the positive effect we make when we are able to get narcotics off the street, it feels as if we are moving slowly while everything around is bypassing us at a quicker pace. The opioid epidemic did not happen overnight either. If someone with foresight would have made a move five to ten years ago, we may not be where we are today with that issue. Marijuana becoming legal and more easily obtainable in our state is a different animal, and once it is fully functional, it will be very difficult to bottle up that genie if matters start sliding sideways.

With prescription marijuana, it appears to be simple math in factoring new users into the consumption group. There is a percentage of the population who illegally use marijuana now, and there is also a percentage of that population who are the growers and distributors of the product. The individuals who will be added to this mix are the individuals who have been reluctant to attempt purchase of marijuana illegally, or may have driven to another state to purchase the illegal substance at a legal distribution point there.

During a recent Marijuana Summit held in Springfield, Missouri, several topics were discussed, but the focus was on problems facing law enforcement, regulations and overall rules. According to the Missouri Department of Health and Senior Services (MDHSS), that will be overseeing this project, they will have around 15 employees in-office to handle all the licensing procedures and 20 employees in the field for licensing compliance checks. Using Colorado as a model, Missouri expects to have approximately 2-3% of the total population utilizing a legal medical marijuana card, which is somewhere around 150,000 individuals. The medical cards will cost $25.00 per person and will expire one year from issue date, requiring the individual to pay another license fee to update their medical marijuana card for another year period. The first issue date for medical marijuana cards was July 4, 2019, and the overall rules for every stakeholder involved was out by June 4, 2019.

'Doctor shopping' is a concern which will be addressed in rules and monitoring, including a seed-to-sale program tied to licensing and a prescription monitoring system. The seed-to-sale program will follow a seed from planting, through harvest, where a number attached to that particular plant and product will follow through to the dispensary and end sale to the consumer. Prescription monitoring will be able to detect any individuals who purchase their legal amount (4 ounces) of medical marijuana at one dispensary, then move to the next for another purchase, then another, and so on. By all accounts, prescription monitoring will take place in real time, yet to detect and catch an offender in the act, someone will need to be watching and researching the database as sales are occurring, otherwise the investigation and punishment will have to occur on the backend when the individual is the subject of a search warrant, arrest warrant, or administratively through reapplication for their medical card. The overall feeling is 'doctor shopping' probably will not be the largest issue. If there are roughly 15,000 doctors in Missouri, the MDHSS estimates around 500 to be the prescribers for patients requesting medical marijuana cards. Of the 500, there will most likely be 80-90 which will be handling the majority of the prescriptions. Those 80-90 prescribing doctors will probably be interested in making a quick $150 through office visit and prescription, and then move on to the next person. Doctor shopping is also a frequent *modus operandi* for opioids.

Medical marijuana is mandated to be utilized in private after being purchased in child-proof containers and transported back to a private location for consumption. It is uncertain how law enforcement will handle traffic stop situations where there are multiple individuals in a vehicle, only one has a medical marijuana card, and there is an odor emitting from the vehicle consistent with a fresh marijuana smell. There may not be consistency across Missouri.

## Home Grown Marijuana and Illegal Growing

The home-grow aspect will be the most difficult to navigate. The MDHSS will be providing licensing for home-grow operations for $100 per license, which will expire one year from issue and be available for renewal upon payment of the licensing fee. A home-grow can expect up to six plants present in the license holders grow area. There is a caregiver section to deal with as well. A caregiver can grow plants for individuals who cannot grow their own and provide that harvest to the designated individual. Additionally, those caregivers will be allowed to possess up to three plants for each individual they are caring for, and there is currently no check and balance in place for compliance. Essentially, law enforcement could somehow find themselves in a residence, for any numerous lawful reasons, and run into an individual possessing a medical marijuana card, home-grows, and claims to be a caregiver. That person could be found in possession of 15 marijuana plants (six for home-grow, three for care recipient A, three for care recipient B, and three for care recipient C), yet lawful compliance is unattainable due to the caregiver not being held to forego recipient information under the Health Promotion and Protection Act (HPPA).

Due to medical marijuana being a mostly cash-oriented business, there are also problems with banking facilities. Federal Deposit Insurance Corporation regulations along with bank policies and procedures, having large cash deposits at the end of the business day at banking facilities may become problematic; total deposit untraceable to fully legal business activities, as well as any involvement with organized crime from outside our borders. According to a current deputy chief of police, who worked several years in Colorado law enforcement, a vast majority of warehouse operations are not legitimate businesses and are connected to cartels located in the country of Mexico. Colorado was the target state for cartels in the supply chain for the eastern portion of the United States, and now decisions will most likely be made to move some operation east to Missouri or Illinois for better logistics for those illegal operations. The trickle effect on a significant amount of marijuana activity moving into the United States is the poppy production increase south of the border, providing more opportunity for heroin production getting pushed north into our country as well.

*Forbes* had an article in March 2018, stating officials in California attribute recreational marijuana use becoming legal as associated with increase in home invasions, robberies, and violent crimes. California expects to show over $5 billion in revenue with current debt around $39 billion; at what cost to society are they willing to wager? Colorado is sharing a similar story, as Governor Hickenlooper told CNN in April 2018, that he would consider recriminalizing recreational marijuana use due to spikes in violent and overall crime, as well as an increase in homeless and transient population in their jail facilities. Colorado shows over $128 million per month in marijuana sales, but increased hospitalization due to marijuana exposure, surge in organized crime, and illegal grows show net losses of revenue not gains.

## Conclusion

It is unrealistic to think that Missouri will enact medical marijuana without the myriad of law enforcement, educational, medical, judicial, social and motor vehicle problems occurring in other states that passed similar legislation the past. It is likely that Missouri will find the net financial costs of easily available medical marijuana are negative rather than adding to government revenue. Experience has shown that those that profit legally and illegally from marijuana sales will begin efforts for recreational marijuana legalization in the not distant future. Law enforcement in Missouri needs additional resources to protect its citizens from the increased demands caused by enacting medical marijuana. **MM**

# Medical Marijuana: The Australian Experience



*by David J. Castle, MD, Nigel Straus, MD, Amanda Norman, BA & Yvonne Bonomo, MD*

**Cannabis is an addictive substance and has the propensity to worsen the course of psychotic disorders such as schizophrenia, and can cause cognitive impairment. Such factors need to be considered in any use of cannabis as medicine.**



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Medical marijuana, more accurately termed medicinal cannabinoids, has become big news in Australia over the past few years. Initially prompted by two states in Australia, the Federal Government has followed suit in recent years. In 2014, the New South Wales state government introduced the Terminal Illness Cannabis (TIC) Scheme (now known as the Medicinal Cannabis Compassionate Use Scheme)[1] and associated amendments to legislation that made it possible for registered persons with a terminal illness to be in possession of lawfully prescribed cannabis.[2] In the state of Victoria, medicinal cannabis was legislated in 2016, under the Medical Cannabis Act. The moves to allow the use of 'marijuana as medicine' in Victoria were driven largely by press coverage of parents of children with severe intractable epilepsy (mostly Dravet's syndrome) who purportedly found cannabis to be the 'only solution' to their children's persistent seizures and who were having to act outside the law to source and administer it.[3] The state government is now supporting a medicinal cannabis industry, with a number of companies developing medicinal cannabis plantations and extraction technologies. The potential for states (e.g. Victoria) to become world-leading producers

and exporters of medicinal cannabis has much appeal to politicians and entrepreneurs alike. Other states of Australia are coming on board, with a view to potential profits accruing, with dividends for the state coffers. Meanwhile, the Federal Government of Australia has amended the Narcotic Drugs Act of 1967 to allow cultivation of cannabis for medicinal or scientific purposes: similar to what already happens with opium production from poppy cultivation.[4]

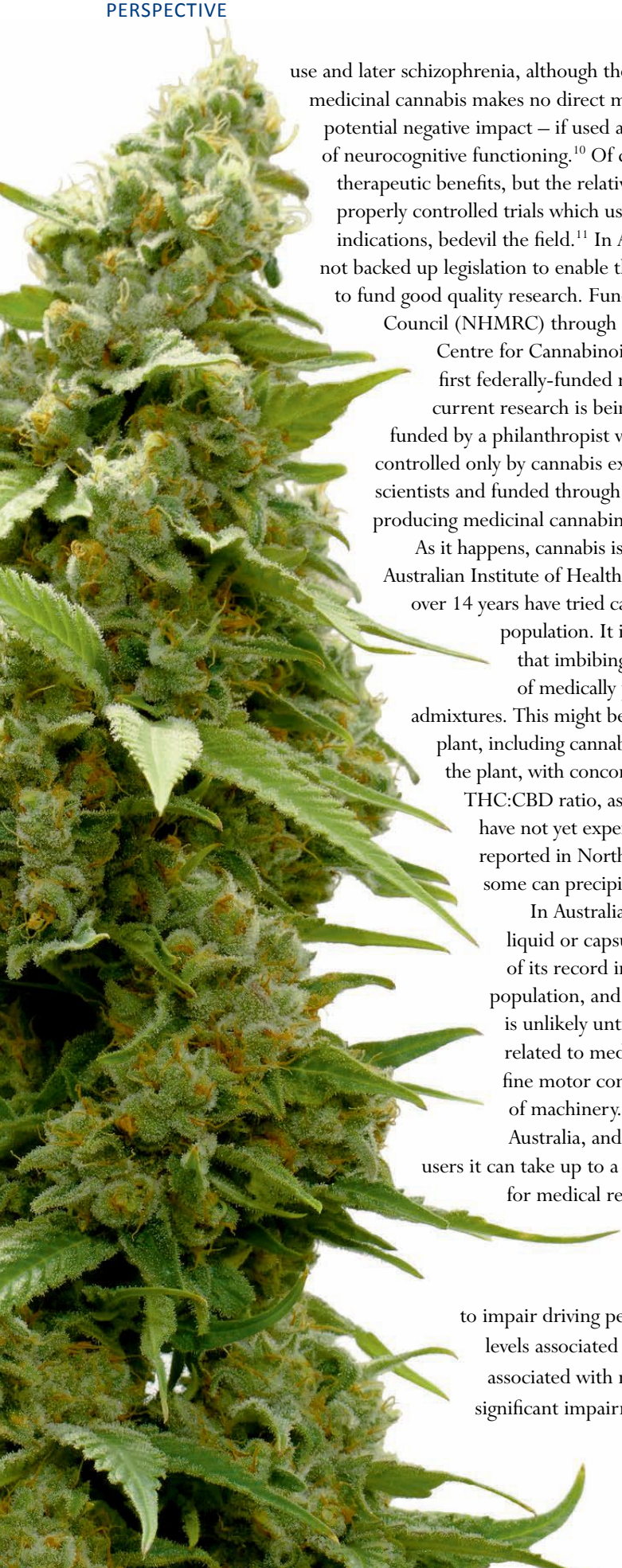
Opening the door to use of cannabis for intractable childhood epilepsy was seen as a highly concerning Pandora's Box by some and a welcome Trojan Horse by others. Most vociferous, perhaps, have been members of the medical profession, with many seeing the potentially addictive and psychotomimetic properties of cannabis to be of particular concern. The field has also been perturbed by the association of drug use and violence, most notably in hospital emergency departments and psychiatric inpatient units. It is alcohol that remains the most troublesome drug in this regard, followed by crystal methamphetamine. These are rarely emphasized in sensationalized reports, and cannabis is tarnished by association. A case in point is the attorney-general of the state of South Australia vowing to get tough on possession of cannabis, after a fatal shooting of a teenager by another teenager who tested positive for ecstasy, alcohol, and cannabis. [5]

On the other hand, many people see the pursuance of criminal controls over cannabis as largely futile, and welcome the opportunity to use it to alleviate suffering. Areas of most interest medically have been spasticity associated with multiple sclerosis. Nabiximols – a spray formulation of tetrahydrocannabinoid (THC) and cannabidiol (CBD) - has a Federal Therapeutic Goods Administration indication for this; childhood epilepsy has a trial using cannabidiol (CBD) that has been supported by the Victorian government; palliative care which the New South Wales government has supported; chronic pain as a specific treatment and for the potential to reduce the use of opioids; and chronic insomnia, with trials funded by industry. Additional studies are planned for both nausea associated with chemotherapy and to promote appetite in people with diseases such as HIV-AIDS. In psychiatry, there has been interest in the use of CBD for anxiety as well for its putative antipsychotic properties. But access to product, cost, and lack of clarity about what combinations of cannabinoids are most likely to be effective for specific conditions are causing considerable difficulty for practitioners. Added to these barriers are bureaucratic complexities, albeit these are becoming more streamlined with time.

In terms of prescribing cannabinoids, a crucial enabler was the Australian Therapeutic Goods Administration (TGA) in 2017 rescheduling cannabis from schedule 9, a prohibited substance, to THC as schedule 8, a controlled drug, and CBD as schedule 4 drug, therefore not subject to the federal or state-based processes required for prescribing other cannabinoids. Thus, technically any medical practitioner can prescribe medicinal cannabinoids, by applying - on a patient-specific basis - for an exemption to do so under the TGA's Special Access Scheme.[6] This requires a specific form of medicinal cannabis to be specified for a particular indication in a particular individual, with a declaration that all other therapeutic endeavours have failed and that the use of cannabis has support from all the patient's treating doctors. Once this approval has been granted, further sign-off is required from the local state health department, along with signed consent from the patient.[7] The patient has to foot the bill for the product. Currently reliance is placed upon imported product, at a cost of some AU$300 a month. This cost is prohibitive for many individuals, resulting in patients, or their carer, turning to illicit sources of cannabis.

The alternative to the individual patient prescribing process is for a practitioner to become an 'authorised prescriber' of medicinal cannabis.[6] This is also administratively somewhat burdensome, with over 50 pages of material having to be completed and delivered to the TGA. Another twist is that the practitioner requires their application to be reviewed and supported by an ethics committee: the Royal Australian and New Zealand (ANZ) Colleges of Physicians, of General Practice and of Psychiatrists have no established mechanisms in this regard, leaving interested practitioners turning to state-based non-for-profit organizations such as the (Victorian) National Institute of Integrative Medicine.[7] Notwithstanding this, Authorised Prescribers are still somewhat restricted in terms of what products they can prescribe, as well as the indications. It is hardly surprising that very few medical practitioners have followed this process; only 35 at this time of writing.

In terms of medical use, the fact that cannabis is an addictive substance and that it has the propensity to worsen the course of psychotic disorders such as schizophrenia, have been evidenced as cautioning against its being used as medicine. Particular concerns have also been raised including by the Royal ANZ College of Psychiatrists (RANZCP),[8] in various submissions to state and federal governments about its use in young people, given evidence suggesting a potential causal association between teenage



use and later schizophrenia, although the latest memorandum from the RANZCP on the use of medicinal cannabis makes no direct mention of this.[9] Australian researchers have also pointed to its potential negative impact – if used at high enough doses and for long enough - on certain aspects of neurocognitive functioning.[10] Of course all this needs to be weighed against its potential therapeutic benefits, but the relative paucity of firm data about efficacy and side effects in properly controlled trials which use specific combinations of particular cannabinoids for specific indications, bedevil the field.[11] In Australia, both state and federal governments have arguably not backed up legislation to enable the use of medicinal cannabis, with any ongoing commitment to fund good quality research. Funded in 2017 by the National Health and Medical Research Council (NHMRC) through the Centres for Research Excellence scheme, the Australia Centre for Cannabinoid Clinical and Research Excellence (ACRE) is Australia's first federally-funded research centre in medicinal cannabinoids.[12] Much of the current research is being conducted under the auspice of the Lambert Foundation,[13] funded by a philanthropist whose grand-daughter's epilepsy was purportedly able to be controlled only by cannabis extract. Other research is largely being driven by interested scientists and funded through the growing panoply of private companies with an interest in producing medicinal cannabinoids and for commercial profit.

As it happens, cannabis is widely used for recreational purposes in Australia. The Australian Institute of Health and Welfare data from 2016[14] show over a third of Australians over 14 years have tried cannabis, and 'recent use' was reported by 10% of the adult population. It is relatively cheap and easy to access. Also, users often report that imbibing whole plant leads to very different effects than ingestion of medically prepared cannabidiol or delta-9-tetrahydrocanabinol admixtures. This might be due to various interaction effects of the constituents of the plant, including cannabinoids and terpines. Many people will thus continue to use the plant, with concomitant risks relating to the variability in potency, in terms of THC:CBD ratio, as well as imbibing it by smoking, often mixed with tobacco. We have not yet experienced the advent of very high potency cannabis as has been reported in North America,[15] but synthetic cannabis products are available and some can precipitate severe psychotic reactions.

In Australia, medicinal cannabinoid products will largely be in oil-based liquid or capsule form (nabiximols is a spray). Australia is rightly proud of its record in reducing rates of cigarette smoking amongst the general population, and support for smoked cannabis, even if for medicinal purposes, is unlikely until thorough evaluation is undertaken. A further problem related to medicinal cannabis is the impact of THC on concentration and fine motor control, and the negative effects on driving ability or the use of machinery. As road-side drug testing is becoming more common in Australia, and given the very long elimination half-life of THC, (in chronic users it can take up to a month to wash out of the body), people prescribed cannabis for medical reasons may be restricted in terms of driving and certain other activities e.g. use of heavy machinery. A recent review which examined the effects of nabiximols in patients with spasticity associated with multiple sclerosis reported it not to impair driving performance.[16] It is worth remembering that the THC blood levels associated with medicinal cannabis are often much lower than those associated with recreational cannabis use. The blood level associated with significant impairment is yet to be determined.

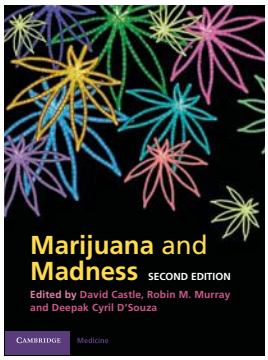
BOOK REVIEW

# Marijuana and Madness

by David Castle, Sir Robin M. Murray, and Deepak Cyril D'Souza

Cambridge University Press
ISBN-13: 978-1107000216
ISBN-10: 1107000211
Available on Amazon

The second edition of this critically acclaimed and award-winning text provides a comprehensive overview of the psychiatry and neuroscience of Cannabis sativa (marijuana). It outlines the very latest developments in our understanding of the human cannabinoid system, and links this knowledge to clinical and epidemiological facts about the impact of cannabis on mental health. Clinically focused chapters review not only the direct psychomimetic properties of cannabis, but also the impact consumption has on the courses of evolving or established mental illnesses such as schizophrenia. Effects of cannabis on mood are reviewed, as are its effects on cognition. This new edition has been extensively updated and expanded with 10 new chapters, to incorporate major new research findings.




### *Reviews*

"The editors and publishers of this book have responded to a need for clear, research-based information on a topic of great current concern. They have done an excellent job." American Journal of Psychiatry

"The chapters are compact but filled with quality research and sophisticated, in-depth analysis. The authors do not oversimplify or overemphasize the evidence. We congratulate them on their accomplishment and recommend this book enthusiastically for all clinicians and researchers interested in substance related issues." Journal of the American Medical Association

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The challenge for Australia will be to make available high quality medicinal cannabis products and develop a sound scientific evidence-base for their use. Of course, this is hardly unique to our country, and many lessons can be learnt from those jurisdictions which have more experience in the field. A potential area of concern is that medicinal cannabis will become touted as a 'cure all' by those with a vested interest in selling it, albeit Australia does not allow direct-to-consumer advertising for prescription medications. We would call on our state and federal governments to put in place comprehensive monitoring systems and tracking of outcomes associated with medicinal cannabis, such that a 'real life' scientific evidence base can be developed.

We also support properly conducted trials of medicinal cannabis in its various forms and presentations; with careful scrutiny of any adverse effects both at an individual patient level as well as more broadly in society as messaging that cannabis is 'safe and good for you' could potential encourage use, with potential detrimental effects, notably amongst young people whose brains are still developing and in whom drugs such as cannabis can have negative effects on cognition and mood and (in those with a vulnerability) psychosis.[17]

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# Mandatory Blood Testing:
## *When can police compel a health provider to draw a patient's blood to determine blood levels of alcohol or other intoxicants?*

*by Wakaba Tessier, JD & Wendy Keegan, JD*

### Introduction

In 2017, 304 of the 930 motor vehicle traffic fatalities in the state of Missouri were alcohol-related. During the same year, there were 12,747 alcohol-related traffic fatalities nationwide.[1] It is no surprise that legislators and law enforcement have taken steps to combat this severe problem. Unfortunately, while providers undoubtedly support the cause, the approach taken in many states has created some tension between the legal and medical worlds.[2]

Health care providers are accustomed to the uncertainty that inevitably accompanies patient care. Consider the following hypothetical situation: an individual involved in a car accident is escorted to the hospital by police who demand the physician take a blood sample. If the patient refuses to consent to testing, the physician may be left in an ethical gray zone with potentially serious legal implications. A question presented the physician might be: "Am I required to perform a blood draw?" This is more than just an anecdote to illustrate the competing responsibilities of health care providers. Alex Wubbels, an emergency room nurse at the University of Utah, experienced this quandary firsthand in 2017.

After reporting to the scene of a fiery car crash, Salt Lake City Detective Jeff Payne transported an unconscious patient, a semi-truck driver and crash victim, to the emergency room. Though the patient was not under arrest, Payne communicated to Wubbels that he wanted to take a blood sample to determine whether or not the patient was impaired. Wubbels calmly refused, citing an internal policy that required either an arrest or a warrant to draw blood from an unconscious patient. Payne responded by explaining Utah law and arguing a blood draw was appropriate under the circumstances. Disagreement then escalated into dispute, and in the highly-publicized body camera footage, Payne can be seen handcuffing Wubbels and forcibly removing her from the ER for failure to comply with his orders.[3]

Heath care providers have dual loyalties that require them to uphold and respect patient autonomy while also serving the public at large by reporting certain public health hazards.[4] As evidenced by Wubbels' story, mandatory blood draw statutes bring these co-existing duties into conflict. "I don't hold any animosity towards [Wubbels]," said Payne in a 2018 interview. "She was doing her job. I was doing my job. Unfortunately, it conflicted."[5] The following article discusses the dilemma Missouri providers may face in adhering to similar laws.

### Competing Theories on Mandatory Blood Draws

Should providers comply with police orders against a patient's expressed wishes and risk exposing themselves to a battery lawsuit, or accept patient refusal in spite of police orders and face potential obstruction charges? There is, unsurprisingly, no easy answer. Not every situation will be





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like Alex Wubbels'. First, Missouri law, discussed below, at least marginally differs from Utah law in ways beyond the scope of this article. Second, internal policies on the subject are inevitably diverse across localities and types of institutions. Third, the circumstances of the accidents precipitating the blood draw requests, as well as the conditions of the patients involved and the training of the requesting officers, will vary widely between each situation. Therefore, it is important that providers seek to understand their specific health care institution's policies regarding mandatory blood draws. Regardless of the nuances of your institution's unique policy, it is important to be aware there are two broad, competing theories on the matter, the details of which may help you decide what to do if similar situations arise in your own health care practice.

### *I. Providers should follow the requests of law enforcement.*

Missouri, along with all 49 other states, is an implied consent state, meaning anyone driving on Missouri's roads has presumptively consented to various chemical tests for intoxicants (including breath and blood tests) unless consent is expressly revoked.[6] Accordingly, Missouri statute Section 577.029 states, in pertinent part: "A licensed physician, registered nurse, phlebotomist, or trained medical technician, acting at the request and direction of the law enforcement officer . . . shall, with the consent of the patient or a warrant issued by a court of competent jurisdiction, withdraw blood for the purpose of determining the alcohol content of the blood."

**Consent.** When patients are cooperative and do not object to blood tests, no problem arises. Similarly, in cases of patient death, unconsciousness, or incapacity, implied consent laws allow police to order providers to perform blood tests.[7] Section 577.033 provides that patients "incapable of refusing to take a test" have not withdrawn consent. Note that even in cases where a patient can and does withdraw consent, "[t]he absence of consent, implied or otherwise, is not an absolute barrier to the admissibility of the results of a blood test."[8] A properly-issued warrant overrides patient refusal.[9] Thus, consent is not generally a requirement if officers present a warrant to obtain blood.

**Warrant.** While a warrant is the "gold standard" in this context, it is also not necessarily a prerequisite to drawing the blood of an objecting patient. Decisions from both the Missouri and U.S. Supreme Court have carved out a narrow exception to the warrant requirement. The court may determine from the totality of the circumstances (a combination of factors that prevent officers from obtaining warrants quickly thereby impeding the preservation of blood evidence) that a warrantless blood draw is reasonable.[10] Improvements in technology in the past decade have decreased the time and effort required to obtain a warrant, making this scenario less likely.[11] Nevertheless, a warrantless blood draw may be appropriate when an officer reasonably believes there to be an exigency, beyond just the natural metabolism of alcohol in the bloodstream, because the delay necessary to obtain a warrant threatens destruction of evidence.[12]

### *II. Providers should refuse to follow the requests of law enforcement.*

Although Missouri statute Section 577.031 provides immunity to persons ordered by the police to draw blood, "willful or wanton acts" are not protected from civil liability. The statute states, in relevant part: "No person who administers any test . . . upon the request of a law enforcement officer, [and] no hospital in or with which such person is employed or is otherwise associated or in which such test is administered . . . shall be civilly liable in damages to the person tested unless for gross negligence, willful or wanton act, or omission." A provider's decision to comply with police orders against a patient's expressed wishes might be under the circumstances found to be a "willful or wanton act" that takes the provider outside the realm of immunity. Based on the language in Section 577.029 and other relevant Missouri statutes, however, providers may be able to refuse to draw a patient's blood absent the patient's consent or, alternatively, a warrant (but see previous discussion regarding warrants).[13]

**Consent.** Even absent outright refusal from a patient, a provision of Section 577.029 allows providers to decline to draw blood in circumstances where he or she believes, based on his or her good faith medical judgment, that doing so would "endanger the life or health of the person in custody." This is further buttressed by medical ethics requiring providers to do no harm.[14]

**Warrant.** If the police do not have a warrant, a patient typically maintains a right of refusal to participate in blood alcohol tests in spite of Missouri's mandatory blood draw statutes.[15] Should a patient choose to exercise that right, however, they may face severe legal repercussions regardless of their reasons for doing so (i.e., a patient who refuses testing because of a fear of needles will face the same consequences as a patient refusing because of what the test will reveal).[16] Missouri statute Section 577.041 evidences the consequences to patients for revoking consent: if a patient who has been arrested or detained for suspected drunk driving refuses to submit to a blood

test, then (1) "evidence of the refusal shall be admissible in any proceeding related to the acts resulting in such detention, stop, or arrest," and (2) "his or her license shall be immediately revoked." This same statute requires that the requesting officer inform the patient of these potential consequences of refusal.

## Best Practices

Based on the above information, what can health care institutions and providers do to resolve the conflict between their competing obligations? We suggest the following be considered.

Health care institutions, such as hospitals, can:

- Educate providers on the applicable laws and clarify institutional positions and policies with regard to mandatory testing.
- Notify local law enforcement of internal policies in advance and work with authorities to establish guidelines that meet both police and provider needs.
- Explore options for joint training to facilitate ethical collaboration and overcome barriers to police-provider partnerships.
- Consider designating an emergency department liaison to work directly with police to optimize communication.
- According to certain literature, consider requesting law enforcement affirm all involuntary blood samples are used solely to determine patient blood alcohol content or asking for written confirmation of sample destruction after testing to further protect patient privacy.[17]

Individual providers can:

- Upon refusing a request, clearly communicate his or her rationale for doing so—including citing internal policies, if applicable—and carefully document conversations and interactions with the police on internal forms.
- Involve the hospital's legal or risk management department(s) as early as possible when mandatory blood draw situations arise.
- Inform the patient, if possible, which actions are primarily intended to ascertain or improve his condition and which are intended to serve the interests of the public.[18]
- Consider not participating in the treatment of a patient whose blood he or she drew on behalf of police to prevent an overlap between law enforcement functions and the provision of medical care.[19]
- Avoid physically restraining patients or performing blood draws on patients who have been restrained by law enforcement.[20]

## Conclusion

Though the circumstances of each patient encounter and blood draw request will be unique, this article offers some general insight into the practical effects of mandatory blood draw statutes for hospitals and health care providers. Hospitals should develop policies and procedures in this regard and communicate these policies to law enforcement before a mandatory blood draw situation arises.

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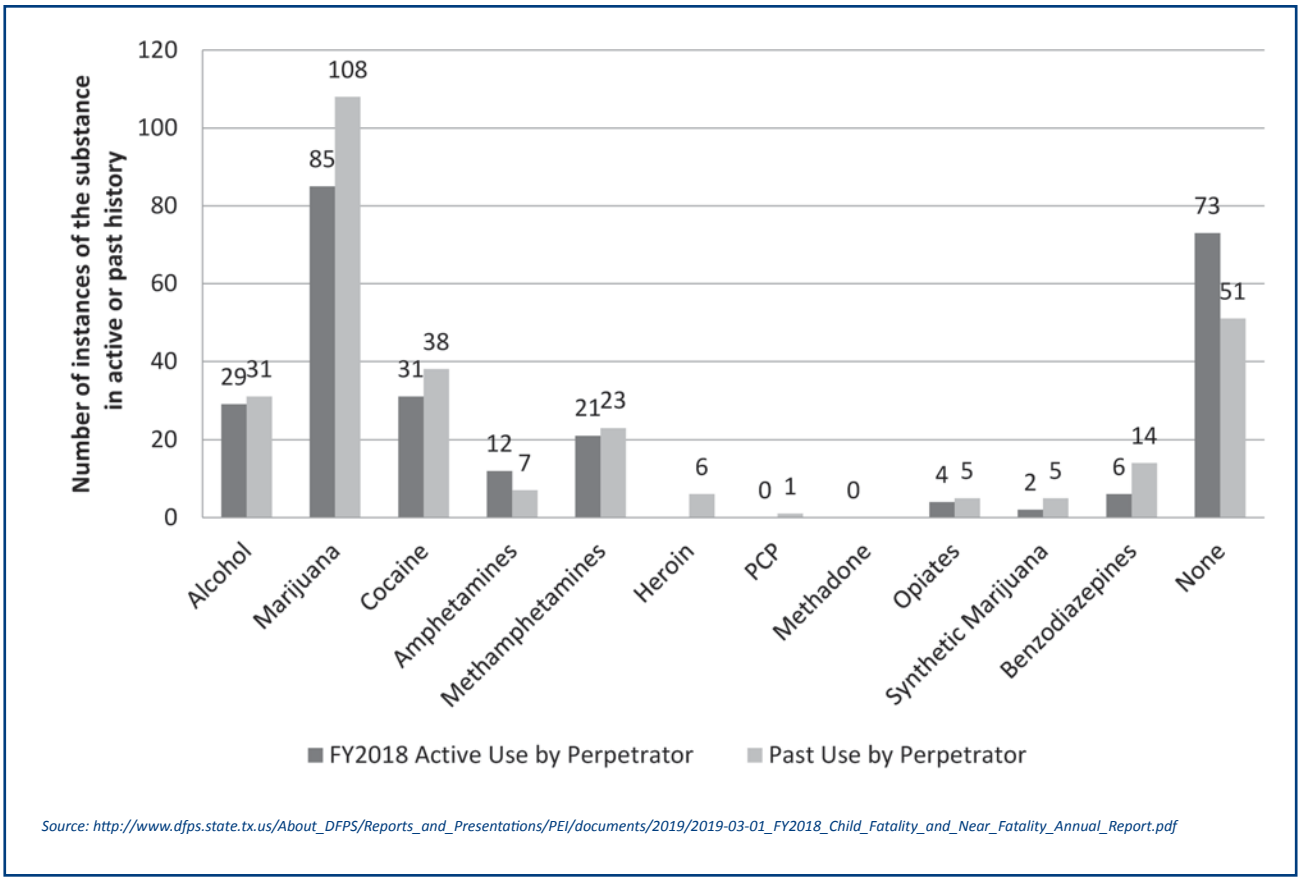
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18. Appel, supra note 4, at 153.
19. Id.
20. Missouri Hospital Association Health Institute Webinar, Federal and State Laws Related to Blood Draws and Requests from Law Enforcement (2017), https://web.mhanet.com/Legal/Resources/MHA_Blood_Draw_Webinar.pdf. Providers should also document the name of the law enforcement officer that requested the blood draw. **MM**

## 1 Picture = 1,000 Words

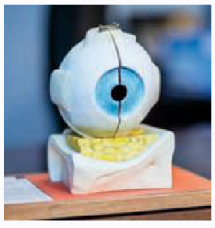


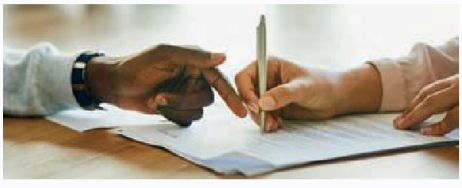
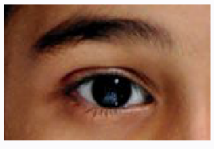

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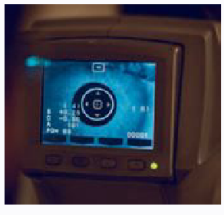
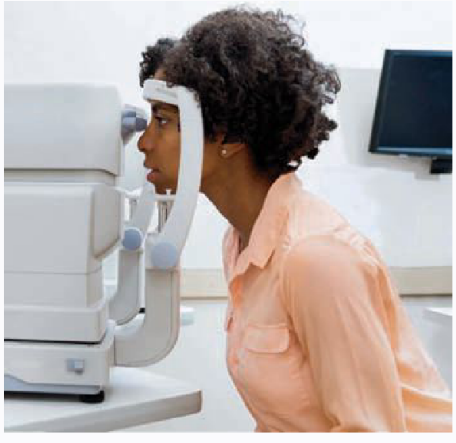
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# Physician Advocacy: The AMA Annual Meeting 2019

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

The Annual Meeting of the AMA House of Delegates (HOD), is democracy at its disorderly finest. Delegates representing all states and most medical societies meet in Chicago to consider what the AMA should do, whether direct action, policy, advocacy, or education. The AMA HOD regularly considers a wide range of issues, but certain areas are emphasized each year. In 2019, the most important issues were:

- Expanding access to affordable health care coverage.
- Making augmented intelligence work for patients and physicians.
- Suicide among physicians and physicians-in-training.

The first session of the HOD was broken into by a group of demonstrators who called loudly for the AMA to support "Medicare for All." Evidently, in the view of these activists, only their views are allowed to be heard. The group of about 50 demonstrators left after about a quarter of an hour, still chanting and waving signs.

As a matter of policy, the AMA has long been skeptical of expanding access to Medicare. Seema Verma, the Administrator of the Center for Medicare and Medicaid Services, spoke to the HOD at a later session. She opposed opening up Medicare to the general public, in large part because it would destroy the program for seniors. She expressed the commitment of CMS to simplify the paperwork burden, improve the transparency of EHR systems, and, as she put it, "level the playing field" for independent physician practices.



Charles W. Van Way, III, MD, FACS, FCCP, FCCM, MSMA member since 1989, Missouri/AMA Delegate, and *Missouri Medicine* Contributing Editor, is Emeritus Professor of Surgery, University of Missouri - Kansas City.
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Universal access to health care is an important guiding principle for the AMA. The debate has always been, how should that be provided? Both the single-payer system and "Medicare for all" substitute government support for the existing system of employee-based insurance. About 180 million people, 60% of those under 65, would lose their coverage, which would be incredibly disruptive. The fee schedules under Medicare are already inadequate to support private practice physicians, and would become even lower under single-payer or "Medicare for all." The AMA has consistently supported supports a pluralistic system which provides various options both to patients and physicians.

A number of other resolutions and reports about health care financing and access were considered by the HOD. Existing policy against the single-payer system was upheld, by a wide margin. There was support for universal access to essential public health services, such as vaccination. There was support for public health efforts to counter vector-borne diseases, which have increased in recent years. Better health care for people in jail and prisons was advocated. The HOD asked for a study of whether or not universal basic income proposals would increase access to care. There is an increasing sense that Affordable Care Act is not adequate, and should be reformed. What form this should take is being enthusiastically discussed. Possibilities include "public option," more Federal subsidies for the insurance purchase, increased incentives for employer-based insurance, and still other proposals. The increased cost of drugs was discussed, with resolutions calling for limits on drug prices, increased transparency, and regulation of pharmacy benefit managers.

Health equity is emerging as an important concern. Many factors, usually lumped together as "determinants of care", can lead to health disparities. These determinants include poverty, lack of education, adverse environments, previous trauma, as well as other factors. The AMA Foundation continues to support additional studies in this area. Promotion of health equity has become an additional goal of the AMA, and provides a standard by which interventions in the health system can be evaluated. For example, a resolution strongly supported universal

access to essential public health services. Another called for elimination of non-medical exemptions to vaccination. Still another called for universal vaccination of immigrant children, whatever their legal status.

The HOD has adopted new policy on augmented intelligence (AI). AI, also called "artificial intelligence," will become increasingly common in both health care and in health care education. An extensive report on the place of AI in medical education was put out by the Council on Medical Education.

In the area of medical practice, the HOD dealt with several important issues. "Prior Authorization" continues to burden physicians and their staff. The AMA is working to do away with it, or at least lessen its burden. Medicare Advantage programs have become increasingly "Medicare Disadvantage" programs, with limited networks, low reimbursement, and arbitrary administrative rules. The AMA has adopted an "Employed Physicians Bill of Rights," continuing its commitment to ensure that all physicians can practice with as much autonomy and as few restrictions as possible. The AMA would like to see restrictions on the purchasing of practices by corporate entities. Especially in oncology, dermatology, and gynecology, this has often produced very unsatisfactory results for physicians. In some cases, the original purchaser has sold a bundle of practices on to a second entity less favorable to the physicians involved.

There was strong support to maintain physician compounding of medicines as a part of the practice of medicine. In a dozen or so states, boards of pharmacy have tried to regulate compounding by physicians, a matter of great concern to many different specialty groups.

Physician-assisted suicide is a major ethical issue. The AMA continues to oppose this, regarding it as a breach of medical ethics. There was a heated discussion concerning this, as some physicians feel it should be authorized, if not encouraged. There are those who wish to rename it "aid in dying," a less harsh description. But the HOD voted to continue the AMA's opposition to physician-assisted suicide, although leaving open the possibility that individual physicians in some states may disagree.

There was discussion of legalization of marijuana. A resolution called for the AMA to study the costs and benefits of legalization. The Surgeon General of the U.S., Jerome Adams, MD, stated that "there was no such thing as medical marijuana." The AMA has opposed marijuana legalization, either medical or recreational. There was very little sympathy in the HOD for marijuana legalization, but there was also a general recognition that it has widespread public support. It is AMA policy that the restrictions should be relaxed enough to permit controlled research on marijuana and its derivatives. A particular resolution questioned what to do when a patient who takes medical marijuana is admitted to the hospital. Across the country, and in Missouri, several large health systems have opted out of issuing certificates to allow the purchase of marijuana.

Nicotine use in general and "vaping" in particular were the subject of several resolutions. The consensus was




David Barbe, MD, addressed the Physician 2030 Conference in Tel Aviv, Israel, in May, sponsored by the World Medical Association. Dr. Barbe, an MSMA member since 1985, Past MSMA President, and the Immediate Past President of AMA, focused on the ways the AMA is shaping the future physician practice environment and patient care as it relates to Augmented Intelligence and health information technology.




Thank you to our Delegates for representing Missouri at the American Medical Association Annual Meeting in Chicago. Your support for the medical profession and patients is appreciated! From left (front row): Charles Van Way III, MD; Warren Lovinger Jr., MD; James Conant, MD; and (back row) MSMA President James DiRenna, DO; Elie Azrak, MD; Edmond Cabbabe, MD; and MSMA Past President Joseph Corrado, MD.

that it should be possible to legally limit nicotine levels in products. The increased use of vaping by children and teenagers is concerning, and should be better controlled by regulations and by law enforcement.

The meeting of the Organization of State Medical Association Presidents (OSMAP) on the day prior to the HOD meeting was, as always, devoted to state issues. AMA President Barbara McAneny, MD, spoke of the current directions of the AMA, and in particular on the importance of health equity. Gary Price, MD, the president of the Physicians' Foundation, spoke of their work on defining determinants of health, and on their support of local initiatives in health. The opioid crisis was discussed. There has been progress. Deaths have stopped increasing, although still excessive. There has been a 33% drop in prescribing over last five years. There was a presentation on the successful joint effort of physicians in New York and New Jersey to oppose legalization of recreational use of marijuana – at least for this year. Physicians from California and Washington discussed their efforts to remove non-medical exemptions to vaccination.

Several people from Missouri served in leadership roles. David Barbe, MD, ended his term on the Board of Trustees, and will be moving on to a leadership role in the World Medical Association. Edmund Cabbabe, MD, serves on the Council for Long Range Planning and Development. Charles Van Way, III, MD, continues to serve on the Steering Committee of OSMAP.

Patrice Harris, MD, was inaugurated as the 174th president of the AMA. A child psychiatrist from Georgia, she is the first African-American woman to lead the AMA. She has promoted universal access to health care, better access to mental health services, and improvement of health care in underserved minorities. She has been a strong advocate of care for abused and neglected children throughout her career.

Susan Bailey, MD, was elected to be President-Elect. A physician from Texas, she has been the Speaker of the HOD for the past four years. She is a strong advocate of private practice. Her election marks the first time that the President, Past President, and President-Elect are all women.

All of the reports and resolutions adopted in the meeting are available on the AMA website. Highlights from the meeting are at https://www.ama-assn.org/house-delegates/annual-meeting/highlights-2019-ama-annual-meeting.

# Young Physicians Section Report *by Albert Hsu, MD & Laurin Council, MD*

The Young Physician Section (YPS) of the AMA includes physicians < 40 years of age *or* within the first 8 years of practice. In Chicago, AMA-YPS adopted three resolutions to be forwarded to the HOD in November, on Basic Courses in Nutrition; Ensuring Access to Safe and Quality Care for our Veterans; and Public Health Impacts and Unintended Consequences of Cannabis for Medicinal and Recreational Use. US Surgeon General Jerome Adams, MD, provided an inspirational lunchtime talk about his efforts to fight the opioid epidemic, reduce stigmas, and ensure patient access to life-saving naloxone. He also mentioned the importance of showing the links between community health and economic prosperity.

In the HOD, several YPS-relevant topics included:

- Legislation for 'Mature Minor' Consent to Vaccinations
- Bullying in the Practice of Medicine
- Destigmatizing the Language of Addiction
- Peer Support Groups for Second Victims
- Dispelling Myths of Bystander Opioid Overdose

If you or someone you know is a young physician who may be interested in getting involved in the MSMA-YPS, please contact Stephen Foutes at stephen@msma.org or 800-869-6762.





Albert Hsu, MD, MSMA member since 2017 and Immediate Past Chair of the MSMA Young Physician Section, is a Reproductive Endocrinologist at the Missouri Center for Reproductive Medicine and Fertility in Columbia, Mo. Laurin Council, MD, MSMA member since 2019, is the American Society for Dermatologic Surgery representative to the AMA-YPS. She is an Associate Professor of Medicine, Dermatology, at Washington University, St. Louis, Mo.
*Contact: scooberhsu@gmail.com*

# MSMA: Let Us Help You

*by James DiRenna, DO*

In April, I was honored to become the President of the Missouri State Medical Association. These past few months I have traveled (when Mother Nature allowed) to the Tennessee Medical Association's annual meeting and Congress of Delegates where a group of robust physicians took on their mission to ban vaping statewide for those 18 years and younger. This resolution moved to the American Medical Association's June meeting in Chicago where they brought forward the resolution to ban underage vaping. Not only was this a well-attended national meeting, but history was made with their electing the first African American female psychiatrist as their 174th President ~ Patrice Harris, MD, of Atlanta, Georgia.

Locally of course, April and May at the state capitol are a hotbed of activity. MSMA was there en masse in their white coats, walking the halls, showing solidarity. We lobbied representatives on scope of practice, prior authorization difficulties, and Medicaid and Medicare issues. We are very fortunate to have savvy lobbyists who kept track of last minute legislative shenanigans in both the House and the Senate that could have been detrimental to medicine.

I'm often asked "Why should I become member of MSMA"? You either believe in organized medicine or you don't. I have always leaned heavily on advocacy because I have learned that medical awareness which honors the role of the physican/patient relationship has to be the focus. But more importantly, an organization is only as good as its membership. Grab a friend, grab an associate, call a member who has not renewed. Our staff is happy to help. Call our 800 number to talk about membership benefits: 800.869.6762

It's very basic - help us help you.



James DiRenna, DO, 2019-2020 MSMA President and member since 1996, is from Kansas City, Mo., and practices Family Medicine for the Blessing Health System.
*Contact: james.direnna@blessinghealthsystem.org*

# RFS Report *by Joanne Loethen, MD*

The Resident and Fellow Section of the American Medical Association (AMA) convened at this year's Annual Meeting in Chicago June 7-8. MSMA members Brette Harding, MD (ENT-MU), Jared Lambert, MD (EM-MU), Joanne Loethen, MD (MP-UMKC), and Nathan Nolan, MD (IM-MU), represented Missouri's physicians-in-training as the section discussed issues pertinent to residents and fellows.

Issues ranged from supporting states who allow mature minors to consent for vaccinations, discouraging the use of non-FDA approved infant oximetry monitors, improving facilitation of physicians-in-training seeking mental health care through physician health programs, and advocating for reclassification of complex rehabilitation technology to improve access for patients.

Aside from policy actions, the RFS heard from Barbara McAneny, MD, AMA President, who spoke to the ongoing priorities of the AMA. Dr. McAneny shared how AMA is actively working to remove obstacles that interfere with patient care, lead the charge on public health crises, and advance the future of healthcare innovation.

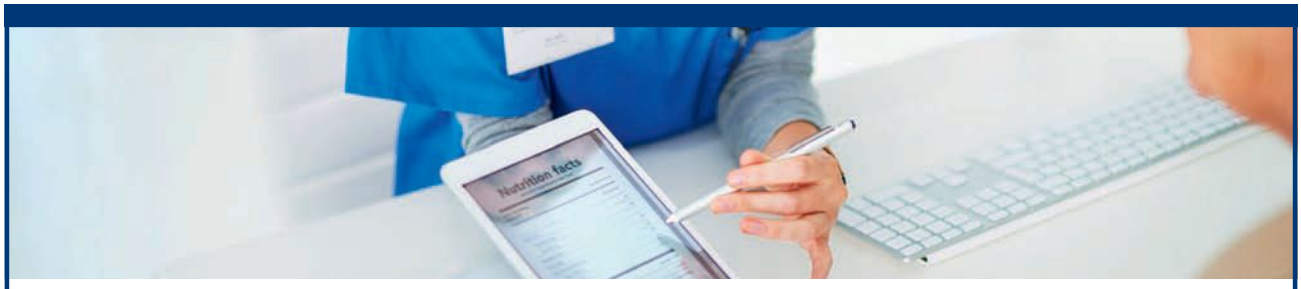
The Surgeon General, Jerome Adams, MD, MPH, spoke to the RFS and encouraged early-career physicians to stay engaged in healthcare change, and then expanded on how the opioid crisis continues to cripple our nation. John Andrews, MD, Vice President of GME Innovations at the AMA, spoke to the RFS about the new Reimaginging Residency Initiative. Through this initiative, a total of $15 million has been awarded to eight GME programs investing in projects that promote systemic change in GME. This initiative compliments the Accelerating Change in Medical Education Consortium of 37 medical schools working to transform medical education across the continuum of medical training.

Missouri's residents and fellows continue to have an active presence at both the state and national level through the support of the MSMA RFS. For more information on getting engaged with the MSMA as a resident, visit www.msma.org/resident-fellow-section. For complete details on the AMA Annual Meeting, visit www.ama-assn.org or follow AMA on Twitter, Facebook, or Instagram using the handle @amermedicalassn.



Joanne Loethen, MD, MSMA member since 2016 and Vice Chair of the MSMA Resident and Fellow Section and MSMA RFS Vice Councilor, is at the University of Missouri, Kansas City in Internal Medicine and Pediatrics, Kansas City, Mo.
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## Youth Marijuana Use Following Commercial Sales of Legal Recreational Marijuana

Missouri recently approved medical marijuana. Based on experience in other states, proposals to legalize recreational marijuana in Missouri will soon follow. The *Journal of the American Medical Association Pediatrics* recently published a flawed research letter purporting to show that past-month teen marijuana use declined after states legalized recreational marijuana.[1] This questionable study is being publicized by Missouri press.

Although the authors did not describe their methods in enough detail to check their work, a few shortcomings stand out. Anderson et al. misled readers by: asserting they used seven states' data after "adoption" of recreational marijuana laws (RML); neglecting to report the actual figures for youth use; and omitting the trends in use in states without legal marijuana.

The authors used data from the biennial Youth Risk Behavior Surveys (YRBS).[2] However, the latest survey, conducted in 2017, occurred after commercial recreational sales began in only two RML states, not seven as the authors claim. Of the four states that legalized in 2012-2014 (Oregon, Washington, Alaska and Colorado), two states (Washington and Oregon) do not submit data to the YRBS. Four states (California, Nevada, Maine, and Massachusetts) voted to legalize in 2016, but none of them opened licensed recreational marijuana shops prior to January 1, 2017. In fact, California and Massachusetts did not open shops until 2018. Maine and the District of Columbia, which voted to legalize in 2014, do not have stores selling recreational marijuana yet.

The distinction between the year that the law passed versus the year when pot shops opened is critical because Anderson et al. disingenuously concluded that youth use decreased because "it is more difficult for teenagers to obtain marijuana as drug dealers are replaced by licensed dispensaries that require proof of age." That conclusion is erroneous because the final year of data collection is prior to the opening of these ethical, age-verifying stores.

To judge the effect of RMLs, we are left with only two early legalizer states that submitted data to the YRBS and had a functioning commercial recreational marijuana market prior to 2017. Colorado did not submit complete data in 2013 and 2015. Moreover, Denver, its largest city, hasn't submitted a report since 1995. Using the last complete year (2011) as a baseline and the most recent year (2017) as the final year, we find that youth use (ages 12-17) in Alaska increased from 21.2% to 21.5% (1.4% increase) and in Colorado decreased from 22.0% to 19.6% (10.9% decrease). Meanwhile, median youth use in the United States as a whole decreased from 21.1% to 18.6% (11.8% decrease). The two states with RML fared worse than the nation as a whole.

To get data from the other early legalizers, we have to turn to the National Survey on Drug Use and Health[3] (NSDUH). During the same time period, the NSDUH showed a nationwide decline in youth use of 14.4%, while Washington only declined by 5.2% and Oregon increased by 5.0%. Once again, RML states showed youth use trends worse than the national average.

The news from Oregon is particularly disturbing, and it might be a harbinger of the future, having a burgeoning commercial market offering cheap prices.[4] Using NSDUH data from 2011-2012 and 2016-2017, Oregon's past month marijuana use among 18- to 25-year-olds increased more than twice the national average (28.4% vs. 13.6%).

The legalization of commercial sales of recreational marijuana does not reduce past month use in teenagers compared to other states. In fact, the data show a trend towards worse outcomes in states that have legalized. We call for further statistical analysis by unbiased experts who want to elucidate rather than obfuscate the trends in marijuana use.

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**Letters to the Editor**
Submissions reflect readers' opinions and may be edited for length.

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## Health Care is Not Just Treating a Disease; It Is Taking Care of a Human Being

Health care involves not only treating a disease, but taking care of the patient, his anxiety, and psychologic status that may effect the healing process. The following encounter I experienced with a patient few years ago exemplified the above fact. The patient should see a friend in their doctor, not a stranger with a white coat and stethoscope.

Peter (not his real name) was a 68-year-old gentleman referred to urology with hematuria, blood in the urine. His CT scan revealed a mass in the left kidney with high probability of cancer. So, he underwent a nephrectomy, removal of the kidney. He did well and was released home on fourth post-op day. I saw Peter all alone, and did not see any family member during the hospitalization. I kept asking him about his family.

Peter told me the story about his only daughter in St. Louis whom he had not seen in two years. Apparently his wife died when he was deer hunting at a time when she was not feeling well. This had made his daughter upset, and she refused to see or talk to him.

I felt sorry for Peter and in the chart found his daughter's phone number and called her. I explained her the situation, that her father was in the hospital after surgery for kidney cancer,and was lonely and depressed. She agreed to visit with him, The next day I saw his daughter and granddaughter at his bed side. I saw Peter being happy with a smile. He did well post-op and moved to St. Louis to live with his daughter.

Thinking about the entire ordeal with Peter and his family, I was very happy my simple phone call helped to get the family together. I realized health care is not treating the disease, but is taking care of a human being.

*Sivaprasad Madduri, MD*
*MSMA member since 1978*
*Urologist, NorthWest Clinic, Poplar Bluff, Missouri*



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# Missouri Medicine in the News

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

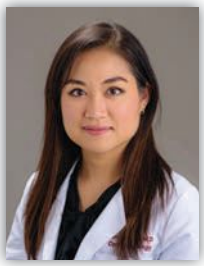
*Missouri Medicine* announces a new member of our Editorial Board. Board members are selected on the basis of exceptional professional accomplishment and expertise in their specialty.



Stephanie L. Graff, MD, FACP, MSMA member since 2012, practices at the Sarah Cannon Cancer Institutes at HCA Midwest Health in Kansas City, Missouri. She has accepted the Editorial Board Member position in Hematology/Oncology. She replaces Kan N. Huang, MD, who moved out of state.



A resolution that established the MSMA Women Physicians Section (WPS) was approved at the 2019 MSMA Annual Convention. All female MSMA members are welcome to participate in the Section's activities. The chair of the section is Joeanne Loethen, MD, Kansas City, MSMA member since 2016. Contact Heidi Geisbuhler at heidi@msma.org if you're interested in receiving more information or visit www.msma.org/women-physicians-section.



Congratulations to Jella An, MD, of Columbia, Mo., for performing the first micro-invasive glaucoma surgery (MIGS) procedure in the country of India while on a mission trip. Dr. An joined MSMA in 2016.



David Chalk, MD, of Washington, Mo., was the keynote speaker for the Adult Education and Literacy Graduation Ceremony in Union on May11. Dr. Chalk has served organized medicine since becoming an MSMA member in 1993.



Congratulations on your new venture with Phelps Health, Kan Huang, MD. Your membership since 2017 is greatly appreciated.



MSMA would like to recognize Dr. N. Scott Litofsky for his election to the Society of Neurological Surgeons. Dr. Litofsky has been a member of MSMA and Boone County Medical Society since 2006.



Congratulations to Julie Margenthaler, MD, professor of surgery at Washington University School of Medicine in St. Louis, on being named president-elect of The American Society of Breast Surgeons. Dr. Margenthaler joined MSMA in 1998.



Dr. Erik Meidl, MD, is encouraging other healthcare professionals to volunteer at Hannibal Free Clinic. MSMA is proud to call Dr. Meidl an MSMA member since 1996.

Burney Miller, MD, of Overland Park, Ks., was recently inducted into the R-7 Public Foundation's Hall of Fame. Dr. Miller has been an MSMA member since 2003.




MSMA is excited to share in Dr. Morrison's success in being chosen as a 2018 Top Doctor by 417 Magazine. He's practices at OMC Pathology in West Plains and has been an MSMA member since 1991.

Governor Mike Parson has recently appointed two MSMA members, Naveed Razzaque, MD, of Bridgeton, and Marc Taormina, MD, (right), of Lee's Summit, to serve on the Board of Registration for the Healing Arts. Dr. Razzaque joined MSMA in 2011 and Dr. Taormina has support MSMA since 1979.



# Groundhog Day: My Constant Headache Due to Spontaneous Cerebrospinal Fluid Leak

*by Alisha Wright, DO & Cindy Schmidt, PhD*

The headache started halfway through my (AW) shift. Busy and thirsty, I diagnosed dehydration, chugged a bottle of water and three ibuprofen. By the end of my shift, it had worsened substantially. Every day, I woke up with the same headache. All day, every day, no matter what time of day, the same headache. At times it would intensify, particularly if I stayed upright for an extended period of time. Regardless, it was there, constantly, even when I would awaken during the night. It reminded me of Bill Murray in the movie Groundhog Day, who relives the same day over and over.[1]

I simply tried to ignore it by lying down, closing my eyes or hiding in my room by myself. I avoided most social situations altogether as my headache persisted twenty-four hours a day. I treated myself for sinusitis, then for viral meningitis. When I couldn't take it anymore, I became a patient in my own Emergency Department. CT, MRI, and lumbar puncture (LP) revealed only two abnormal findings – pachymeningeal enhancement on MRI and a low opening pressure on LP. A few days later, the pain was too intense and distracting to work, and my neurologist recommended admission. Imaging didn't inform, and medication didn't help. Three days passed without progress on the pain or diagnosis, so my neurologist suggested we pursue my cerebrospinal fluid (CSF) leak theory by doing a diagnostic/therapeutic lumbar blood patch. Within minutes I felt some relief – the first since the onset of my headache. Twelve hours later, however, all my symptoms returned. A second lumbar blood patch brought the same, temporary relief.

I was transferred to KU Medical Center in Kansas City, Ks., where they found the focus of my leak – near C2. Three more blood patches directed at C2 didn't help, so I decided to find a facility with more expertise. After hours and hours of research, I found only three centers in the U.S. that seemed to have what I was looking for, years of experience and a large volume of patients with spontaneous CSF leaks. The three that met my criteria were Cedars-Sinai Medical Center, Duke University Medical Center, and the Mayo Clinic in Rochester, Minnesota. I arranged my travel to Mayo Clinic with hopes of a cure for my headache.

Imaging had indicated I had a "fast" leak, so the Mayo Clinic performed a dynamic CT myelogram and found the leak at T3. A sixth unsuccessful blood patch there led me to my cure. I subsequently underwent removal of the spinous process of T2 with complete laminectomies at T3/T4 to allow enough mobilization of my spinal cord to open the dura, find the leak on the anterior side and repair it. Even with tremendous back pain, I arose from bed the next day and realized my headache of five months duration was gone!

My cure came with quite the cost. I still have back pain and am hopeful that I may regain my old fitness regimen – pushups, pullups, lifting weights, etc. I had been in pretty good physical condition prior to the onset of the headache and worked out routinely. After the back surgery, I have had a lot to overcome with pain and loss of muscle. Initially, the fatigue was a huge hurdle but I am thankful to say that has already improved substantially. After eight months of medical leave, though, I've returned to my full professional capacity in the ED as physician and Program Director.

Spontaneous intracranial hypotension (SIH) from a dural leak classically presents with an orthostatic headache.[2-4] This is not always the case, however. Many features of SIH headache have been described, including pain that improves in the upright position. The headache may be absent upon awakening with immediate onset after sitting or may progressively worsen throughout the day. It may be described as annoying or completely incapacitating. The postural component may decrease with time.[5] There may be brainstem signs of tinnitus, diplopia, and vertigo. Pulsatile tinnitus is a strong sign of CSF leak. Historically thought to be due to CSF leakage from lumbar puncture, today it is recognized as leakage in the spine, and quite rarely cranially.[2]



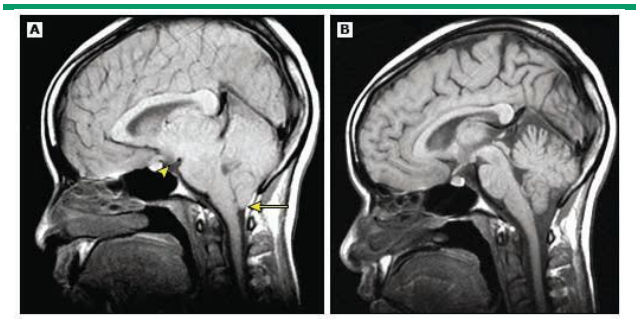
Alisha Wright, DO, (left), practices Emergency Medicine in the Freeman Health System in Joplin, Mo. Cindy Schmidt, PhD, is Director of Scholarly Activity and Faculty Development and Assistant Professor, College of Osteopathic Medicine, Kansas City University of Medicine and Biosciences
*Contact: drwright2b@hotmail.com*

It typically occurs from minor trauma (e.g., sports injury, sudden twist or sneeze, sexual intercourse, military combat or training experience) tearing the dural nerve sheath or possibly from an underlying connective tissue disorder. Furthermore, some have occurred in association with osseous abnormalities, congenital defects in the dura itself or with diverticuli.[3,6-9]

Spontaneous dural leaks are difficult to diagnose. Neurologic exam is usually normal.[6] Head CT will typically be normal, and brain MRI may be normal in up to 20% of patients.[3] Recommended imaging is use of brain MRI with gadolinium and spinal MRI without gadolinium.[8] Look for SEEPS: subdural fluid, enhanced pachymeninges, engorged venous structures, pituitary enlargement, and "sagging" of the brain.[3] Sagging of the brain may mimic a Chiari I malformation identified by cerebellar tonsillar descent below the foramen magnum, descent of the Sylvian aqueduct below the incisural lines, obliteration of the prepontine or perichiasmatic cisterns, crowding of the posterior fossa or flattening of the optic chiasm and/or anterior pons. Enlargement of the pituitary may be evident on MRI T2, as well as engorged cerebral venous sinuses and ventricular collapse.[10] Pooling of contrast material may be apparent in the epidural space on spinal MRI when associated with a boney lesion and a fast leak. This may be extensive, impeding localization. Slow leaks usually lack this finding.[5]

Treatment of a dural leak varies from institution to institution although conservative measures predominate initially. Davidson et al. proposed an algorithm for diagnosis and treatment of suspected spontaneous intracranial hypotension.[11] When suspected, admit the patient and obtain hourly neuro checks. The patient should lie flat while awaiting a lumbar epidural blood patch (EBP). A repeat CT should be obtained after 24 hours.[11] For patients who improve clinically within the first 24 hours and also show stable or improved imaging, have the patient sit up gradually over the next 24 hours.[11] If tolerated and asymptomatic, patients may be discharged and follow-up outpatient with CT.[11] If upright positioning is not tolerated and patients remain symptomatic, conduct a repeat EBP, maintain patient lying flat for 24 hours and repeat CT.[11] For patients who do not improve clinically within the first 24 hours, anesthesia, interventional neuroradiology, and neurosurgery consults are appropriate.[11] If the patient clinically declines after the first EBP, Trendelenberg positioning, repeat EBP, and MRI of the spine should be completed to attempt localization of the leak.[11] If this approach does not identify a CSF leak, repeat EBP, keep patient flat for 24 hours and repeat CT.[11] If this approach does identify a possible CSF leak, CT/MR myelogram ± DS myelogram should be performed.[11] If the leak is identified, conduct a targeted EBP.[11] If patient improves, gradually sit up over 24 hours.[11] If patient does not improve with the targeted EBP, surgical repair of the leak is recommended.[11]

**MRI of brain sagging with low cerebrospinal fluid pressure headache**




Brain MRI of a patient with low CSF pressure headache (spontaneous intracranial hypotension). Noncontrast T1-weighted sagittal images were obtained before (A) and after (B) treatment. There is crowding and pointing of the cerebellar tonsils at the foramen magnum mimicking a Chiari 1 malformation on the first study (arrow, image A). In addition, there is sagging of the brain resulting in inferior displacement of the floor of the third ventricle (arrowhead, image A) as well as loss of CSF space in the suprasellar cistern. These findings have resolved on MRI six months later after treatment (B), which included draining of associated subdural collections.

MRI: magnetic resonance imaging; CSF: cerebrospinal fluid.

Graphic 77679 Version 3.0

Spontaneous CSF leaks occur in 5 in 100,000 people.[3] The typical patient would be like me – female, 40 years old, healthy, thin, low blood pressure.[3,9] Although this is not common, it is a treatable cause of headaches warranting inclusion in the differential.

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MM

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# Strengthening Our Collaborations

*by Steven Zweig, MD*

While this is a time of transitions at the University of Missouri School of Medicine, it is also an opportunity for us to strengthen the collaborations that make us a unique and vital institution. Dr. Patrick Delafontaine resigned as dean in April of 2019 to return to Tulane School of Medicine, and I became interim dean. Although a new job for me, I am not new to MU, having spent 35 year as a faculty member in the Department of Family and Community Medicine with the last 11 years as chair. In fact, when I had the privilege of distributing diplomas to our 94 graduates in May, I crossed that same stage in Jesse Hall exactly 40 years before as a member of the MU School of Medicine class of 1979.

When stepping into a new role, we build on a foundation created by those who came before us. Soon before my appointment, Rick Fraunfelder, MD, who also serves as chair of the Department of Ophthalmology, took over from the retiring Michael Misfeldt, PhD, who spent more than 20 years as dean for faculty affairs. Similarly, Bill Fay, MD, succeeded the retiring Jerry Parker, PhD, as dean for research. The dean's office is also strengthened by Vic Arnold, chief financial officer, and the newly appointed Pam Mulholland as chief administrative officer.

Changes in leadership also create an opportunity for us to renew our collaborations within our system and across the state. To successfully grow an academic health system, we need to strengthen both our internal and external collaborations. Under the leadership of the four campus UM System President Mun Choi, MU Chancellor Alexander Cartwright, and Provost Latha Ramchand, we are building new connections. The MU campus is establishing a new resource allocation model which will create a more reliable and accountable funding structure for each of its schools and colleges. The NextGen Precision Health Initiative is a four-campus enterprise (including University of Missouri-Kansas City, University of Missouri-St. Louis and University of Missouri Science and Technology) to advance research collaborations and health outcomes in the areas of neurosciences, cancer and vascular disease. We held the groundbreaking ceremony on the NextGen Precision Health Institute in June, which is being constructed next to the medical school and hospital complex in Columbia. This is the largest investment ever by the UM System to advance research and innovation.

We are also strengthening our collaborations with MU Health Care. Under the leadership of CEO Jonathan Curtright, MU Health Care has grown financially and in the scope of services provided. The bond between MU Health Care, the MU School of Medicine and the University Physicians practice plan is only growing stronger. University Physicians, led by Vic Arnold and Dr. Ted Choma, UP Chair, recently had its most successful year with over $220 million in revenue. The hard work of our physicians and staff is augmented by stronger mutual commitments to enhancing health care quality and patient safety, while growing collaborations in human resource management, space allocation, communications and philanthropy. This spring, we have begun a strategic planning process that includes not only these entities but also leaders from the MU Sinclair School of Nursing in Dean Sara Thompson and School of Health Professions in Dean Kris Hagglund, as well as colleagues from across the MU campus.



Steven Zweig, MD, MSPH, is the Interim Dean of the University of Missouri School of Medicine, the Jack and Winifred Colwill Endowed Chair and Professor of Family and Community Medicine.
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Finally, we are also working across the state to advance our mission: to improve the health of all people, especially Missourians, through exemplary education, research, and patient-centered care. This year, we sent 28 students to our Springfield Clinical Campus to complete the final two years of their medical school education. Mark Costley, MD, as our interim associate dean for that campus, has done fantastic work in assisting in the recruitment of more than 260 volunteer physician faculty members with the help of our partners CoxHealth and Mercy hospitals. This year, our 28 M3s at the Springfield Clinical Campus is the largest cohort date. They are joined by 11 M4s in Springfield. Recognizing the need for more rural primary care physicians, the Department of Family and Community Medicine, MU Health Care, and Bothwell Regional Health Center are working to create a rural training track family medicine residency program based in Sedalia.

We will advance our MU School of Medicine vision to be a transformational leader in improving health by enhancing existing and building new collaborations. We will look toward these partnerships and future ones to grow our commitment to education, research and patient-centered care in serving the people of Missouri and beyond. **MM**



Medical Students at the new Springfield Clinical Campus.



2019 MU School of Medicine Commencement.



NextGen Precision Health Institute.

## *A Quality Improvement Initiative:*

# Developing a Multi-Disciplinary Team for Infective Endocarditis

*by Hariharan Regunath, MD, Archana Vasudevan, MD, Kapil Vyas, DO, Chen Li-Chien, MD, Sachin Patil, MD, Jane Terhune, MD & Stevan P. Whitt, MD*

School of Medicine
University of Missouri Health

**Hospitalists often care for patients with infective endocarditis (IE), a complex disease that requires a multi-disciplinary team approach for its management.**



Hariharan Regunath, MD, (above), Kapil Vyas, DO, and Stevan P. Whitt, MD, are in the Department of Medicine, Division of Pulmonary, Critical Care and Environmental Medicine, and the Division of Infectious Diseases. Archana Vasudevan, MD, Chen Li-Chien, MD, and Sachin Patil, MD, are in the Department of Medicine – Division of Infectious Diseases. Jane Terhune, MD, is in the Office of Clinical Effectiveness, University of Missouri Hospital and Clinics. All at the University of Missouri-Columbia, Columbia, Mo.
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## Abstract

### *Background*

**As guidelines do not describe how to develop a multi-disciplinary team(MDT), we provide a model using quality improvement tools to design a MDT for infective endocarditis (IE).**

### *Methods*

**Primary service, specialty teams and whether they had surgery or not (indications, reasons, outcomes and complications) were recorded for IE patients for January-December 2016. Criteria: age >18years and definite IE per modified Duke criteria.**

### *Results*

**Of all cases, 29/82 met criteria. Primary service: internal medicine 18(62.1%), medical intensive care and cardiology 4(13.8%) each, family medicine 2(7.9%) and pediatrics 1(3.4%). Surgery was indicated in 21(72.4%), 9 (42.9%) underwent surgery, 12 (57.1%) did not [6/9(66.67%) left side IE died, all right side IE (3,25%) survived] and 2 (22.2%) had missed opportunities and this was chosen as the leverage point. MDT was developed to reduce the number of left sided IE patients not undergoing surgery despite indications.**

### *Conclusions*

**Quality improvement and team development tools help in developing MDT for IE.**

## Introduction

Hospitalists often care for patients with infective endocarditis (IE), a complex disease that requires a multi-disciplinary team approach for its management.[1,2] Infectious diseases, cardiology and cardio-vascular surgery specialists are integrally involved in the management of most cases of IE, but other specialties including pharmacists, dental/maxillo-facial surgery and behavioral health/psychiatry (e.g. de-addiction services for intravenous drugs users) are also required for comprehensive care. Individualization based on the clinical, financial and social variables is often necessary. The American Heart Association (AHA)/Infectious Diseases Society of America (IDSA) guidelines offer recommendations for evaluation and management of IE.[1] However, no specifics are provided to guide

the optimal development of multidisciplinary teams. An international working group has outlined recommendations applicable for health care organizations across the globe for the development of a multi-disciplinary team (MDT) for the management of IE.[3] Guidance is also available from Europe where a multi-disciplinary team for management of IE at their institutions was successful.[4-9] In this manuscript, we describe our utilization of quality improvement principles to justify the need for an MDT, thereby, engaging providers from various other subspecialties to develop a standardized process aimed at reducing care variation in the management of IE.

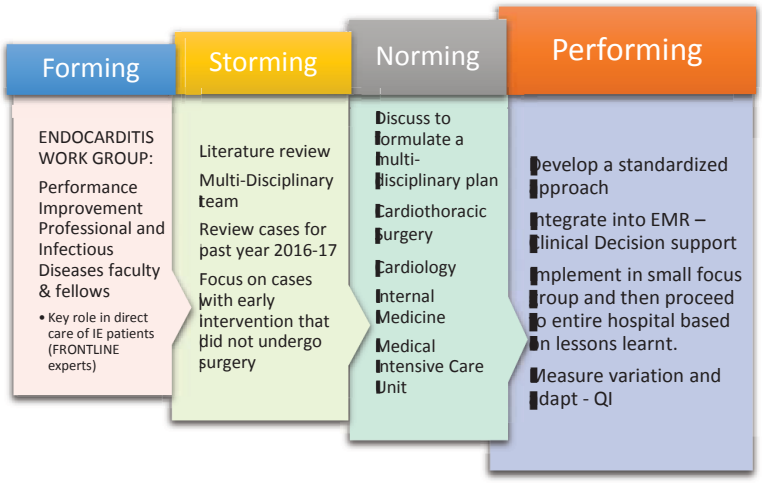



Figure 1. Developing the endocarditis work group using Tuckman's model (Abbreviations: EMR – electronic medical records, QI – quality improvement)

## Methods

The University of Missouri Hospital and Clinics (UMHC) is a premier tertiary referral center for mid-Missouri. Cardiology and Cardiothoracic surgery (CTS) function in-liaison as a cardio-vascular service line for heart valve surgery. Through our continuous performance improvement work, we identified opportunities in improving clinical management of infective endocarditis. Using Tuckman's model, an endocarditis work group was formed (Figure 1) and created the following mission statement and goals.[10,11]

## Mission Statement

To standardize and improve care for patients with infective endocarditis by developing a workflow algorithm and a multi-disciplinary team to enable continued quality improvement.

## Goals

Implement a standardized approach to the management of these patients by the following steps. Step 1: Develop multi-disciplinary team comprising of – ID, cardiology and CTS. Step 2: Develop a clinical decision support tool by incorporating the multi-disciplinary team workflow and integrate it into the electronic health record.

An Ishikawa diagram was constructed to identify potential problems or causes that result in care variation for IE (Figure 2). Prior institutional data (2007-2012) on IE at our institution was reviewed.[12] In that study, 30.7% (35/114) had surgery with an average time to surgery of 18.8 days (range 1-60

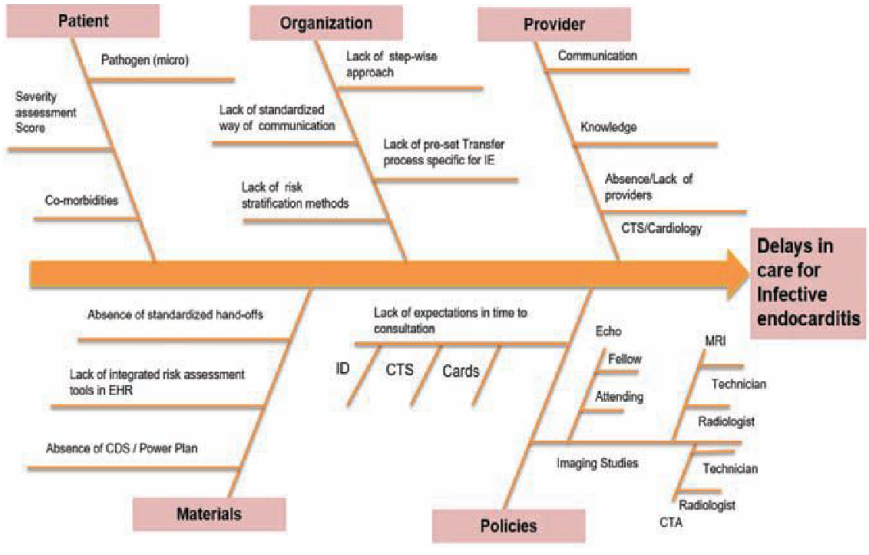



Figure 2. Ishikawa diagram: Possible causes contributing to infective endocarditis care variation (Abbreviations: EHR – electronic health records, IE – infective endocarditis, CTS – cardiothoracic surgery, CDS – clinical decision support, MRI – magnetic resonance imaging, Cards – Cardiology consult service)

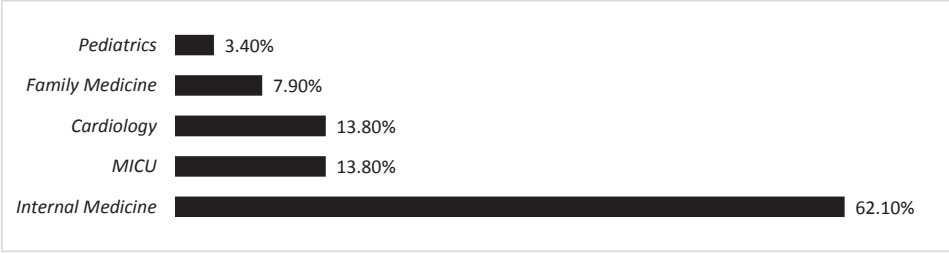



Figure 3. Distribution of primary services caring for endocarditis patients (Abbreviations: MICU – medical intensive care unit)

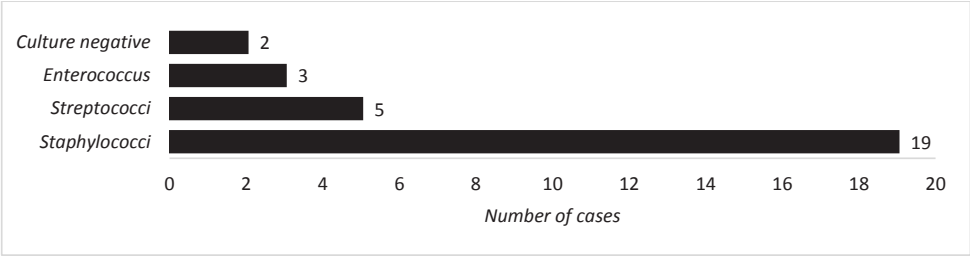



Figure 4. Microbiology of all cases

days). In hospital mortality was 9.6% and early surgery was rare.[12]

For our current study, we identified cases of IE using the following ICD-9 (421/AC, 4210, 4211, 4219, 4249, 42490, 42491, 42499); and ICD-10 codes (I33, I330, I339, I38, I39, M3211) from Vizient ™ (https://www.vizientinc.com/) for 1 year (January – December 2016).[13] Current literature on early intervention for left sided endocarditis was reviewed and the following criteria were applied: 1) Age ≥ 18 years, 2) Fulfill modified Duke Criteria for definite IE. All other cases were excluded. We noted the primary service provider, the details of specialty teams involved, indications for surgery, the number of qualifying cases who had underwent surgery and those who did not. For all cases we noted the reasons on decision for surgery or not, outcomes and complications. Microsoft Excel 2016 was used for descriptive analysis and for constructing the process control charts where needed. Data was expressed as numbers and percentages as appropriate.

## Results

For the study period, we identified 82 cases from Vizient™, of which 29 met modified Duke Criteria for definite endocarditis. The primary teams caring for IE patients were internal medicine in 18 (62.1%), medical intensive care unit and cardiology in 4 each (13.8% each), family medicine in 2 (7.9%) and pediatrics in 1(3.4%) patients respectively (Figure 3). Of all, 27 cases (93.1%) were culture positive and all were caused by gram positive organisms (Figure 4). In two cases, other co-pathogens were also isolated (*Stenotrophomonas* [with staphylococci] and *Propionibacterium* [with coagulase negative staphylococci]).

A total of 21 (72.4%) cases had indications for surgery per AHA/IDSA guidelines and the indications included the following overlapping causes: Heart failure unresponsive to medical therapy (6, 28.6%), persistent vegetation after systemic embolization (9, 42.9%), increase in vegetation size despite appropriate antibiotic therapy (8, 38.1%), more than one embolic event within 2 weeks of therapy (6, 28.6%), anterior mitral vegetation size > 10 mm (9, 42.9%), new heart block (1, 4.7%), myocardial abscess or valve rupture or fistula (2, 9.5%), acute aortic or mitral valve regurgitation with signs of heart failure (8, 38.1%) and persistent bacteremia for > 5 days (6, 28.6%).

Of all 21 cases, only 9(42.9 %) underwent surgery. In the rest (12, 57.1%) who had indications for surgery and did not undergo surgery, 6 (50%) died and all were left sided IE and at least 2 cases had a potential for early surgical intervention. In the rest of six cases (50%) who survived, 3 were right sided endocarditis (Figure 5). The time to surgery (range 1-24 days) for nine cases who underwent surgery was plotted in a process control chart and there were no outliers to indicate that a process change would be required. We suspected that improving the total number of cases qualifying for surgery to actually undergo surgery would probably be the best leverage point (Figure 5).

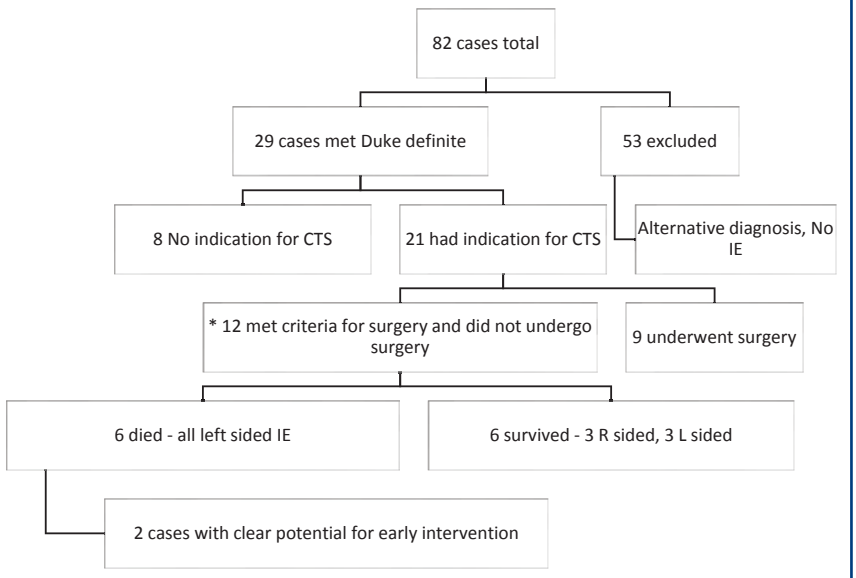



Figure 5. Summary of results and the leverage point (* Leverage point) (Abbreviations: IE – infective endocarditis, CTS – cardiothoracic surgery)

From the leverage point, we developed the following aim statement and targets for quality improvement. Aim statement: Reduce the number of patients with left sided IE who did not undergo surgery despite indications for early intervention by 50% (from 57.1% to 28.6%). Targets for quality improvement: (1) Risk stratification: Early identification of with high risk for mortality and escalate level of care quickly. (2) Communication: Improve communication between subspecialties. (3) Standardization: Standardize approach to enables measurement of care variation.

## Discussion

While there is good evidence for improving mortality in IE with implementation of dedicated multi-disciplinary teams, the outline of how this can be developed has not been described well. Guidelines and recommendations from experts describe the components essential for such a team very well, but the actual process of team development is lacking. In our literature review, we did not identify publications describing a multi-disciplinary team for the management of infective endocarditis for the US setting. Hence, we emailed authors of the 2015 IE Guidelines from AHA/IDSA.

In their email correspondence, they referred to Miro et al (University of Barcelona, Barcelona, Spain) and Habib et al (C.H.U. De La Timone, Bd Jean Moulin, Marseille, France), who had authored the 2015 European Society of Cardiology (ESC) IE guidelines. Habib et al. described their endocarditis team structure in EuroValve Congress 2017.[9] Their team involved cardiology, cardiothoracic, infectious diseases, radiology, nuclear medicine, research fellows, and other subspecialties (e.g. neurologist, anesthesiologists, etc.) on a case-by-case basis with close follow up (1 month, 3 months, 6 months and 1 year after hospitalization by ID providers, and cardiology if need be) of all patients with IE seen within their system. For every case, they had weekly meetings and the summary of decisions were emailed to all members of the team at the end of each mandatory meeting. As a team they reviewed echocardiography, cardiac magnetic resonance imaging results, biological features, etc. They have systematically entered data from more than 1000 cases in their database, since its inception to date.[9] Likewise, Miro et al. also recommended a similar design.[4]

At a systems level thinking, leverage points are defined as actionable points within the structure of any system, where application of a solution would result in a desirable change.[14,15] We selected our leverage point as missed opportunities in those who did not undergo surgeries despite indications because, any solution for this leverage point will mandate collaboration of all of the essential subspecialty services namely ID, cardiology and CTS. Complete engagement of subspecialty providers is important to success of the MDT. Once we presented our data as objective evidence, cardiologist (specialized in imaging and heart failure), and the cardiovascular valve surgeons engaged without reservation as the process would hasten pre-operative evaluation to determine surgical

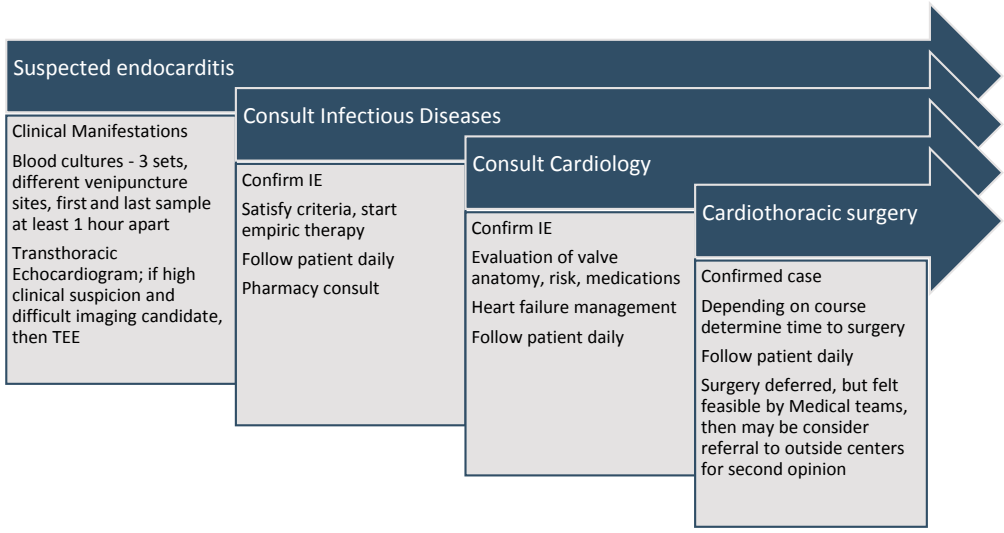



Figure 6. Overview of work flow of the management of infective endocarditis (Abbreviations: IE – infective endocarditis, TEE – transesophageal echocardiogram)

candidacy earlier than present, irrespective of primary teams. Infectious diseases providers will be at the forefront of orchestrating the MDT, followed by cardiology and cardiothoracic surgery. Our proposed plan for a multi-disciplinary team is seen in Figure 6 and this was considered appropriate for our academic hospital setting.

The outline of the standardized electronic process in implementing this plan is displayed in Figure 7. Our process targets specifically those who will benefit from an early surgical intervention and fast-track their pre-operative evaluation. The triggers for the fast-track included one or more of septic or cardiogenic shock, acute pulmonary edema, symptoms and signs of worsening heart failure while on medical therapy. ID and cardiology teams are quickly and automatically consulted in a sequential and time targeted fashion, diagnosis will be confirmed by both ID and cardiology, followed by determination of level of care based on severity of illness. If intensive care unit was necessary, cardiac intensive care unit was determined as the destination in order to allow seamless communication between cardiology and CTS. All of this will facilitate CTS to make an early decision regarding surgical candidacy. Our algorithm was then approved by our hospital administration prior to the advancing towards developing a clinical decision support tool. This tool is under development and once ready, will be implemented as a care pathway that will provide step by step guidance for the right choices in care of IE. This will help to minimize care variation and at the same time offer opportunities for electronic tracking of the process for continuous clinical quality improvement.

## Conclusion

The effective use of team development and quality improvement tools can assist institutions to identify an actionable leverage point to justify the need for MDT for IE. Our study is probably the first to describe MDT development for IE using quality improvement tools for the US setting and may serve as one example to assist other institutions to develop their own MDT.

## Acknowledgments

The authors acknowledge the valuable assistance and guidance from Karen Cox, PhD, RN, and Kristin Hahn-Cover, MD, from the Office of Clinical Effectiveness at University of Missouri Hospital and Clinics with this study.

These data were also presented as a poster at the IDWeek 2018, San Francisco, Cal. The poster abstract has been published in an online supplement of Open Forum Infectious Diseases as an abstract publication. [16]

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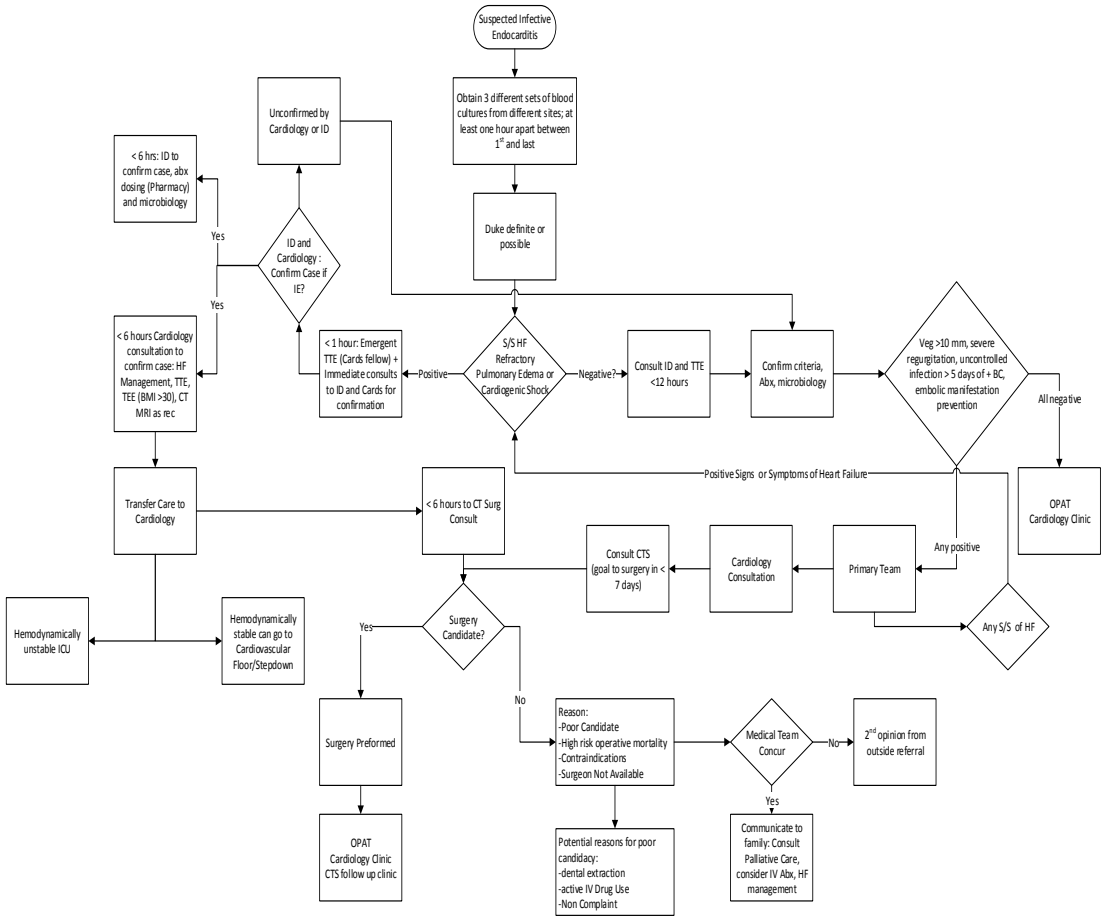



Figure 7. Proposed Algorithm for developing the clinical decision support tool (Abbreviations: ID - Infectious Diseases, S/S – Symptoms/ Signs, HF – Heart Failure, TTE – transthoracic echocardiogram, TEE – Transesophageal echocardiogram, Veg – vegetations, BC – blood culture, OPAT – Outpatient parenteral antimicrobial therapy, BMI – body mass index, Abx – antibiotics, CT- computed tomography, MRI – Magnetic resonance imaging, ICU – intensive care unit )

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## Disclosure

H. Regunath received honoraria from ©Getinge AB and ©Hamilton Medical. **MM**

# TIGER Team: Rapid Response at the University of Missouri

*by Catherine Messick Jones, MD, Kelly J. Butler, LPC & Karen R. Cox, RN*

School of Medicine
University of Missouri Health

**The University of Missouri Health Care TIGER Team has been a major success which continues to grow and evolve based on new knowledge in the international community working on Rapid Response Systems and local tailoring of our response to best meet the needs of our patients with the available resources.**



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## Abstract

**By the end of the 20th century, health care organizations world-wide were recognizing the benefits of a quick response when patients were experiencing a clinical decline and the difficulty in achieving that goal. The University of Missouri STAT Nurse program, developed in 1989, was an early innovation to deliver the "right care" at the "right time" every time. Over the years, the STAT Nurse program evolved and became the core component of a Rapid Response System. Today Rapid Response at University of Missouri Health Care is called the Targeted Interventional Group Emergency Response Team, also known as the TIGER Team after the much beloved University mascot.**

## Background

The grim survival statistics for in-hospital cardiac arrest were a major impetus to the development of Rapid Response Systems. Survival after in-hospital cardiac arrest has been relatively stable around 17-18% over the last 40 years despite many other advances in hospital care. [1-3] Studies have shown that the majority of patients in hospitals around the world have evidence of physiologic deterioration within a few hours prior to a cardiac arrest.[4-6] Among surgical patients, complication rates are similar in hospitals with high and low mortality. The difference in outcomes appears to be related to the timeliness and adequacy of the response to a complication. Deaths after a post-surgical complication with a slow or suboptimal response have been conceptualized as a "failure to rescue". [7-8]

The documented failures to recognize or act when patients have evidence of clinical decline or a postoperative complication led to a series of care innovations around the globe that we now recognize as Rapid Response Systems. Hospitals in Australia implemented "Medical Emergency Teams" consisting of an intensivist and critical care nurse who came to the general floors to assist staff there when patients were declining.[9-10] In the United Kingdom, nurse-led Critical Care Outreach teams were formed after the National Health Service committed to improving critical care services.[11-12] Borrowing ideas from overseas, hospitals in the United States also began to innovate, most commonly using the term Rapid Response Team to describe their programs which varied in composition from institution to institution depending on locally available resources.[13-14] Published data from before and after evaluations of these early programs suggested that cardiac arrests on the general floors, ICU days and hospital mortality could all be reduced. [9-14]

In 2005, a randomized control trial of Medical Emergency Team implementations in Australian hospitals was published that unexpectedly showed no significant difference in cardiac arrests, unplanned ICU admissions or unexpected death between the intervention and control hospitals. However, there were numerous confounding factors in the study that led many to question the results. Only 30% of the patients in the study hospitals actually had a MET activation when they met the criteria for clinical decline and greater than 50% of the "code team" calls in control hospitals were for patients that had not experienced a cardiac arrest suggesting that clinical practice in the control hospitals had already shifted to a Rapid Response model. Post hoc analyses showed a significant reduction in cardiac arrests and unexpected deaths over the course of the study period when data from intervention and control hospitals were combined consistent with the early before and after studies.[15]

Additional data supporting the development of Rapid Response Systems comes from studies of ICU patient outcomes. One such study, done in a community teaching hospital in Utah without a formal Rapid Response program, showed significant outcome differences between patients who met predetermined physiologic instability criteria but had delays in transfer to an ICU bed of greater than 4 hours in comparison to patients who were transferred more rapidly. Hospital length of stay and costs from the time the patients' were first noted to have instability were both markedly elevated in the delayed group. Although both groups of patient were equally ill as measured by Apache II scores when they first met the physiologic instability criteria, the hospital mortality was much higher in the delayed transfer group (44% vs 11%).[16] An accompanying editorial described delays in ICU transfer as "preventable adverse events".[17] A similar study done in Brazil in a hospital where the number of ICU beds was inadequate to meet the demand also demonstrated excess mortality in patients who met the criteria for ICU admission but could not be immediately transferred. They were able to calculate that each hour that ICU admission was delayed was independently associated with a 1.5% risk of ICU death.[18]

The results of the Medical Emergency Team randomized controlled trial led some to question the benefits of Rapid Response despite the positive outcomes in the earlier before and after studies and the poor patient outcome data from studies of delayed ICU admission. Many others felt intuitively that there were benefits and intensified their efforts to understand implementation and improve effectiveness of the teams. Rapid Response began to be seen as a two-pronged approach that consisted of an afferent or sensing arm to identify patients who were experiencing a clinical decline and an efferent or action arm that implemented the optimal medical response. It was also recognized that a true Rapid Response system would need governance to supply and organize the necessary resources as well as a performance improvement mechanism to monitor the process and outcomes.[19]

The Rapid Response "afferent limb" has evolved over the years from simple single vital sign criteria (used in most of the early studies previously cited) to include more sophisticated mechanisms. Single vital sign triggers are easy to implement since they are based on long-standing hospital practices but they lack specificity resulting in unnecessary calls. Aggregate weighted vital sign scoring systems can discriminate patients at risk of adverse outcomes with greater accuracy which prevents alarm fatigue at the bedside and reduces the workload required to generate a consistent Rapid Response.[20] Even more precise discrimination may be possible with commercially available computer algorithms that rely on electronic health record data including demographics, diagnoses and laboratory data.[21]

The Rapid Response "efferent limb" originally referred to the different team structures that have been used internationally ie Medical Emergency Team referring to a physician-led team, Critical Care Outreach Team indicating a nurse-led team and the more generic Rapid Response Team designation used in the United States where team membership and leadership is quite varied. Team members include experienced practitioners with appropriate professional credentials and additional certifications such as ACLS and PALS. Responders may or may not have other clinical responsibilities. In academic settings, trainees may also be involved in Rapid Response. The bedside nurse and primary physician are usually included as members of the response as well. Due to the high frequency of respiratory concerns, a Respiratory Therapist is a common

addition to physicians and nurses. Over time, Rapid Response Systems have often assumed responsibility for managing cardiac arrests in addition to responding to deteriorating patients. Some institutions have developed internal protocols for the management of other time-sensitive conditions that develop in hospitalized patients including stroke, ST elevation myocardial infarctions and severe sepsis.[22-23]

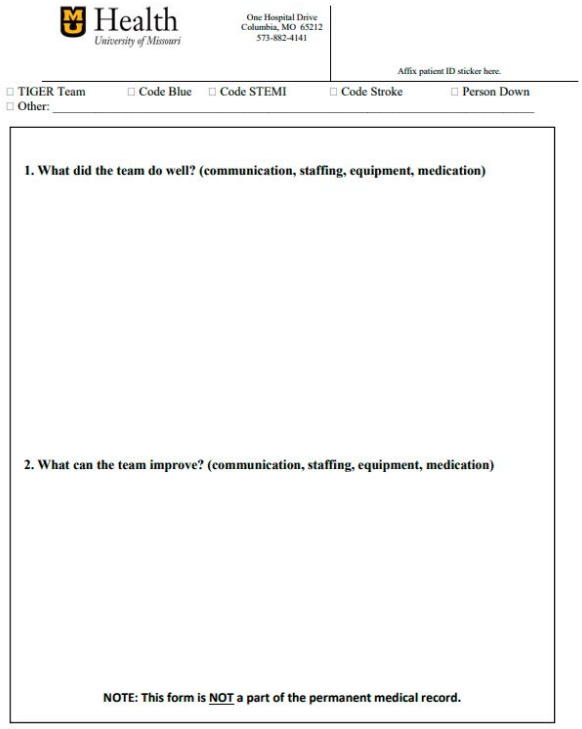
Performance metrics for the evaluation of Rapid Response Systems are still being developed. Common concerns include the frequency with the Rapid Response System is activated for patients who meet the institutional criteria and the response time reflecting staff performance. Patient outcomes include repeated activations, the time to ICU transfer when indicated and cardiac arrest outside of the ICU.[24] Some studies have suggested an institutional "dose effect" for Rapid Response calls so many organizations monitor the number of calls per 1000 admissions or patient-days.[25]

## University of Missouri Health Care Experience

In 2004, the Institute for Healthcare Improvement (IHI) announced a major initiative called the 100,000 Lives Campaign. U.S. hospitals were challenged to make six changes with a goal of saving 100,000 lives during an 18 month period from January 2005 to June 2006. In addition to delivering evidence-based care for acute myocardial infarction, implementing medication reconciliation, giving perioperative antibiotics to prevent surgical site infections, preventing central line infections and ventilator-associated pneumonia by using scientifically grounded bundles of care, IHI advocated that hospitals deploy Rapid Response Teams. Like most other health systems, the University of Missouri was an active participant. The University already had ongoing programs in all the targeted areas but decided to use the challenge to revamp the Stat Nurse program into a broader Rapid Response System which continues to serve our hospitalized patients today.[26]

The Stat Nurses remain an integral part of the Rapid Response System but their efforts are supplemented by ICU nurses who help with the response. Each ICU is partnered with general floors and other patient care areas that serve patients cared for by the same service line. The Medical ICU is partnered with the General Medicine floors and the GI

Table 1. TIGER Team Debrief Tool



Health
University of Missouri

One Hospital Drive
Columbia, MO 65212
573-882-4141

Affix patient ID sticker here.

☐ TIGER Team ☐ Code Blue ☐ Code STEMI ☐ Code Stroke ☐ Person Down
☐ Other: _____

1. What did the team do well? (communication, staffing, equipment, medication)

2. What can the team improve? (communication, staffing, equipment, medication)

NOTE: This form is NOT a part of the permanent medical record.

Table 2 . TIGER Team Activation Criteria

**Guidelines for TIGER team Activation**

Including, but are not limited to, the following indications or situations:

1. When a staff member is "worried" about the patient
2. New or symptomatic change in HR below 40 or above 120
3. New or symptomatic change in SBP below 90 mmHg or more than 40 mmHg change
4. New or symptomatic change in RR below eight (8) or above 28
5. New or symptomatic change in SpO2 below 88%
6. New or symptomatic change in temperature below 35°C
7. Acute change in urine output below 50ml in a four (4) hour period
8. Any acute respiratory distress (i.e. threatened airway, dislodged trach, stridor, bleeding, aspiration, etc.)
9. Changes in neurological status (level of alertness,v confusion, agitated, motor strength, ability to communicate, behavior change)
10. Unexplained or repeated seizures
11. Any acute decline in patient condition
12. Unanswered or prolonged response by physician
13. Chest Pain
14. Imminent non-ICU intubation
15. Requires non-rebreather mask for oxygenation
16. Needs urgent transfer to ICU

Table 3. National Early Warning Score Education Tool

| Early Warning Score = Sum of All Points | | | | | | | | Total Score |
|---|---|---|---|---|---|---|---|---|
| Points | 3 | 2 | 1 | 0 | 1 | 2 | 3 | |
| Temp (°C) | ≤ 35 | | 35.1-36 | 36.1-38 | 38.1-39 | ≥ 39.1 | | EWS ≥ 8<br>High risk<br>Consider ICU<br>VS Q 2 Hours |
| Heart Rate | ≤40 | | 41-50 | 51-90 | 91-110 | 111-130 | ≥ 131 | |
| Resp Rate | ≤ 8 | | 9 - 11 | 12 – 20 | | 21 – 24 | ≥ 25 | EWS 5 – 7<br>Increased risk<br>Consider PCU<br>VS Q 4 Hours |
| SBP | ≤90 | 91-100 | 101-110 | 111-219 | | | ≥ 220 | |
| Oxygen Saturation | ≤ 91 | 92-93 | 94 – 95 | ≥ 96 | | | | |
| Inspired $O_2$ | | | | Room Air | | Supple-mental $O_2$ | | |
| Alertness AVPUScale | | | | Alert | | | Voice, Pain or Unresponsive | EWS 0 – 4<br>Normal risk<br>VS Q 8 Hours |
| Smith GB et al. The ability of the National Early Warning Score to discriminate patients at risk of early cardiac arrest, unanticipated intensive care unit admission and death. Resuscitation 2013 84: 465-70 | | | | | | | | |

Table 4. Standing Orders

**Adult TIGER Team Orders**

(Targeted Interventional Group Emergency Response Team)

**Protocol Orders & Administration Record**

*Please check box [ ] and/or fill in blank to indicate implementation of that order*

**Treatments:**

*General:*

[ ] Finger stick Glucose
[ ] Obtain IV Access

*For **respiratory distress** or **hypoxemia**:*

[ ] albuterol HFN 2.5 mg/3 mL (0.083%) Neb Solution every 4 hours PRN impaired breathing.
[ ] ipratropium HFN 0.5 mg/2.5 mL (0.02%) Neb Solution every 4 hours PRN impaired breathing.
[ ] Oxygen Therapy: oxygen to keep saturation ≥ 92%
[ ] BiPAP (Bi-Level Positive Airway Pressure) [ ] CPAP (Continuous Positive Airway Pressure)

*For **reversible opioid toxicity**:*

[ ] naloxone Total of _____ mg naloxone administered.
0.4mg IV every 2 minutes PRN Somnolence/Respiratory Depression

If no response after 10 mg naloxone, question the diagnosis.

*For **reversible benzodiazepine toxicity**:*

[ ] flumazenil Total of _____ mg flumazenil administered.
0.2mg IV every 2 minutes PRN Somnolence/Respiratory Depression

If no response after 3 mg flumazenil, question the diagnosis.

*For **cardiac chest pain**:*

[ ] nitroglycerin Total of _____ mg nitroglycerin administered.
0.4mg sublingual every 5 minutes PRN Chest Pain

If no response after 3 doses nitroglycerin, question the diagnosis.

*For **hypotension**:* [ ] Normal Saline 500 mL over 10 minutes.

*For **symptomatic hypoglycemia (glucose < 60 mg/dL)**:* [ ] give 50 mL of D50W IV every 5 minutes PRN Hypoglycemia once.

For **anaphylactic reaction**:

[ ] Epinephrine 0.5 mg IM every 5 minutes PRN Anaphylaxis

For **seizures**:

[ ] Initially give lorazepam 4 mg IV over 5 minutes PRN seizure activity. Give lorazepam 2 mg IV every 2 minutes thereafter PRN unres
seizure activity.

**Laboratory:**

[ ] Type & Screen or Cross
[ ] HPD [ ]CK and CKMB [ ] Troponin-I [ ] BMP
[ ] Ionized Magnesium [ ] PT [ ] PTT

**Radiology:**

[ ] XR Chest Portable

**Cardiology:**

[ ] EKG, Adult

**Respiratory Care:**

[ ] ABG/Na/K/Ca RC

| | | | |
|---|---|---|---|
| Physician signature | pager | date | time |
| TIGER team Nurse Signature | pager | date | time |
| Respiratory Therapist signature | pager | date | time |

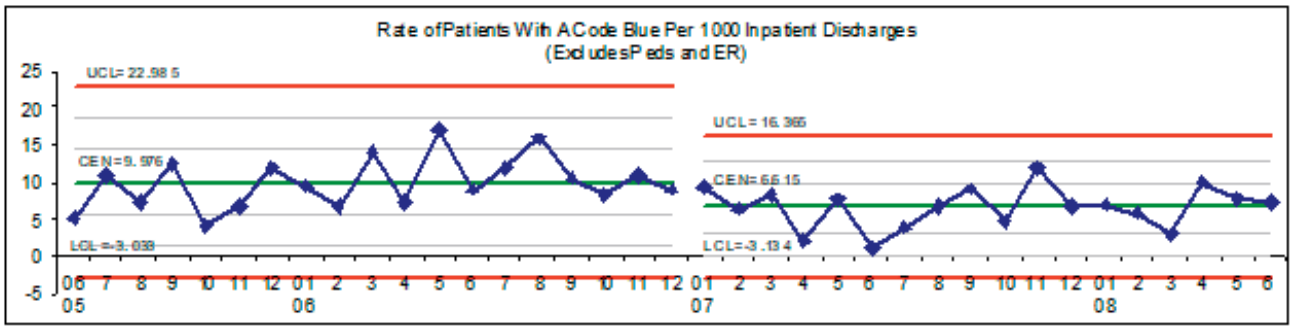



Figure 1. Control chart comparing the number of adult Code Blue patients per 1000 discharges pre- and post-TIGER team implementation.

Endoscopy Suite, the Surgical ICU with the Surgical floors and the Cardiac Intensive Care Unit with the Cardiology floor and Cath Lab, etc. The ICU nurse designated for TIGER Team calls is typically the nurse who will be assigned the next admission to that unit in order to provide nursing continuity of care for patients who need to move to a higher level of care. A respiratory therapist is also available to the team if needed and Anesthesia provides stat intubation services when requested. Although not originally designated as a formal TIGER Team member, over the years as patient volume has increased and resident duty hour restrictions have been implemented, the senior medicine resident on call has stepped in to provide physician coverage until someone from the patient's primary physician team arrives. The House Supervisor also responds to facilitate bed placement, free up any needed patient care resources and help coordinate activities.

Members of the team receive crew resource management training. The goal is to support the care being provided by the bedside nurse and primary team, not critique it. Standard response mantras regardless of the situation include "Thank you for calling" and " Better safe than sorry". After every call, the House Supervisor conducts a brief but formal debriefing session to identify opportunities for improvement and successes (Table 1).

The TIGER Team is usually activated by the patient's bedside nurse who is guided by a single vital sign trigger tool but any member of the health care team can call if they are worried about the patient (see Table 2). Patients and visitors can also activate the team by calling a number posted in every patient room. The University is currently working with Cerner to implement the National Early Warning Score[20], an aggregate weighted vital sign scoring system, as a trigger tool within the electronic medical record (Table 3). TIGER Team calls are announced via text paging rather that overhead paging.

The TIGER Team uses standing orders to initiate care for unstable patients (Table 4). Members are ACLS and / or PAL certified in the event the patient is in full arrest when they arrive. The TIGER Team is also the official "Code Blue" response team for cardiac arrest victims in any non-ICU and non-ED location. TIGER Team response has been extended to new inpatient locations away from the main campus including the Missouri Orthopedic Institute and Women and Children's Hospital. Specialized Code Stroke and Code STEMI protocols have been developed for inpatients with focal neurologic changes or chest pain. Recently STAT nurses have been trained in the use of power driver intraosseous devices for those situations where an unstable patient does not have IV access.

The activities of the TIGER Team are overseen by the Clinical Decline Committee which meets monthly. Members are drawn from clinical areas as well support services including quality improvement, pharmacy, telecommunications and distribution. Recently, representatives of the house staff have joined the committee to learn from the group and add the voice of trainees to the deliberations. The group reviews performance metrics, works on new protocols as well as reviewing and revising policies. Particular attention is given to the debriefs of actual calls in order to identify opportunities for improvement. System-wide changes in equipment, medications and the role of ancillary support personnel have resulted.

Initial before and after implementation statistics suggested that the TIGER Team reduced Code Blue events by 34% (Figure 1). Increasing utilization and the implementation of new protocols have increased the number of patients who have benefitted from this Rapid Response System.

The University of Missouri Health Care TIGER Team has been a major success which continues to grow and evolve based on new knowledge in the international community working on Rapid Response Systems and local tailoring of our response to best meet the needs of our patients with the available resources. Lives have been saved, our students and trainees have learned from a model system and our successes have been shared with others in order that they too may learn from our experiences. As we say here in Columbia, "Go TIGERs!"

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## Disclosure

None reported.

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# Update on Dual Antiplatelet Therapy for Secondary Stroke Prevention

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**Dual antiplatelet therapy post-acute minor stroke or high-risk TIA has proved to be efficacious in preventing a future ischemic event, but also puts patients at a higher risk for bleeding complications.**



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## Abstract

**Aspirin is recommended for patients with acute ischemic stroke within 24 hours of symptom onset. It may be beneficial for dual antiplatelet therapy including clopidogrel and aspirin to be administered in patients with minor stroke or transient ischemic attack for early secondary prevention, however, bleeding risk remains uncertain. This article will review the published literature concerning the role of dual antiplatelet therapy for secondary stroke prevention with focus on balancing both risk and benefit.**

## Introduction

Numerous studies have evaluated the safety and efficacy of dual antiplatelet therapy (DAPT) with clopidogrel, prasugrel or ticagrelor in combination with aspirin (ASA) to prevent secondary ischemic events including stroke and TIA. The 2018 Guidelines for Management of Acute Ischemic Stroke state that clopidogrel and aspirin could be beneficial for secondary stroke prevention if initiated within 24 hours of the stroke and then continued for 21 to 90 days.[2] This review will detail the published data for each of the three P2Y12 agents in combination with aspirin for secondary stroke prevention incorporating recent study information and provide updates to current guideline recommendations.

## Literature Review

A PubMed search was performed using the search terms P2Y12 stroke, dual antiplatelet therapy AND stroke, clopidogrel AND stroke OR transient ischemic attack, prasugrel AND stroke OR transient ischemic attack, ticagrelor AND stroke OR transient ischemic attack. All English-language clinical trials with human subjects were evaluated for inclusion. Articles pertaining to acute coronary syndromes, platelet reactivity, monitoring of P2Y12 inhibitors, atrial fibrillation and peripheral artery disease were excluded.

## Clopidogrel[1]

Clopidogrel was the first P2Y12 inhibitor on the market and is the only drug in its class to be indicated for prophylaxis after a cerebrovascular accident.[3] The CAPRIE trial first demonstrated clopidogrel effectiveness as compared to aspirin in reducing ischemic events in patients with atherothrombotic disease.[4] Following the findings of CAPRIE along with promising studies of DAPT therapy for coronary disease, the Aspirin and Clopidogrel Compared with Clopidogrel Alone After Recent Ischemic Stroke or Transient Ischemic Attack in High-

risk Patients (MATCH) trial evaluated the addition of 75mg of aspirin to clopidogrel for secondary stroke prevention in a randomized, double-blind, placebo-controlled trial.[5] The primary outcome was the first occurrence of an event included in the composite of ischemic stroke, myocardial infarction (MI), vascular death or re-hospitalization for an acute ischemic event. Secondary outcomes included individual components of the composite outcome as well as any incidence of death. Safety endpoints included any life-threatening bleeding event (a drop in hemoglobin of $\geq$50 grams per liter (g/L), significant hypotension requiring inotropes), symptomatic intracranial hemorrhage or transfusion of four or more units of red blood cells as well as major bleeding defined as significantly disabling intraocular bleeding or transfusion of three or less units of red blood cells. Patients included had an ischemic stroke or transient ischemic attack (TIA) in the previous three months plus one or more risk factors of a previous ischemic stroke, previous MI, angina pectoris, diabetes mellitus, or symptomatic peripheral arterial disease within the previous three years. The investigators excluded patients $<$40 years old, those with severe comorbid conditions, increased risk of bleeding, severe hepatic insufficiency, current peptic ulceration, history of systemic bleeding or other history of coagulopathy, as well as anyone with a contraindication to aspirin or clopidogrel. The groups were well-matched in terms of baseline characteristics. A total of 7,599 patients were randomized and after 18 months of follow-up no statistically significant difference was found between clopidogrel and aspirin (16%, n=596) versus placebo and clopidogrel (17%, n=636,) in regards to the primary outcome, p=0.244. There was, however, significantly more life-threatening bleeding in the combination group (3% vs. 1%, p$<$0.0001) as well as three times the amount of major or minor bleeding episodes. The MATCH study was the first large trial to evaluate DAPT in stroke patients and its findings concluded an unfavorable risk to benefit tradeoff for secondary prevention. The authors attributed the results in part to inclusion of patients with lacunar or microangiopathic cerebrovascular accidents as these events may not originate from an atherothrombotic origin.[5] This hypothesis was later supported in the SPS3 trial, which did not demonstrate a difference in secondary stroke prevention but rather an increase in major bleeding and death in patients with recent lacunar infarcts randomized to either clopidogrel plus aspirin or aspirin alone.[6]

Despite the negative findings of the MATCH study investigation into the role of DAPT in acute stroke continued with Hankey and colleagues who evaluated the combination of clopidogrel plus aspirin versus aspirin alone after a TIA or ischemic stroke in a subgroup analysis of the CHARISMA study.[7] The CHARISMA study was a multicenter, multinational, randomized, parallel group, double-blind trial that compared clopidogrel versus placebo in a mix of high-risk patients at risk for atherothrombotic events who were taking low-dose aspirin at the time of randomization. This sub-analysis of the CHARISMA trial hypothesized that the maximal benefit of DAPT could be seen within the first 30 days after the indexing event. The primary outcome evaluated was any stroke during the follow-up period of one, three and six months, and every six months thereafter until the trial ended. Secondary outcomes included MI, vascular death or the composite of stroke, MI or vascular death. Primary safety endpoints included any type of severe bleeding that was fatal, intracranial or caused hemodynamic compromise or surgical intervention. Secondary safety outcomes included any severity of bleeding, moderate bleeding that led to a transfusion and intracranial hemorrhage. Among the 4,320 patients with history of TIA or stroke, 1,331 patients were randomized within 30 days of a qualifying event while 2,989 were enrolled following 30 days of a TIA or stroke. There were no significant differences between the two groups in terms of baseline characteristics. Recurrent stroke rates trended less with combination therapy for patients randomized within 30 days (HR, 0.74; 95% CI, 0.48-1.16) compared to those randomized later (HR, 0.83; 95% CI, 0.60-1.14). There was an increase in any type of bleeding (37.4% vs. 20.5%, HR, 2.08; 95% CI, 1.86-2.34) as well as moderate bleeding (2.4% vs. 1.1%, HR, 2.15; 95% CI, 1.32-3.49) in the combination group versus aspirin monotherapy. Although not statistically significant this study suggested that patients randomized sooner after their qualifying event may experience a more favorable outcome at the expense of increased non-

severe bleeding.[7] Based on the results of MATCH and CHARISMA additional questions remain including the optimal duration of DAPT post-stroke as well as in what stroke sub-populations DAPT offers the best balance of safety and efficacy.

The Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack (CHANCE) trial was a randomized, double-blind, placebo-controlled trial in China that tested the hypothesis that three weeks of dual antiplatelet therapy with clopidogrel and ASA would decrease the risk of a recurrent stroke in comparison to ASA alone in patients with acute high-risk TIA or minor ischemic stroke.[8] Patients that were $\geq$40 years old, diagnosed with an acute minor ischemic stroke or TIA and were able to be randomized within 24 hours after symptom onset were included. A minor acute stroke was classified as a National Institutes of Health Stroke Scale (NIHSS) score of 3 or less at the time of randomization. The investigators' definition of a TIA was a focal brain ischemia with resolution of symptoms within 24 hours after onset as well as a moderate-to-high risk of stroke recurrence based on the ABCD criteria that includes age, blood pressure, clinical features, the duration of the TIA and diabetes history. Patients were excluded if they had a hemorrhage or other condition such as a vascular malformation, tumor, abscess or other major non-ischemic brain disease or changes in vision or isolated dizziness or vertigo without evidence of acute infarction on imaging studies, a modified Rankin scale score of $>$2, NIHSS score of $\geq$4 at time of randomization, a distinct indication for anticoagulation or a contraindication to antiplatelet medications, received anticoagulation in the past 10 days, history of intracranial hemorrhage, history gastrointestinal bleeding or major surgery in the past three months, future planned surgery or investigational treatment, TIA or minor stroke due to angiography or surgery, or a severe non-cardiovascular coexisting condition with a life expectancy of less than 3 months. Pregnant women or women of childbearing age that did not have a documented negative pregnancy test were also excluded. Patients were randomized to receive either 21 days of clopidogrel and aspirin or only aspirin with placebo and then clopidogrel only for days 22 to 90. The primary outcome was a new stroke event (either ischemic or hemorrhagic) at 90 days. The primary safety outcome was a moderate to severe bleeding event based on the Global Utilization of Streptokinase and Tissue-Plasminogen Activator for occluded Coronary Arteries (GUSTO) definition. Secondary outcomes included new clinical vascular event (ischemic stroke, hemorrhagic stroke, MI or vascular death) as a composite outcome and individual outcomes. A total of 5,170 patients were randomized between the two groups. The median time from the onset of qualifying minor stroke or TIA to randomization was 13 hours. Approximately 28% (n=1,145) of the patients were included due to a TIA. For the primary outcome, stroke recurrence was significantly reduced with DAPT (8.2%, n=212) versus monotherapy (11.7%, n=303), $p<0.001$. The composite secondary outcome of vascular events also occurred less with combination therapy (8.4% vs. 11.9%, $p<0.001$). Both groups had an equally low rate of moderate to severe hemorrhage. The CHANCE trial demonstrated for the first time administration of aspirin and clopidogrel within 24 hours of symptom onset of TIA or minor stroke reduced 90-day stroke recurrence without an increased rate of bleeding. Furthermore, in a one-year outcome follow-up study, the benefit of treatment with clopidogrel and aspirin for 21 days followed by clopidogrel alone for 90 days reduced the risk of subsequent stroke for up to one year.[9] The CHANCE trial has several important limitations including enrollment of Chinese patients who present with different stroke pathology (large versus small vessel infarcts) as well as a higher rate of cytochrome P450 2C19 polymorphisms associated with a decrease in clopidogrel effect. To address these issues and evaluate early DAPT therapy in a population including North Americans the Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA (POINT) trial was conducted.[10]

POINT was a randomized, double-blind, placebo-controlled trial from May 2010 to December 2017 at 269 sites in 10 countries. Patients were randomized to receive clopidogrel plus aspirin or placebo plus aspirin for 90 days. There were no significant differences between the two groups. The primary outcome was a composite of major ischemic events (ischemic stroke, MI or death from an ischemic vascular event) at 90 days. The primary safety outcome was risk of major hemorrhage. Secondary outcomes included each component of the primary outcome, composite

of primary outcome and major hemorrhage, and total number of ischemic and hemorrhagic strokes. The secondary safety outcomes were hemorrhagic stroke, symptomatic intracerebral hemorrhage, other symptomatic intracranial hemorrhage, other major and minor hemorrhage, or death from any cause. Results of the study demonstrated dual treatment patients experiencing fewer events (5%, n=121) compared to aspirin monotherapy (6.5%, n=160), p=0.02. A statistically significant difference was also seen in the individual secondary efficacy outcomes of ischemic stroke as well as ischemic or hemorrhagic stroke. Although more efficacious, the clopidogrel and aspirin group also had a statistically significant increase in major hemorrhages (0.9% vs. 0.4%, P=0.02), major hemorrhages other than intracranial hemorrhages (0.7% vs 0.3%, P=0.04) and minor hemorrhages compared to aspirin.[10] No difference was seen in hemorrhagic stroke, intracranial hemorrhage, or 90 day modified Rankin scores. These results starkly differ from CHANCE findings where efficacy was not offset by major bleeding in the exclusively Asian population. Therefore, the risk to benefit profile of early DAPT does not seem to translate to North American populations and therefore should be used with caution. Potential explanations for the higher observed bleeding rates in POINT include use of a higher clopidogrel loading dose (600mg vs. 300mg), longer duration of DAPT (90 vs. 21 days), more prevalent small vessel disease, and potentially fewer patients with cytochrome P450 2C19 polymorphisms.

Lastly, investigators of the Antiplatelet Therapy with Aspirin, Clopidogrel, and Dipyridamole versus Clopidogrel Alone or Aspirin and Dipyridamole in Patients with Acute Cerebral Ischemia (TARDIS) compared three antiplatelet medications for an intensive therapy regimen versus guideline-based monotherapy in a randomized, open-label, phase 3 superiority trial. 3,096 patients from 106 hospitals in four non-U.S. countries were randomized within 48 hours from onset of TIA or ischemic stroke. The trial was stopped early due to significantly more bleeding in the triple therapy group (20% vs. 9%, p<0.001) without a decrease in the primary outcome of recurrent stroke or TIA within 90 days (6% vs. 7%, p=0.47).[11] Findings from TARDIS further underscore the uncertainty in using combination antiplatelet regimens for preventing recurrent events in stroke patients.

## Prasugrel[1]

The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) was a phase 3, randomized clinical trial that evaluated clopidogrel versus prasugrel in patients with an acute coronary syndrome awaiting percutaneous coronary intervention (PCI).[12] This study found a benefit of prasugrel over clopidogrel for the composite primary endpoint of MI, stroke or death from cardiovascular causes (9.9% vs. 12.1%, p<0.001). Although prasugrel had fewer cardiovascular complications, the rate of non-CABG TIMI major bleeding was higher in the prasugrel versus clopidogrel group (2.4% vs 1.8%, p=0.03). Importantly, post-hoc analysis also revealed a lack of benefit and harm to patients in the prasugrel group that had experienced a previous ischemic stroke or TIA, weighed <60 kilograms or were >75 years old. Based on this data, prasugrel is contraindicated in patients with a history of a stroke or TIA and therapy should be discontinued if a patient currently receiving prasugrel experiences one of these events.

## Ticagrelor[1]

Currently, two independent studies have been completed evaluating the role of ticagrelor in patients with non-severe stroke or TIA. The Acute Stroke or Transient Ischemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes (SOCRATES) trial was an international double-blind, controlled study comparing the risk of major vascular events between ticagrelor and aspirin when given within 24 hours after symptom onset of a non-severe ischemic stroke or high-risk TIA.[13] 13,199 predominantly European patients with non-severe ischemic stroke (67.4%) were randomized to receive either a 180mg bolus followed by 90mg twice daily of ticagrelor or 300mg bolus followed by 100mg daily of aspirin. The primary outcome was time to the occurrence of stroke, MI, or death within 90 days. Although fewer patients receiving ticagrelor experienced the primary end point, statistical significance was not achieved (6.7% vs. 7.5%, p=0.07). Major bleeding including intracranial hemorrhage occurred similarly between the two groups (0.5% vs. 0.6%, p=0.45). Although the role of dual therapy was not assessed in this trial, the safety of ticagrelor demonstrated supports further evaluation for its use in combination therapy for secondary stroke prevention.

The Effect of Ticagrelor with Clopidogrel on High On-treatment Platelet Reactivity in Acute Stroke or Transient Ischemic Attack (PRINCE) trial evaluated whether the combination of ticagrelor and aspirin is superior to clopidogrel and aspirin in reducing 90-day high on-treatment platelet reactivity for acute minor stroke or transient ischemic attack, especially in patients with cytochrome P450 2C19 polymorphisms.[14,15] Preliminary data (n=675) demonstrated a non-statistically significant decrease in stroke with ticagrelor (6.3%) compared to clopidogrel (8.8%), p=0.20. However, a significant increase in non-severe bleeding (19% vs. 10.6%, p=0.003) was observed. Further study for use of ticagrelor in combination with aspirin to prevent recurrent ischemic stroke is warranted, and recruitment is ongoing for the Acute Stroke or Transient Ischemic attack Treated with Ticagrelor and Aspirin for Prevention of Stroke and Death (THALES) study (ClinicalTrials.gov number, NCT03354429). This is an industry sponsored trial evaluating 30 days of combination therapy compared to aspirin for preventing first subsequent stroke or death following a high-risk TIA or non-severe ischemic stroke. Target enrollment is 13,000 patients and the study is anticipated to complete in late 2019.

## Conclusion

Dual antiplatelet therapy post-acute minor stroke or high-risk TIA has proved to be efficacious in preventing a future ischemic event, but also puts patients at a higher risk for bleeding complications. Individual patient characteristics such as stroke pathology and potential for cytochrome P450 2C19 polymorphisms must be considered when weighing against each patient's risk of a recurrent ischemic event and potential for major bleeding. More potent P2Y12 inhibitors including prasugrel and ticagrelor as well as intensive therapy with three antiplatelet agents may exacerbate bleeding risk and should be avoided until more data become available. Further studies are also needed to determine the optimal duration for DAPT as benefit appears to be most pronounced in the short-term period post-stroke or TIA (within 7 days) while bleeding risk remains elevated throughout the extended duration of therapy. Lastly, additional clinical trials are needed to provide evidence for treatment preferences in patients with more severe ischemic strokes who are also not candidates for thrombolysis.

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## Disclosure

None.

MM

# Hepatic Encephalopathy in the Hospitalized Patient: A Review for Hospitalists

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**Involvement of multidisciplinary team consisting of clinicians, social workers, case managers, and pharmacists etc. at the time of admission or in an outpatient setting has the potential to lead to better outcomes, reduce readmission rates, and ease the burden of other financial and social costs.**



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## Abstract

**Hepatic encephalopathy is a well-recognized complication of decompensated cirrhosis. It is a reversible state of neurocognitive decline, the etiology of which is multifactorial. Diagnosis is predominantly clinical and usually a diagnosis of exclusion. The identification of precipitating factors and their correction is an essential part of the management along with medical therapies such as lactulose and rifaxmin.**

## Introduction

Hepatic encephalopathy (HE), also referred to as portosystemic encephalopathy (PSE), is one of the known complications of chronic decompensated liver disease. It is a reversible impairment of the neurocognitive function with the degree of impairment lying on a spectrum. It carries a significant burden on the patient as well as the healthcare system. It contributes to recurrent hospitalizations and ultimately the morbidity and mortality of the patient. As a consequence of the acute metabolic encephalopathy that accompanies hyperammonemia, the unsupervised patient may not be able to adequately take the lactulose and can present as stuporous or even comatose. The repeated hospitalizations also predispose to health care acquired infections as well which in turn negatively impact the morbidity and mortality. As decompensated cirrhosis is becoming more prevalent, there number of cases of hepatic encephalopathy are also increasing. Overt hepatic encephalopathy is reported in 30-40% patients suffering from cirrhosis and in 10-50% of those who have underwent transjugular intrahepatic portosystemic shunt (TIPS).[1] The cover form of hepatic encephalopathy occurs in about 20-60% patients with cirrhosis.[1] Once a patient with hepatic encephalopathy requires a hospitalization, they are usually cared for primarily by the hospitalist (exceptions being hepatology centers). This review article provides a brief overview regarding the management of hepatic encephalopathy in the hospital setting.

## Pathophysiology

The exact pathogenesis underlying hepatic encephalopathy has yet to be deciphered. It is thought to be due to a combination of factors and is considered to be multifactorial. The major factors involved in hepatic encephalopathy can be broadly categorized to include the following:[2,3]

Key factors involved in HE:[2,3]

### *1) Neurotoxins*

The most well recognized neurotoxin that is linked to HE is ammonia.[2] There are several mechanisms via which ammonia mediates neurotoxicity. The major sources of ammonia include the diet (production from amino acids), peripheral tissues (especially

skeletal muscle) and gastrointestinal tract.[4] The gut is the predominant source with the generation of ammonia from enterocytes (via the action of glutaminase on glutamine) and by the enzymatic action of urease-producing bacteria on nitrogen based compounds (like blood, urea, protein that has been ingested).[3-5] Helicobacter pylori has also been recognized as a contributor to ammonia production due to the degradation of urea[6] though the association between HE and H. pylori remains unclear at this time.[7] A healthy liver effectively prevents hyperammonemia by removing the ammonia from the portal venous system via the urea cycle (transformation to glutamine).[2] Due to portosystemic shunting as well as the compromised functionality of the liver there is accumulation of ammonia within the systemic circulation.[2] As extrahepatic clearance of ammonia takes place in the periphery in muscle, protein calorie malnutrition that occurs in cirrhotic patients also attributes to hyperammonemia.[2] Cerebral edema occurs due to the increased intracellular osmolarity that develops in astrocytes from the conversion of ammonia to toglutamine.[3] The glutamine that is generated in the cytoplasm of the astrocytes gets delivered to the mitochondria with a specialized carrier and is then covered to glutamate and ammonia (via the enzyme phosphate-activated glutaminase).[3] The increased concentrations of ammonia within the mitochondria of the astrocytes generates a mitochondrial permeability transition along with the formation of free radicals and exposure of the intra-mitochondrial contents to oxidative injury.[3,8] This leads to impairment of astrocyte function as well as edema of the astrocytes which is considered a major determinant in the pathogenesis of HE.[3] The resultant increase in the intracranial pressure can lead to the devastating potential of cerebral herniation. Oxidative stress also stimulates mitogen-activated protein kinases further potentiating astrocytic edema (via the protein aquaporin-4 which is the water channel present in large quantities on astrocytes).[3,9] Ammonia also exerts neurotoxicity by promoting the uptake of neutral amino acids (such as tyrosine, phenylalanine, and tryptophan) by the brain by augmenting the L-amino acid transporter (located on the blood-brain barrier) and hence impairing the production of neurotransmitters.[3,10]

### *2) Neurotransmission Impairment*

There are several modifications that take place within the cerebral tissue that impact the neurotransmitter pathways. There are changes that occur in the neural membranes (including receptor expression), functionality of enzymes, uptake of neurotransmitters that all lead to imbalance between excitatory and inhibitory signals.[3] There is augmentation of the gamma-aminobutyric acid (GABA)A-benzodiazepine transmission hence leading to neural inhibition.[3] Chemicals known as neurosteroids (allopregnanolone and tetrahydrodeoxycorticosterone) are present in increased amounts in cirrhotic patients and also further potentiate the effects of the this inhibitory system.[3] There are also alterations in the glutaminergic system along with changes in catecholamine levels (reduced levels of dopamine and norepinephrine) and serotoninergic system.[3]

### *3) System Inflammatory Response*

The System inflammatory response syndrome (SIRS) also plays a role in the pathogenesis of HE. Cirrhotic patients are known to be immunocompromised as compared to the general population hence more prone to developing infections. Cytokines are released during this pro-inflammatory response. Neuro-cognitive changes such as slowing of mentation (from mild to comatose state) occur with an entity known as sepsis-associated encephalopathy.[11] The impairment of cerebral function is thought to be secondary to changes in the blood flow, modifications in the metabolites in the brain as well as pro-inflammatory cytokines.[12] The cerebral tissue in the periventricular region has the ability to participate in the immune response (both adaptive and innate) and cells in that region such as the astrocytes, endothelial cells, microglia secrete cytokines.[3] This leads to the production of prostanoids and nitric oxide.[3] The translocation of microorganisms across the gastrointestinal tract mucosa can lead to chronic endotoxemia and hence the generation of inflammatory cytokines.[13] Ammonia can further potentiate the inflammatory reaction and SIRS by negatively impacting the function of neutrophils and even astrocytes.[14] All of these pathways ultimately generate a pro-inflammatory milieu and cause neuro-inflammation and hence contribute to development of HE.

### *4) Modifications in Metabolism of Brain Energy*

The main substrate for cerebral energy is glucose and hypoglycemia is a common phenomenon that is observed in cirrhotic patients. Hypoglycemia can impair the neurocognitive function to the extent of precipitating a comatose state. Impairment in the metabolism of glucose in the brain also takes place and

some studies suggest that elevated ammonia levels may play a role.[3]

### *5) Modifications in the Blood-Brain Barrier*

The permeability of the blood-brain barrier is increased in acute liver failure and this makes the cerebral tissue vulnerable to harmful agents.[3] The changes in the permeability also contribute to swelling of astrocytes and hence cerebral edema.[3] Alterations in the cerebral transport of amino acids also occurs due to the modification of permeability of this barrier.[3]

### *6) Bacterial Overgrowth*

Evaluating the composition of the gut bacterial flora in cirrhotics revealed that they had a predominance of pathogenic bacteria.[15] Pathogenic microorganisms were more often seen such as Enterobacteriaceae and Fusobacteriaceae (both linked to inflammation) and Alcaligenaceae (linked to neurocognitive dysfunction).[3]

## Classification

Hepatic encephalopathy can be categorized under four groups:[16]

1. Based on underlying disease[1]
- Type A: due to acute liver failure
- Type B: due to portosystemic bypass/shunting
- Type C: due to cirrhosis

2. Based on the severity of manifestations[16]
- The West Haven Criteria (minimal HE to grade IV) is used along with the International Society of Hepatic encephalopathy (ISHEN).
- Can be subdivided as covert (minimal or grade 1 HE) or overt (grade II-IV) forms.

3. Based on the time course[16]
- Episodic
- Recurrent: discrete spells that occur less than six months apart
- Persistent: neurocognitive changes that are present continually and superimposed with episodes of overt HE

4. Based on the presence of precipitating factors[16]
- Non-precipitated
- Precipitated

### *Common Triggers for HE[17]*

- Infections (such as spontaneous bacterial peritonitis)
- Excess use of diuretics
- Gastrointestinal bleeding
- Imbalance of electrolytes
- Constipation
- Medications: CNS depressants
- Non-compliance to treatment of HE (lactulose, rifaximin)

## Clinical Features

Hepatic Encephalopathy can present with a wide range of neurocognitive or psychiatric disturbances. Clinical features can range from mild confusion to coma. Clinically, patient with HE can be broadly categorized into minimal HE and overt HE. In minimal hepatic encephalopathy, patient have no recognizable clinical symptoms of HE but can have minor abnormalities on psychomotor and electrophysiological testing.[18]

The West Haven Criteria is a useful clinical tool that can be used to assess the severity and symptomatology of hepatic encephalopathy. Stage I presents with mild confusion, impairment of simple tasks such as subtraction and addition, or shortened attention span.[19] Stage II is characterized by lethargy, disorientation to time, or personality changes.[19] Stage III presents with even more severe symptoms consisting of somnolence to semi-stupor and gross disorientation.[19] Stage IV is coma and unresponsiveness to pain.[19]

In addition to these symptoms, disturbances of the sleep-wake cycle with excessive daytime sleepiness is frequently seen. Patients with hepatic encephalopathy can also exhibit motor symptoms such as asterixis, hypertonia, hyperreflexia.[19] EPS dysfunction in the form of muscular rigidity, bradykinesia, monotony, slowed speech, parkinsonian tremor, and dyskinesia can be present to varying degrees as well.[19] Although findings associated with HE are relatively nonspecific, the diagnosis can be reached with a fair amount of certainty under the proper context of history of underlying liver disease, typical lab abnormalities, and assessment and exclusion of other causes of altered mentation.

## Diagnosis

The diagnosis of hepatic encephalopathy is one that is predominantly clinical and is also a diagnosis of exclusion. Other etiologies of altered mentation have to be ruled out prior to attributing the neurocognitive impairment

to HE. There are tests available to define the degree of cognitive dysfunction and those are at times useful when evaluating altered mentation in a patient with cirrhosis. The gold standard clinical test that can be performed at the bedside and is very commonly used is the West Haven Criteria, though it has limitations due to being a subjective test.[17] Disorientation and asterixis are considered to be reliable clinical indicators of overt HE.[17] The diagnosis of overt HE is more readily made and it's covert HE that creates a diagnostic dilemma. The tests can be categorized into neuropsychological and psychometric tests.[20,21] The ISHEN also recommends that a minimum of two tests should be utilized as HE can impact numerous aspects of cognition.[17] The evaluation for minimal and covert hepatic encephalopathy is important as it can assess for the high risk patients. It can identify patients who are prone to develop overt HE and the presence of the subclinical impairment of mentation suggests that there may be a negative impact on the quality of life.[17] Patients with minimal and covert HE will likely have some impairment of their professional life as well.[17] Identifying such cases will allow for the education of family/caregivers as well as the patients themselves.[17] As testing can be expensive, it should only be carried out for cases that lack the presence of medical conditions or factors that may alter mentation (such as psychiatric illnesses, sedating medications, alcohol use).[17] It is recommended that the test be repeated in 6 months if it is normal.[22]

### *1) Neuropsychological and Psychometric Tests*

- Portosystemic encephalopathy (PSE) syndrome test: a paper pencil test that measures cognitive and psychomotor processing speed and visual-motor coordination.[17]
- Continuous Reaction Time (CRT) test: a computerized test that evaluates the time it takes to have a motor response in response to an auditory stimulus, hence it does require coordination between the reception of the auditory stimulus and the motor response.[17]
- Critical Flicker Frequency (CFF) test: a fused light is shown to the patient and the frequency at which it is noted to be flickering is noted and the frequency tends to decrease with the decline of neurocognition.
- The Stroop test: a computerized test that assesses psychomotor speed along with cognitive flexibility and is also available as an app for the smartphones.[17]
- Inhibitory Control Test (ICT): a computerized test that is based on response inhibition as well as evaluates working memory.[17]
- SCAN Test: a computerized test that assesses speed and accuracy while asking the patient to carry out digit recognition of increasing difficulty.[17]
- Electroencephalography (EEG) : it evaluates the activity of the cerebral cortex and does not require any effort on the behalf of the patient.[17] However metabolic etiologies of encephalopathy such as hyponatremia or sedative medications can impact the EEG results as well and this can confound the interpretation.[17]

### *2) Laboratory Tests*

Ammonia levels are not considered to be diagnostic for HE and do not correlate with the severity or the staging.[23] Conversely, a normal level will point towards an alternative diagnosis. Additional lab testing would be performed to exclude other etiologies if they are suspected.

### *3) Neuro-Imaging*

This should be carried out if an intracranial process is suspected and often a CT brain is obtained given the presentation of altered mentation in patients with HE.

## Management

Initial management of hepatic encephalopathy requires accurate determination of severity of encephalopathy.[24] Those at risk of airway compromise require prompt ICU care and elective intubation.[24] Alternative causes of altered mental status need to be ruled using imaging, labs, or other diagnostic modalities.

The mainstay of medical treatment in hepatic encephalopathy is to identify, control, and treat the underlying precipitating causes of hepatic encephalopathy. Some common precipitating factors include infections, GI bleeding, acid base disturbances, electrolyte abnormalities, overdiuresis, TIPS, medications noncompliance, sedatives, narcotics, or progression of liver dysfunction.[24] Actively searching and treating for the underlying cause is crucial to management as treating the precipitant cause can reverse overt hepatic encephalopathy in 90% of cases.[25]

Additionally, reducing the levels of ammonia in bloodstream via medical therapies is an equally important aspect of treatment. Non-absorbable disaccharides such as lactulose and lactitol are the initial treatment for overt HE. Lactulose dosing can be initiated with 25mL of syrup every 1-2 hours until at least 2 soft bowel movements per day with eventual uptitration of dose to maintain 2-3 bowel movements per day.[2] Lactulose is also the recommended therapy for prevention of recurrence of HE. Rifaximin is

used as an add-on agent to lactulose to maintain remission of HE by decreasing serum levels of ammonia and preventing bacterial translocation.[2] Rifaximin is usually given in cyclical or continuous dosing with daily therapy being the preferred treatment in the US.[26] The most commonly used total daily dose is 1100mg/day usually given in two split doses.[26]

Oral branch chain amino acids and IV L-Orthinine-L-Aspartate can be used as alternative agents for treatment of patients unresponsive to conventional therapy with lactulose and rifaximin.[2] Other antibiotics such as neomycin, metronidazole, and vancomycin have been used as alternative therapies but their use is limited as first line or long term therapy due to their side effect profile.[26] Assessment of nutrition status is another key component of treating HE effectively. Recommended daily energy intake and protein intake is 35-40kcal/kg ideal body weight and 1.2-1.5g/kg/day respectively.[2] Once an acute episode of overt hepatic encephalopathy is over, lactulose is recommended for prevention of future episodes of OHE.[17] Rifaximin is added to lactulose for prevention of OHE after the second episode.6 Routine prophylactic therapy with either lactulose or rifaximin is not recommended for post-TIPS hepatic encephalopathy.[17]

Assessment of home environment and ensuring proper follow-up and access to medications is an integral part of comprehensive hepatic encephalopathy treatment. Due to the nature of disease, patients with hepatic encephalopathy can often require significant help from family or other loved ones in managing their disease. Thus, involvement of multidisciplinary team consisting of clinicians, social workers, case managers, and pharmacists etc. at the time of admission or in an outpatient setting has the potential to lead to better outcomes, reduce readmission rates, and ease the burden of other financial and social costs.

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## Disclosure

None reported.

MM

# Approach to Positive Blood Cultures in the Hospitalized Patient: A Review

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**Blood cultures are a very useful tool in the diagnostic kit that a hospitalist carries and also one that is commonly utilized.**



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## Abstract

**The use of blood cultures as a diagnostic tool has increased over the years along with improvements in techniques and results. The diagnostic dilemma arises when blood cultures are positive and there is possibility of contamination. Hence obtaining blood cultures in the appropriate setting and the interpretation of blood cultures by the hospitalist is imperative to the management of the hospitalized patient.**

## Introduction

Blood cultures are an extremely important tool that is employed in the diagnosis and management of the hospitalized patient. The methodology and the techniques used in the collection of the specimens has certainly evolved over the years to provide more accurate results. Blood cultures are commonly obtained in patients with concerns for an underlying infectious process, whether it is bacterial or fungal. However at times they are also obtained unnecessarily by providers that are not aware of the indications for collection. Consequently, patients are being subjected to further testing, prolonged hospitalizations, and unnecessary antibiotic treatments leading to an increased expenditure with potential for patient harm. In the event of positive blood cultures, many factors need to be taken into account to appropriately decide the next steps of management. This review article focuses on the techniques of obtaining blood cultures, the indications as well as how to interpret the positive blood cultures.

## Techniques

The process of obtaining blood cultures is crucial as the yield can be negatively impacted if one does not exercise caution. Use of sterile technique is important as the chances of obtaining contaminated samples can drastically increase if not followed. As there are normal bacterial commensals on the skin, there are chances of having blood cultures become contaminated with these organisms. Obtaining blood cultures can be technically challenging in patients with morbid obesity and difficult to access veins increasing the risk for skin contamination, ESRD patients with limited access for venipuncture sites, critically ill patients with prolonged hospital stay having poor peripheral access sites. Hence, it becomes challenging to distinguish between an active infection as opposed to a false positive result. This not only poses a diagnostic dilemma but can also give rise to unnecessary testing or repetition of blood cultures which is costly. By properly cleaning the site of venipuncture[1] and not obtaining samples from peripheral intravenous lines the opportunity

Table 1. Common indications for blood cultures[9]

| | |
|---|---|
| **Sepsis: suspected or confirmed** | **Septic arthritis: native joint or prosthetic joint infection** |
| **Osteomyelitis** | **Meningitis** |
| **Endocarditis** | **Peritonitis** |
| **Pneumonia** | **Fever of unknown origin** |
| **Catheter associated blood stream infections** | **Immunocompromised patients with fever and/or leukopenia/leukocytosis** |
| **Soft tissue infections:** | **if severe systemic manifestations, underlying malignancy, immunocompromised state or unusual predisposing factor (immersion injury, animal bites)** |

for contamination can be minimized.[2,3] The Centers for Disease Control and Prevention (CDC) recommends that alcohol should be used to disinfect the skin overlying the site of venipuncture and then chlorhexidine is applied after which the site should be permitted to dry.[4] The tops of the blood culture bottles should also be sterilized with the application of 70% isopropyl alcohol.[4] Disinfecting agents such as iodine tincture, chlorhexidine gluconate, chlorine peroxide are more effective as compared to agents with povidone-iodine.[2,3] A key factor that is most important in yielding positive results and capturing bacterial or fungal bloodstream infections is the total volume of blood sample collected from a set of blood cultures.[2,3] Approximately 20-30 ml of blood is recommended to be collected per set of blood cultures in cases of adults whereas in children age and weight are factored in when deciding the optimal volume needed.[5] The number of sets of blood cultures is also imperative to having a good yield and in adults the recommendation is to obtain at least two sets of blood cultures and even at times up to four sets (such as in suspected endocarditis).[6,7] In each set one of the bottles should be aerobic and one should be anaerobic.[5] Many hospitalized patients have long term intravenous access in the form of central lines, peripherally inserted central catheter (PICC), ports or dialysis access lines. In these cases it is also imperative to obtain blood cultures from these sites in addition to peripheral venipuncture sites when evaluating for bloodstream infections. For catheter-associated blood stream infections (BSI), the catheter tip should be sent to the microbiology lab in addition to a blood culture from a peripheral venipuncture site.[8] A 5 cm of the distal portion of the catheter is recommended to be sent for roll-tip cultures .[8] Another important aspect of methodology is the timing of collection of the blood cultures, though this is not as important as the volume of blood that is obtained.[5] Ideally blood cultures should be obtained a few hours apart and trying to obtain them during times of febrile episodes if possible, as bacteremia may be intermittent.[5] Given the current technology, in most cases the blood cultures can be expected to show growth in 48 hours and monitoring for any growth beyond 5 days is rarely needed.[2,3] However prolonged incubation times as well as specific media may be needed in cases of infectious agents such as mycobacteria and certain fungi.[5] A point to be noted is that in cases of candidemia, blood cultures may not be positive in up to 50% of cases.[5] Hence if there is strong suspicion for this and the patient is not clinically improving then one should consider adding empiric anti-fungal coverage instead of completely relying on cultures to return as positive.

As described above, the process of collection of blood cultures is just as imperative as the interpretation of the results as it can significantly impact a clinician's decision. Therefore key factors such as sterilization techniques, volume of specimen, timing of the sample, and avoiding the use of peripheral intravenous lines for obtaining blood cultures should be taken into account for the practice of collection of blood.

## Indications

Blood cultures are used to aid in the diagnosis of patients with suspected sepsis secondary to either a fungemia or bacteremia. Ideally the collection of blood cultures should precede the initiation of appropriate anti-bacterial or anti-fungal therapy. Table 1 summarizes some of the common indications for obtaining blood cultures.

The white blood cell count is notoriously known to mislead clinicians and hence the clinical context and associated patient factors need to be considered. The presence of leukocytosis does not necessarily imply infection and nor does the absence of leukocytosis exclude it.[10] Hence clinical scores such as the SIRS (Systemic inflammatory response syndrome) criteria are often used to help in

assessing the need for blood cultures. Another set of clinical criteria that was coined by Shapiro et al knows as the Clinical Decision Rule, looks at variables that are categorized as major and minor and can be utilized when making the decision of whether or not to obtain a blood culture.[11] As per the criteria, blood cultures should be obtained if there is one major or two minor criteria that are being met.[11] See Figure 1.

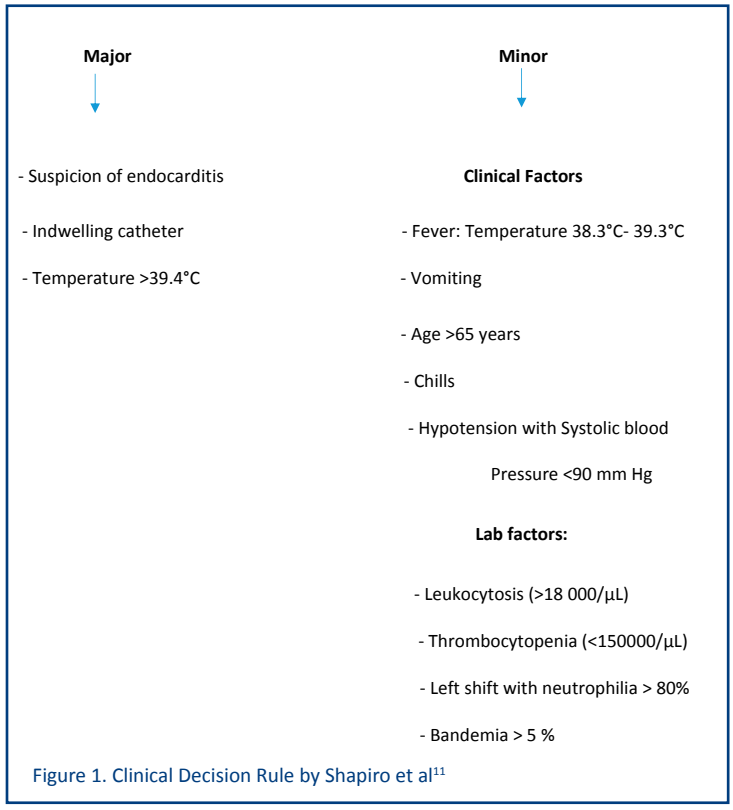


Figure 1. Clinical Decision Rule by Shapiro et al[11]

Hence, the clinical scenario needs to be considered along with the recognizing the pretest probability when ordering blood cultures for patients.[12] This will help to limit the number of blood cultures that are obtained and thereby lowering the associated cost of additional evaluation of the positive blood culture. The criteria developed by Shapiro et al. does not take into account leukopenia or hypothermia which the SIRS criteria does factor in. The presence of either of these in a patient with concern for an underlying infection or immunocompromised state should prompt the collection of blood cultures as well. The rule created by Shapiro et al is found to be highly sensitive but like the SIRS criteria has a low specificity.[12] As no clinical criteria is infallible, a clinician has to use their own judgement when using such scoring systems to execute a decision.

At times blood cultures should be repeated after the initiation of antimicrobial therapy to ensure that the bacteremia is cleared of infection and subsequent blood cultures are negative. The table below summarizes some of the common indications for obtaining follow-up blood cultures. See Table 2.

In cases of gram negative bacteremia there is evidence now to suggest that follow up blood cultures may not be needed. A study conducted by Canzoneri et all revealed that obtaining repeat blood cultures in the setting of gram negative bacteremia did not improve overall management and that mortality in patients admitted to intensive care was not linked to positivity on follow up blood cultures.[13]

## Interpretation of Positive Blood Cultures

Once blood cultures are obtained the next step is to carefully interpret the results taking into account the organism that is growing and combining it with the clinical picture. Bacteremia can be divided into two forms and it can be either continuous or intermittent form of bacteremia. Intermittent bacteremia is more prevalent as compared to the continuous and the organism sporadically enters thebloodstream.[9] Common scenarios in which it occurs include procedures in which mucosal surfaces such as the gingiva, urethral or rectal mucosa are involved (e.g. sigmoidoscopy, cystoscopy, oral procedures).[9] Other cases include bacterial infections of the joints, bone, lungs, deep soft tissues, central nervous system[9]. The continuous form of bacteremia is seen on cases such as infected endovascular grafts, endocarditis, infection of blood vessels (e.g. suppurative thrombophlebitis, endarteritis, infection of aneurysm).[9]

Bacteremia can also be classified based on whether it originates from within the vascular system or external to it.[9] Infections that originate within the vasculature are known as intravascular infections and can occur due to mycotic aneurysms, infective endocarditis, infections of endovascular grafts, other intravascular devices, or suppurative thrombophlebitis.[9] Infections that arise in infected organs and tissues enter the blood stream through the lymphatics and include infections such as those of the lungs.[9]

It is imperative that differentiation be made between a contaminant and a true bloodstream infection and at times this can be very challenging to do so. Institutional rates of contamination should not exceed 3% and if they do, then steps should be taken to minimize the rates.[14]

If blood cultures become positive > 72 hours after collection, depending on the organism, then contamination should be considered.[9] However, giving antibiotics before obtaining blood cultures can delay or prevent the growth of

Table 2. Indications for Repeating blood cultures:[9]

| | |
|---|---|
| **Endocarditis: confirmed or suspected** | **Suspicion of central nervous system or intra-abdominal infection** |
| ***Staphylococcus aureus* bacteremia** | **Signs and/or symptoms suggestive of infection > 72 hours after start of therapy** |
| **Poor penetration at site of infection: e.g. infection of joint space, abscess** | **Cases of intravascular lines, prosthetic vascular grafts, pacemakers** |
| **Infection with multi-drug resistant organisms: confirmed or suspected** | **Bacteremia with unidentified primary source** |

the bacteria and the growth of fastidious micro-organisms themselves should also be considered.[9] Common fastidious organisms include Kingella, Eikenella, Cardiobacterium, species of Haemophilus.[9]

The following microbiological organisms should always be considered as true infections and not as mere contaminants:[15]

- *Staphylococcus aureus*
- Group A streptococci
- Streptococcus pneumoniae
- Pseudomonas aeruginosa
- Enterobacteriaceae
- Bacteroidaceae
- Haemophilus influenzae
- *Candida* species

In cases of *Staphylococcus aureus* bacteremia or candidemia, infective endocarditis needs to be excluded with the use of an echocardiogram (ideally a trans-esophageal echocardiogram). For patients with candidemia, an ophthalmological exam needs to be performed to assess for features of endophthalmitis.

On the other hand, agents such Viridans group streptococci or enterococci can be either contaminants or actual infections.[9] For microbiological agents such as *Cutibacterium/ Propionibacterium acnes, Bacillus* species, coagulase-negative staphylococci as well as species of Corynebacterium it becomes much more challenging to differentiate a contaminant from an infection.[16-18] Evaluation for infective endocarditis needs to be kept in mind as well for cases of patients with prosthetic cardiac valves, intra-cardiac or intra-vascular devices and positive blood cultures with these organisms.[9]

Recent decades have seen an increase in rate of contamination that has been attributed to drawing cultures through indwelling catheters, improved lab techniques to detect minuscule quantities of microorganisms, changing specimen collection techniques aimed at minimizing needlestick injuries.[19] Additional cost incurred due to hospitalization, repeat blood cultures, therapy with IV antibiotics, imaging to evaluate the source not to mention emotional burden, waste of time and resources, add a significant financial burden to both the patient and the institution.

Factors that impact the possibility of a microorganism detected in blood being a contaminant include the cultured species, number of positive blood cultures obtained from different sources in a set, positive cultures in different sets, time to positivity, quantity to growth per culture sample. Positive blood cultures in a patient with clinical features of infection increases the likelihood of the blood culture being significant. Conversely, the rate of false positive blood culture increases in a patient with very low likelihood of bacteremia. Chang et al. found that in emergency departments with high volume of patients, those with critical illness, end-stage renal disease and the elderly were more likely to have blood culture contamination.[20] They attributed these findings to the time restriction and urgency of obtaining blood cultures in critically ill, and potential for antimicrobial resistance in the skin commensal of ESRD and elderly patients.

For bacteremia due to catheter- associated blood stream infections (BSIs), the diagnosis is usually made by exclusion of other sources of primary infection[5]. There are two major steps in the diagnosis with the first being that bacteremia has to be confirmed and then proving that the source of the bacteremia is the catheter itself.[5]

There are three main approaches used in the diagnosis of the catheter-associated BSIs:[5]

1. Time to positivity

Blood cultures are obtained from a peripheral vein and from the catheter/port simultaneously. If an identical organism grows from both sites, with the blood culture from the catheter/port turning positive > 2 hours prior to the peripheral blood culture then this usually indicates a catheter associated infection.[21]

2. Quantitative Blood cultures

Simultaneous blood culture are obtained from the catheter/port and one from a peripheral site. If an identical organism grows from both sites with the one obtained from that catheter/port having a five-fold increased growth in comparison to the peripheral culture then this favors a catheter associated infection.[22,23]

3. Catheter tip or segment cultures

The method developed by Maki et al involves obtaining a blood culture from peripheral venipuncture site and obtaining about a 5 cm length tip of the distal portion of the catheter after removal .[8] However this is able to diagnose the microbial agents that are growing on the external surface of the catheter (hence producing a biofilm that does not allow for penetrance of antibiotics) and not the ones presence in the lumen itself.[5] There are other methods that involve an endoluminal brush or a technique referred to as 'vortexing of the catheter tip' that may detect organisms in the lumen itself.[5]

If a catheter- associated bloodstream infection is diagnosed then ideally the intravascular device (catheter or port) needs to be removed. However in some cases, salvage with systemic and antibiotic lock therapy is used to prevent intravascular access from being removed (especially in cases of ports).

## Conclusion

Blood cultures are a very useful tool in the diagnostic kit that a hospitalist carries and also one that is commonly utilized. Hence the proper use of this is crucial to the management of the hospitalized patient. From the indications to the process of collection of blood cultures, a clinician should be aware of what this entails. Once the results of positive blood cultures are obtained then one should be cautious on how to interpret them. Further steps need to be carried out accordingly and one should not overlook a true infection from an uncommon organism and nor should a contaminant receive superfluous work-up. The consequences of further blood draws, unnecessary treatment with patient harm, increased consultations, additional diagnostic tests, prolonged hospitalizations among many others can all be prevented. Therefore, blood cultures can predispose to dilemmas regarding management and hospitalists need to be cognizant of how to interpret them.

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None reported.

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# Opioid Use Disorder Assessment Tools and Drug Screening

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**To optimize a combination of universal precautions and risk assessment prior to prescribing, clinicians should also make use of urine drug screening to provide the most consistent approach for opioid risk assessment.**



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## Abstract

**Opioid use disorder risk assessment tools cannot be used in isolation. In combination with standardized clinical examination, and, when indicated, urine drug screening, a validated risk assessment tool, improves the ability to detect opioid misuse. Even though no single tool has been shown to have both high interobserver reliability and high sensitivity, the standardized approach has still been shown to be superior to subjective care giver assessment. This article will provide a global approach to risk assessment in addition to reviewing the available tools.**

## Introduction

This is the fifth essay in the *Missouri Medicine* series stemming from the Larry Lewis Symposium in August 2017 exploring the transdisciplinary responses to an ongoing opioid epidemic.[1] The series moves beyond a focus on epidemiology and blame to evaluate actions to simultaneously address pain compassionately while mitigating the potential risks of opioid exposures. This essay explores evidence-based approaches to risk-stratifying individual patient's current or future likelihood of developing an opioid use disorder (OUD).

Interacting with patients who you suspect suffer from a substance use disorder (SUD) - and who may deny they have such a disorder - can often result in a confrontational, emotional situation. It may be stressful to both the caregiver and the patient. Minimizing such an emotional response and avoiding escalation of situations are critical in providing compassionate and optimal care. Despite requirements by oversight agencies, available guidelines, and widespread epidemic rates of overdose and death, many practitioners do not use a standardized approach for the risk assessment for substance misuse or addiction either at the time of the initial evaluation, or at follow-up visits. Many are still relying on their subjective impressions or poorly validated red flags (specific medication requested or dose) for judging risk level when screening patients.[2]

The concern for addiction risk is shared by physicians, patients, and their families. An important subset of patients with chronic pain syndromes may suffer from a SUD or a prior history of addiction. Similarly, some patients without any prior substance use issues may go on to develop aberrant drug related behaviors (ADRB) and SUD. It is difficult to label particular behaviors as ADRBs for many of the same features are also seen in patients suffering from oligoanalgesia. These include using other people's analgesics, accelerating dosing, running out of medications early, and seeking opioids from

more than one physician. Other behaviors inherently suggestive of SUD include: selling prescription drugs, forging prescriptions, using alternative routes of ingestion, multiple incidences of lost medications or prescriptions, or theft of paraphernalia from hospitals for injection.[3] There is considerable variability in the literature about the risk for de-novo addiction or SUD in patients who are started on opioid therapy for acute or chronic pain, but that risk exists. In a structured evidence-based review Fishbain estimated that 0.19% of chronic pain patients undergoing chronic opioid analgesic therapy developed ADRB's or SUD when no prior or current history of abuse or addiction was reported at the time of opioid initiation.[4]

Assessment requires the care giver use a standardized systematic approach to all patients who will be receiving (or are at risk of misusing) opioids. Practitioners are encouraged to embrace a "universal precautions" and rational approach to the treatment of pain, as published by Douglas Gourlay in 2005.[5] When HIV first entered the medical world, emotions also ran high: fear - even paranoia – was pervasive. Patients with HIV were isolated both medically and socially. It was only after universal precautions for blood borne pathogens became standard practice that those fears dissipated, and care improved.[6] Such an approach to the emotional situation surrounding opioids can be equally effective: assume all patients who are being prescribed opioids are at risk for addiction; screen all patients with a tool to establish possible or already existing opioid risk. When in a situation of uncertainty or of moderate risk, know that urine drug testing may provide additional help.

Any other approach, such as reserving risk assessment tools for patients in whom you have a clinical suspicion of misuse or addiction could lead to suboptimal patient care:

1. We will miss patients who have a SUD. We will prescribe opioids unwittingly to patients with a SUD and fail to initiate steps to help treat that disease. We will also appear to be inappropriately suspicious of those not suffering from, or who never develop a SUD.
2. We will not prevent the development of addiction. Many patients that we encounter have already been 'primed' to develop an addiction disorder due to genetic traits as well as social experiences and nutrigenic factors.[7] If that is the case, a single prescription can place them in danger. First do no harm. Identification of patients at high risk prior to prescribing an opioid can allow for movement toward a pain management approach not involving opioids. It can also make them aware of risk of addiction if use of opioids might seem to be a good option for pain relief in the future.

In the next sections, we will review the various risk assessment tools, how they help minimize patient risk in those suffering from chronic pain, and discuss briefly how urine screening might complement an addiction risk assessment tool.

Although this essay's focus is on the use of risk assessment tools, these tools cannot be used in isolation. The assessment of a patient presenting with either acute or chronic pain involves several distinct steps:

1. Biological assessment: history and physical examination should be performed to assess the anatomical and pathophysiologic sources of pain as well as previous diagnoses and treatment modalities for similar or other pain episodes. The pain intensity, pattern, quality and location are essential elements of this initial step. All of these descriptors aid in correctly diagnosing the type of pain a patient suffers and the types of analgesics that would be optimal. For many types of chronic pain, including neuropathic and diffuse wide spread pain, opioids offer little or no benefit.
2. Social assessment: home and work circumstances, social functioning, and any possible disability or impairment resulting from or related to pain
3. Psychological Assessment: It is important to assess patient's coping skills, any ADRB, SUD, addiction risk and history. The focus on addiction risk assessment and ongoing risk mitigation is outlined in the following sections.

## Overview of Risk Assessment Tools

Many studies have examined the prevalence of SUD and non-medicinal opioid use in specific populations, including those suffering from chronic pain. Important risks to patients who are prescribed opioids for pain include death, overdose and the development of an OUD. Given the enormous burden of opioid addiction, chronic non-cancer pain guidelines strongly suggest screening all patients for risk of substance abuse, misuse, and addiction before prescribing opioids.[8] Quantifying that risk can be challenging.

Multiple risk assessment tools were developed in an attempt to help quantify and identify patients more likely to suffer from SUD. These often rely on self-reporting and are

thus dependent on patients answering questions honestly: misrepresentation of their past histories or behaviors may significantly impact the resulting risk score. While the possibility of dishonesty may make us skeptical of answers, it should not preclude using these tools. Variability in the patient populations included in derivation studies as well as in some of the outcomes measured also weaken the ability to generalize the value of these tools. As a result, there is no one risk assessment tool that can guarantee accurate risk for any one patient. Until we incorporate DNA testing in our routine clinical care, the only way to prevent the development of an OUD is to keep a patient opioid-naïve, a solution that for many is neither practical nor optimal care. Ongoing prescribing of an opioid should be made understanding the limitations of the risk assessment tools, following the patient appropriately, and screening for ADRB on a regular basis. The performance of these tools in specific clinical environments (e.g. emergency department, hospital ward, pain clinic) has not been sufficiently studied for a specific tool to be recommended for a specific environment. Despite these limitations, it has been shown that use of a standardized tool is superior to practitioner subjective impressions; the latter is not recommended for risk assessment. The extra time to do a standardized risk assessment is well worth it, not only by reducing stress but also by providing better patient outcomes. For example, the Opioid Risk Tool takes only a minute, and usually provides useful information in a standardized manner. The authors use a risk assessment tool for every patient for whom they are considering prescribing an opioid outside of the hospital setting. This aligns with the 'universal precautions' mindset described above.

Once a risk is estimated, the use of that information is not always straightforward. As stated above, the tools are not infallible. The results need to be placed in context with other efforts to help reduce risk, such as limiting the quantity or duration of prescriptions, urine drug screening, communication with other care providers, making sure that the patient is obtaining the expected benefits from the opioids, ensuring access to appropriate follow-up for pain management[10] and other efforts to monitor for SUD[11] or ADRB.

Included in the review are 16 different opioid risk assessment tools, listed alphabetically in Table 1. The next few paragraphs will outline what the authors consider to be the best performing of those tools. The two tools most used by the authors are the Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R)[12], and the Opioid Risk Tool (ORT)[13]. The other two tools discussed are perhaps the best to use when working with a patient already being prescribed opioids. It is to be noted that some of the tools, such as the Aberrant Drug Behavior Index include some of the other tools as part of their overall assessment.[14]

## Recommended Risk Assessment Tools

### *Current Opioid Misuse Measure (COMM®)*

The COMM is a 17-question patient assessment tool designed to identify ADRB's during chronic opioid therapy. Each of the 17 items is scored 0-4 points. Total score can range from 0-68. A score of ≥9 is suggestive of current ADRB with 77% sensitivity and 66% specificity. The COMM is one of the most commonly used tools for patients on long-term opioid therapy and has been validated by high quality studies.[15] One validation study found 71% sensitivity and 71% specificity using the cutoff of 9.[16] A subsequent study has shown a 77% sensitivity and 77% specificity when a cutoff of 13 is used.[17]

### *Opioid Risk Tool (ORT)*

This is a 5-question screening tool designed for use in adults to assess the risk for opioid abuse or ADRB. A score is given for a range of responses on each of the 5 items and the total used to predict for low, moderate or high risk for ADRB. A score of 0-3 is low risk, 4-7 moderate risk, and 8 or higher is considered high risk for opioid misuse. The ORT is widely used, despite lack of evidence demonstrating superior performance over other tools. In fact, there have been no trials comparing performance of any of these tools side by side. The original study demonstrated that patients in a low risk category had no ADRB's 94% of the time while 91% of those categorized as high risk exhibited ADRB's.[13] Subsequent studies found the range of sensitivity to be much lower, varying between 18%-75%. Specificity was found to be between 54%-88%.[18,19,20,21] A benefit of the ORT is that it is included in Smartphone apps such as MDCalc® increasing bedside accessibility.

### *Patient Medication Questionnaire (PMQ)*

The PMQ is a 26-question assessment tool using 0-4 point scale to assess for ADRB in patients already taking opioid medications for pain. Scores can range from 0-104. In the derivation study, a score <25 is considered low risk for opioid misuse, 25-30 indicates problematic use, and >30 close monitoring and consideration of titrating the patient off opioids.[22] One validation study found 74% sensitivity and 93% specificity for a reduced item PMQ.[23] A subsequent high quality study, however, demonstrated 36% sensitivity and 78% specificity.[18]

Table 1: Opioid Risk Assessment Tools

| Tool | Validated (y/n) | Year of publication |
|---|---|---|
| **Aberrant Drug Behavior Index**[14] | N | 2007 |
| **Addiction Behaviors Checklist**[25] | Y | 2006 |
| **Brief Risk Interview**[26] | Y | 2013 |
| **Brief Risk Questionnaire**[20] | Y | 2015 |
| **Current Opioid Misuse Measure**[15] | Y | 2007 |
| **Diagnosis Intractability Risk and Efficacy Score**[9] | Y | 2006 |
| **Drug Misuse Index**[27] | N | 2007 |
| **Opioid Compliance Checklist**[28] | N | 2014 |
| **Opioid Risk Tool**[13] | Y | 2005 |
| **Patient Medication Questionnaire**[22] | Y | 2004 |
| **Prescription Drug Use Questionnaire**[29] | N | 1998 |
| **Prescription Drug Use Questionnaire Self-Report**[30] | Y | 2008 |
| **Prescription Opioid Misuse Index**[31] | N | 2008 |
| **Prescription Opioid Therapy Questionnaire**[32] | N | 2004 |
| **Screener and Opioid Assessment for Patients with Pain-Revised**[12] | Y | 2008 |
| **Screening Instrument for Substance Abuse Potential**[33] | N | 2008 |

### *Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP®-R)*

This is a 24-question screening tool, and is a revision of the original SOAPP®. It is designed to predict ADRB prior to initiation of long-term opioid therapy. Each of the 24 items is rated 0 (never),1, 2, 3, 4 (very often) for a total maximum of 96. A score of ≥18 indicates a patient is at higher risk for misusing prescribed opioids.[12] Validation studies suggest 81% sensitivity and 68% specificity. External studies found sensitivity to range between 41%-79% and the specificity between 50%-71%.[21,24] The SOAPP-R has been extensively studied and is very methodologically compelling, but its sensitivity seems to be lower than other tools.

## What Research Do We Need to Move Forward?

To reach the point where a risk assessment tool can be highly reliable for the patient in front of you will be extremely difficult – it is why the use of the available tools must be combined with other factors as we have indicated. How do researchers overcome possible dishonesty of patients, something almost never seen in other types of clinical research? We would need to identify and demonstrate reproducibility of test results, interobserver reliability and consistency of results in different clinical settings. It is easy for the clinician to be skeptical of these tools and continue to rely on subjective impressions; nevertheless, such an approach, as stated above, may lead to worse outcomes for the patient. Next steps should be evaluating the more used tools in conjunction with the universal precautions approach so see if the standardized approach is superior to a risk tool alone.

### *Urine Drug Monitoring*

Healthcare providers who treat chronic pain should be familiar with urine drug monitoring as risk assessment is greatly enhanced by properly employing and interpreting these tests. In fact, it is one of the few objective measures available that can provide valuable information often not forthcoming when implementing other comprehensive strategies for risk mitigation. Furthermore, there is some evidence that urine drug monitoring improves patient compliance with opioid treatment.[34,35] Despite evidence to support it, many physicians do not use drug monitoring in their patients on opioid therapy.[36]

Urine drug monitoring is an essential part of clinical assessment of patients before and during opioid therapy. As with other risk assessment tools, a "universal precautions" approach simplifies patient expectations and conversations about urine drug monitoring. Both routine and random

urine testing may be useful in specific contexts of chronic pain management. In the lowest risk groups and in those who show a high degree of reliability with results, it may be reasonable to screen infrequently and on a scheduled basis. In high-risk individuals or in those who have unexpected results, are clinically unstable, or exhibit ADRB's, frequency may need to be as frequent as every week and incorporate random screening.

Clinicians need to understand test characteristics including the possibilities for false positive and false negative results before ordering or attempting to interpret urine drug tests. Communicating with the lab facility may allow clarification of the limitations and proper interpretation of results; consultation with the lab you will use should be sought out before employing urine drug testing with patients. The tests should include a package insert which explains their limitations, i.e., what will turn the test positive. Not understanding this leads to poor patient care. For instance, patients have been fired after receiving a prescription for oxycodone and having a negative opioid screen as the provider did not realize the assay did not detect oxycodone.

Planning for discussions or conversations with patients is time well spent before employing urine drug monitoring. It is essential to strategize and discuss with patients how abnormal test results will be treated. A positive point of care test result may be sent for confirmatory testing using gas chromatography or mass spectrometry. In addition, a planned consequence of abnormal test results often includes an increased frequency of testing. All results, patient responses, and ADRB's should be addressed as soon as possible, with the actions taken documented. In patients being treated for an OUD, a positive screen should not automatically result in patients being removed from treatment.

### *Point of Care Testing*

Point of care or screening urine drug monitoring "dipstick" testing is cheap, quick to interpret, and sensitive enough to be useful for most situations where the risk or reliability of patient reporting is in question.[37] It is the usual office-based test that can help guide more specific tests. Results are immediate and may be interpreted and appropriate actions can be taken during the office visit.

Although quite specific, these tests can be tampered with and results altered. Temperature measurement, specific gravity, and pH can all be helpful in identifying tampering, but centers dealing with opioid agonist therapy for addiction may require more elaborate efforts to detect and prevent tampering. This may include observed urine collection. It should be noted that some opioids require specific testing, as some drugs such as methadone, oxycodone, hydrocodone, buprenorphine, or fentanyl are not identified by the specific antibodies used for the immunoassay testing for morphine. Understanding this is growing increasingly important as the illicit opioid supply changes as few of the designer drugs will result in positive tests. As such, a patient can easily have a current OUD and a negative urine drug monitoring test. Other tests for non-opioids may be very specific. A positive result for cocaine, marijuana, or heroin is rarely falsely positive because of the specific analytes measured. However, benzodiazepines suffer many of the same limitations as do non-heroin opioids. Just as important is that even though these tests result in a binary 'positive' or 'negative', there are cut-offs to turn them positive. This is why eating a poppy seed bagel or being around marijuana smoke will not result in a positive immunoassay.

### *Confirmation Testing*

These tests, which are generally done by very large laboratories, take much longer than point of care tests and are significantly more expensive but provide reliable, definitive results. Confirmation testing includes gas chromatography/mass spectrometry or liquid chromatography. They generally provide evidence for a specific level of detection and may detail information about metabolites. Interpretation of these results may still require a detailed understanding of timing, substances prescribed, and the metabolism of specific opioids and other drugs. Additionally, these tests are more expensive than immunoassays and are not readily available for bedside testing in the office or the hospital.

## Risks from Concurrent Use of Other Substances: Screening for Non-opioid General Substance Abuse

Further complicating the issue of opioid therapy and SUDs, many other substances interact with opioids and alter the effectiveness and safety of opioid therapy for analgesia. Smoking tobacco alters the metabolism of opioids; chronic smokers are more likely to exhibit

ADRB and suffer from drug dependence.[38] Additionally, combining opioids with other sedatives increases the morbidity and mortality from opioids.[39]

### *Written Agreements*

There is poor evidence for the effectiveness of opioid treatment agreements, but they may help clarify a "universal precautions" approach. Furthermore, a written agreement may clarify the goals of opioid trials, tapers, and also when it may be reasonable to terminate opioid therapy. The authors recommend using treatment agreements for use of opioids for chronic non-cancer pain.

### *Tamper Resistant Formulations*

Some formulations may help reduce the possibility or convenience of misusing or changing the route of administration of certain medications. These formulations intend to make it more difficult (but not impossible) to inject, nasally insufflate, or manipulate the release timing in order to achieve a more desirable intoxication effect. Although tamper-resistant formulations may be helpful in specific circumstances, individuals may switch to using other opioids without tamper resistant strategies in order to achieve intoxication or to decrease drug costs.

## Risk Assessment for Opioid Use Disorder After Hospital Discharge

Patients who are on opioid agonist therapy, but who require admission for an acutely painful condition are at high risk for returning to opioid misuse. There is understandable reluctance – both from the provider and the patient – to include opioids within the pain management plan. It has been recognized however that failure to adequately control acute severe pain carries greater risk of return to opioid misuse than does proper – controlled – use of opioids to manage the pain. For those patients who do require opioids as part of their pain management, a locked patient-controlled analgesia pump is the preferred method of delivering the opioids. In addition, if they are discharged on opioids, having a responsible adult monitor their use is also recommended.

Predicting chronic opioid therapy after hospital discharge has been studied.[40] Whether use of such a model can also identify the subgroup of these patients requiring longer opioid use who are at risk for opioid misuse remains unknown. It would also be of value to see if combining this predictive model with an existing opioid risk assessment tool could better identify at-risk patients.

## When Addiction is Highly Suspected or Confirmed

For patients in acute opioid withdrawal and a clear history of addiction, referral to appropriate opioid agonist therapy addiction services is recommended.[41] Methadone and buprenorphine programs are effective strategies for OUD that are cost-effective and reduce mortality and morbidity. Initiation of buprenorphine is an option in the emergency department or hospital ward in some jurisdictions, but should only be undertaken by those with a clear understanding of the mechanisms and pathway to ongoing care.[42] Ideally, patients who have buprenorphine initiated in the emergency department should be referred to an opioid-agonist therapy clinic (or a buprenorphine certified primary physician) within the next 48 hours.

## Summary

None of the risk assessment tools are able to predict perfectly which patients will ultimately suffer from OUD if prescribed opioids in their pain management. Of the tools used to assess risk for ADRBs in patients being considered for opioid therapy, the SOAPP-R, and ORT most accurately add to the clinician's ability to predict OUD risk. Each instrument has unique limitations and validity across different populations is unclear. Once patients have initiated opioid therapy and transitioned to long-term opioid therapy, the PMQ and the COMM appear to be somewhat better than other tools to predict the development of ADRB in that setting. Despite relatively weak evidence to support the use of any one tool, recommendations strongly encourage use of risk assessment tools prior to initiating opioid therapy. Risk assessment should be repeated regularly during the course of opioid therapy. To optimize a combination of universal precautions and risk assessment prior to prescribing, clinicians should also make use of urine drug screening to provide the most consistent approach for opioid risk assessment. Risk assessment tools and urine drug screening both have flaws, but using them provides better patient outcomes than physician subjective impressions.

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## Disclosure

None reported.

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# Factors in Accessing Routine Health Care: Mental Health and Postpartum Mothers

*by Patricia J. Norton, MD, Mary Mosley, MA, David G. McBride, PhD & Venkata Garikapaty, PhD*

**Women who do not seek prenatal care are at significantly higher risk of not accessing a postpartum care visit.**



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## Abstract

### *Objectives*

**One strategy proposed to decrease the maternal mortality and morbidity in the United States is to increase the rate which new mothers access routine postpartum care. Using Missouri's Pregnancy Risk Assessment Monitoring System (MO PRAMS) data, this retrospective study analyzed whether a self-reported history of depressive symptoms during the postpartum period was associated with a decreased rate of accessing the postpartum care visit (PPCV).**

### *Methods*

**Data were collected on 7,357 new mothers who completed the Missouri PRAMS survey between 2009-2014. New mothers, in the Missouri's registry of birth certificates who have given birth in the last 2-4 months, were randomly selected for inclusion in the survey. A mixed-mode survey method with a prescribed protocol for data collection was utilized.**

### *Results*

**Fourteen percent of the respondents (1,093 new mothers) reported symptoms associated with postpartum depression. A logistic regression analysis showed that among these women a weak association was found between not accessing routine PPCV and the report of depressive symptoms (p=.0254; OR=1.344 with 95%CI=1.037-1.741). This association is a new finding.**

### *Conclusions*

**The study finds a weakly negative association between self-reported symptoms of postpartum depression and accessing routine postpartum care. As this is a new finding, further research is needed for verification of this association.**

## Introduction

The maternal mortality ratio (MMR) is rising in the United States (see Appendices for definitions of MMR).[1] Data from 1990–2013 in the Global Burden of Disease Study show an annual increase of 1.7%.[2] A subsequent research collaborated this study.[3] By analyzing the Center for Disease Control and Prevention data 2010-2014, the United Health Foundation finds Missouri ranks poorly at 42nd in the nation in maternal mortality with a ratio of 28.5 deaths per 100,000 live births.[4] The rising maternal mortality has prompted increasing resources within both medical and public health professionals to identify contributing factors and implement new protocols to improve pregnancy outcomes.

One strategy proposed to lower the United States' maternal mortality and morbidity in the postpartum period and in subsequent pregnancies is to increase the rate at which new mothers access postpartum care (postpartum care visit, PPCV).[5,6,7] The rate at which American mothers access PPCV varies, dependent on the instrument used in measurement. Studies using self-reported data indicate rates of PPCV between 85% and 94%.[8,9,10] Using medical charts and insurance claims data (Healthcare Effectiveness Data and Information Set, HEDIS data) from 2014, U. S. National Committee for Quality Assurance finds lower rates of PPCV. The rates vary by type of health care plan: private HMO, 76.9%; private PPO, 68.4 %; and Medicaid HMO, 61.8%.[11]

Previous studies have searched for associations between various demographic characteristics and lower rates of postpartum care utilization. No consensus exists on how race/ethnicity[7,8,9,11,12] or maternal age [9.10.12,13] affects rates of accessing PPCV. Lower rates of accessing PPCV are associated with lower educational attainment [9,10,14] and lower socio-economic status.[9,10,12] Three studies[9,10,12] report mothers who did not access prenatal care are associated with lower rates of PPCV (OR = 3.39).[10] Additionally, women who did not provide routine well-child visits for their child are less likely to access PPVC.[9] Other studies link marital status, smoking in the last 3 months of pregnancy, drinking in the last three months of pregnancy, never breastfeeding and lack of well-child care checkup of the newborn to lower PPCV rates.[9,10]

A review of the literature suggests a possible link between symptoms of depression and lower rates of seeking medical care.[15, 16] The first article is from a primary care practice in England which looks at mental health diagnosis in relationship to failure to keep appointments to a primary care provider (specifically prenatal or postpartum care visits are excluded). The retrospective case-control study consists of 203 men and women, age 15 to 35. For individuals with a history of depression the adjusted odds ratio (OR) of missing an appointment is 3.62 (95% C.I. =2.12–6.20) in comparison to their matched controls without a history of depression.[15] The second article is a qualitative study from Maryland which reports perceived barriers to PPCV among 22 new mothers with a history of gestational diabetes. Eighty-two percent (18/22) of the women attended a PPCV.[16] Of note, among the four women who did not attend a PPCV, one new mother reports her depressed mood as a barrier that prevented accessing the postpartum visit. These two studies suggest a possible association of depression or depressed mood affecting accessing health care. These two studies suggest an observational study examining the relation between postpartum depression and the rate of accessing PPCV is an area for investigation.

In new mothers, depressive symptoms typically begin at ≥ 4 weeks postpartum with the highest rates of postpartum depression symptomology occurring at 2-3 months.[17] Most studies place the postpartum depressive symptoms rate at between 10 to 15% in the U. S.[18,19,20] Is postpartum depression a factor in obtaining routine, potentially life-saving, postpartum medical care? The objective of this study is to ascertain whether a self-reported history of depressive symptoms during the postpartum period is associated with a decreased rate of accessing postpartum care.

## Methods

This retrospective cohort study uses the data from the MO Pregnancy Risk Assessment Monitoring System (MO PRAMS), which is maintained by the MO Department of Health and Senior Services (DHSS). The MO PRAMS recruits participants by random selection from the Missouri registry of birth certificates on file; approximately 200 Missouri mothers, per month, are randomly selected who have given birth to a live infant in the past 2-4 months.[21,22] The data collection occurs by a mixed-mode survey method: a detailed, timed protocol is followed in delivering a self-reporting survey to the new mother; a written survey is first sent to the maternal residence and if no response has been received after three attempts, a phone interview is pursued to complete the survey. Excluded from the study are those who are mentally incapacitated, deceased, and mothers of multiple births (> 3). Missouri PRAMS received responses from 10,513 mothers for the 2009-2014 survey years, with an aggregated weighted response rate of 70.9%.

The CDC creates the national PRAMS survey of 59 "core questions," which cover topics including health insurance coverage, pre-pregnancy, prenatal and postnatal maternal health, and health behaviors along with questions on delivery, newborn nutrition, and care. All state PRAMS surveys contain these core questions. States can add additional questions from a list of 185 "standard questions" vetted by the CDC. State can also develop additional questions. The Missouri PRAMS adds 23 standard questions to the 59 core questions.

This study cohort includes all mothers in the MO PRAMS database for the years 2009, 2010, 2011, 2012,

2013, and 2014. The primary predictive variable under inquiry is a self-report of depressive symptoms during the postpartum period. A woman is defined as having symptoms of depression in the postpartum period if she answers "always" or "often" to PRAMS questions regarding postpartum depression (see Appendix B).[23,24] Other predictive variables assessed for their relationship to accessing postpartum care include: race/ethnicity, marital status, age, educational level, breastfeeding, accessing prenatal care, entering prenatal care in the first trimester, and use of Medicaid insurance for prenatal care. The outcome variable is the status of postpartum care utilization, a yes/no answer to the question in the survey concerning having received postpartum care.

After determining initial frequency and chi-square values to assess association between predictive variables and the outcome variable, five variables are used in a logistic regression model. These five variables show a statistical significance: less than high school education, Medicaid insurance (at any time), lack of prenatal care, entering prenatal care after the first trimester and self-report of depressive symptoms postpartum. The $\alpha$-value is set at $<0.05$ for all data analyses. Wald Chi-Square tests are performed using SAS, version 9.4.

## Results

In the Missouri PRAMS of 2009, 2010, 2011, 2012, 2013, and 2014, a total of 10,513 new mothers completed the survey. Three thousand one-hundred fifty-six mothers are excluded from the analysis by SAS PROC SURVEYFREQ because of non-positive weighting values. The remaining 7,357 new Missouri mothers became the final cohort. Demographic information is available in Table 1.

In the final cohort, 6,359 (90%) of new mothers reported obtaining routine postpartum care. The logistic regression analysis shows positive associations for all five predictive variables selected by their significant p-values: less than a 12$^{th}$ grade education, Medicaid insurance usage (at any time), no prenatal care, no prenatal care in the first trimester, and self-report of depressive symptoms (Tables 2 and 3).

Among 7,259 respondents, 1,093 new mothers (14%, weighted) report symptoms of postpartum depression (Table 1). A logistic regression analysis shows that among these 1,093 women a weak association is found between not accessing routine PPCV and the report of depressive symptoms ($p=.0254$; OR=1.344 with 95%CI=1.037-1.741).

In the study, other predictive variables are also associated with lower rates of PPCV. Lack of prenatal care is strongly associated with not accessing a PPCV (OR= 3.69 with 95%CI=1.775-7.668). Of note, only 0.8% of the cohort report no prenatal care. New mothers with Medicaid insurance usage (OR=2.119 with 95%CI=1.669-2.689) and women without a high school diploma (OR 1.9 with 95%CI=1.51-2.496) show a moderate association. Entering prenatal care late is weakly associated with not accessing PPCV (OR=1.728 with 5%CI= 1.359-2.197).

The following predictive variables have no association with rates of accessing PPCV: age; breastfeeding; or race/ethnicity. Smoking and marital status (unmarried) are associated with not accessing PPCV.

## Discussion

Strategies for decreasing maternal mortality and morbidity are being sought. One identified strategy is to increase entrance into medical care during the prenatal and internatal period. Increasing usage of the six-week postpartum care visit is one such targeted intervention. Research on barriers to the PPCV have focused on demographic factors, obstetrical history, type of health insurance, and substance use (alcohol, tobacco, and illegal substances). Little is known about post-partum depression as a barrier.

This study analyzes six years of the Missouri PRAMS data looking at the self -reported incidence of symptoms of post-partum depression and the rate of post-partum care visits among new mothers. The rate of accessing postpartum care for these new mothers (90%) and the rate of reporting symptoms of depression postpartum (14%) fall within the typical rates given in other studies using self-reported data. Our study finds a weakly negative association between self-reported symptoms of postpartum depression and accessing routine postpartum care (OR=1.344). This association is a new finding. Other studies focus on women, experiencing post-partum depressive symptoms, seeking medical treatment for their symptoms.[27,28,29] As far as we can ascertain, this is the first report analyzing the incidence of PPCV visit for these women.

In this study, a lack of receiving prenatal care is a predictive variable with strong association to decreased rates of PPCV. Three other studies also find lower rates of PPCV associated with mothers who did not access prenatal care ($p<0.001$; OR=3.39 with 95%CI= 1.98-5.81; OR=3.08 with 95%CI=1.68-5.63, respectively).[9,10,12]

The other predictive variables with moderate, weak or no association to decreased PPCV have all been previously studied. Our results sometimes support other studies and sometimes fail to support previous findings.[9,10,12]

Table 1. Demographics of Final Cohort of New Mothers in this Study, MO PRAMS 2009-2014, n=7,357.

| | No. of Respondents | Weighted Percent | Percent Accessing PPCV | Weighted % Accessing PPCV |
|---|---|---|---|---|
| **Characteristics** | | | | |
| **Race** | | | | |
| NH-White | 5745 | 77.3% | | 69.9% |
| NH-Black | 978 | 14.4% | | 12.3% |
| Hispanic | 627 | 4.2% | | 8.1% |
| Other | 7 | 4.0% | | <0.1% |
| Total | 7357 | | | |
| **Age** | | | | |
| <20 years | 625 | 9.3% | | 7.8% |
| ≥ 20 years | 6731 | 90.7% | | 82.6% |
| Total | 7356 | | | |
| **Marital status** | | | | |
| Married | 4539 | 59.2% | | 55.3% |
| Not married | 2811 | 40.8% | | 35.1% |
| Total | 7350 | | | |
| **Education Level** | | | | |
| High school/GED or greater | 6265 | 84.2% | 92.0% | 77.8% |
| Less than high school graduate | 1066 | 15.8% | 79.6% | 12.6% |
| **Total** | 7331 | | | |
| **Smoking in last 3 months of pregnancy** | | | | |
| No | 5894 | 82.4% | | 75.9% |
| Yes | 1338 | 17.7% | | 14.5% |
| Total | 7232 | | | |
| **Drinking in last 3 months of pregnancy** | | | | |
| No | 6850 | 93.6% | | 84.7% |
| Yes | 435 | 6.5% | | 5.7% |
| Total | 7285 | | | |
| **Medicaid Insurance (at any time)** | | | | |
| No | 4056 | 54.9% | 94.6% | 51.9% |
| Yes | 3277 | 45.1% | 84.6% | 38.6% |
| Total | 7333 | | | |
| **Entered prenatal care after 1st trimester** | | | | |
| No | 5967 | 82.2% | 92.2% | 75.9% |
| Yes | 1207 | 17.8% | 81.3% | 14.2% |
| Total | 7174 | | | |
| **No Prenatal Care** | | | | |
| No | 7108 | 99.2% | 90.6% | 90.1% |
| Yes | 66 | 0.8% | 62.5% | .4% |
| Total | 7174 | | | |
| **Report symptoms of postpartum depression** | | | | |
| No | 6166 | 86.0% | 91.1% | 78.4% |
| Yes | 1093 | 14.0% | 85.5% | 12.1% |
| Total | 7259 | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |

Table 2. Chi Square analysis, predictive variable and not receiving PPCV, MO PRAMS 2009-2014, n= 7,357.

| Predictive variable | P -value |
|---|---|
| *Used in the Logistic Regression* | |
| Less than high school graduate | <.0001 |
| Entered prenatal care after 1st trimester | <.0001 |
| Medicaid Insurance (at any time) | <.0001 |
| No Prenatal Care | 0.0005 |
| Report symptoms of postpartum depression | 0.0254 |
| *Not Used in the Logistic Regression* | |
| Marital status (unmarried) | 0.0078 |
| Age <20 | 0.0608 |
| Never Breastfeeding | 0.0234 |
| Smoking in the last 3 months of pregnancy | <.0001 |
| Drinking in the last 3 months of pregnancy | 0.0867 |
| Race/ethnicity | |
| Black | 0.0622 |
| Hispanic | 0.0574 |
| White | 0.8085 |

Table 3. Associations with no postpartum care visit, Logistic Regression analysis. MO PRAMS 2009-2014, n= 7,357.

| Predictive variable | Odds Ratio | 95% C. I. |
|---|---|---|
| Less than high school graduate | 1.942 | 1.510-2.496 |
| Entered prenatal care after 1st trimester | 1.728 | 1.359-2.197 |
| Medicaid Insurance (at any time) | 2.119 | 1.669-2.689 |
| No Prenatal Care | 3.690 | 1.775-7.668 |
| Report symptoms of postpartum depression | 1.344 | 1.037-1.741 |

Understanding the healthcare seeking behaviors in new mothers is a research area needing more studies. Are there other models of standard of care in the post-partum period that would increase PPCV usage for women especially those who are experiencing mental health issues? One qualitative study by Henderson et.al suggests increasing healthcare provider contact with new mothers prior to the standard six-week postpartum checkup as one possible intervention strategy.[30]

## Limitations

All data are by self-report and thus subject to recall bias and limitations of memory.

Two studies have evaluated the validity of self-reported insurance coverage and breastfeeding responses in PRAMS surveys by evaluating sensitivity, specificity, and positive predictive value using birth certificates and medical records as gold standards for comparison. Ahluwalia, Helms, & Morrow, using birth certificates for comparison, report moderate validity for self-reported breastfeeding initiation and Medicaid insurance.[25] Research, by Dietz et al., compares the self-report by 1,267 women, in two states' 2009 PRAMS surveys, to medical records. Their analysis finds moderate-to-excellent validity for breastfeeding initiation and Medicaid insurance reporting at delivery.[26] However, as noted earlier, the study, by the National Committee for Quality Assurance looking at insurance reimbursement data, reports much lower rates of PPCV. This study calls into question the higher rates seen in all self-reported studies on postpartum care.

Various groups of women are expected to have lower response rates. Women with unstable home address or phone number cannot be reached. Both Phases 6 and 7 of the MO PRAMS questionnaire booklets are published only in English; therefore, those not proficient in reading or speaking English are considered less likely to respond. Birth certificates lacking maternal information or those delayed in processing prevent participation in the survey.

## Recommendations

The result of this study would direct further investigation into two areas. First, more research into the issue of new mothers experiencing symptoms of post-partum depression and their entrance into routine postnatal health care visits is necessary; research is needed to verify our findings of an association of decrease usage of the

PPCV. Second, women who do not seek prenatal care are at significantly higher risk of not accessing a postpartum care visit. For these women, research into effective strategies that could be implemented during the time between delivery and hospital discharge is warranted.

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## Disclosure

None reported.

**MM**

# External Intensivists Versus In-House Intensivists: Analysis of Outcomes of Nighttime Coverage of ICUs by External On-Call and In-House On-Call Intensivists

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UMKC School of Medicine

**Hospitals wishing to invest in 24-hour intensivists should perform pilot studies to investigate not only the meaningful changes in patient outcomes but also the cost vs benefit and house staff (resident and fellow) education.**



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## Abstract

**A 24/7 intensivist model may improve important outcomes such as mortality, length of stay, and number of ventilator days. In this retrospective, single-center study at Saint Luke's Hospital in Kansas City, Missouri, we examined patient outcomes before and after adopting a 24/7 model from 2014 to 2016. The addition of a nighttime intensivist did not lead to a statistically significant improvement in mortality (hospital and ICU) and LOS (hospital and ICU).**

## Background

Accumulating evidence has indicated that the quality of care in intensive care units (ICUs) and patient outcomes, such as mortality and length of stay (LOS), are influenced by the structure and organization of ICUs.[1] Studies have consistently demonstrated that, compared to a low-intensity staffing structure ("open" ICUs without a mandatory intensivist consult), high-intensity staffing (mandatory intensivist consultation or "closed" ICUs with intensivist staffing) improves outcomes.[2] The recommendations of the Leapfrog Group's ICU Physician Staffing (IPS) Safety Standards require high-intensity staffing and are based on the results of that research.[3] However, the Leapfrog Group's 2015 hospital survey results indicated that only 44% of the responding hospitals fully met the recommended standards.[4]

There are several models of ICU staffing that range from low- to high-intensity coverage with critical specialists. One such model is an open ICU with a non-mandatory critical care consultation. Another requires mandatory consultations while maintaining an open ICU. High-intensity staffing involves closing ICUs and staffing them with critical care specialists during the daytime and having the same staff be on call to provide coverage at night as needed. The 24/7 in-house intensivist coverage for ICUs is the highest-intensity staffing model and involves higher costs and utilizes more manpower under the assumption that additional staff will improve patient outcomes. Tele-ICU and/or hiring advanced nurse practitioners is being used as an adjunct to all of the above ICU models and might be an alternative when 24/7 staffing is not feasible.[5-6] Demand is exceeding supply for intensivists, and the lack of available personnel or the resources to hire them is an obvious barrier to the 24/7 intensivist model.[7] The availability of intensivists at the time of patient admission and/or follow-up may have the potential advantage of better assessment and management than that of patient

care provided by an External intensivist, with or without Tele-ICU or advanced nurse practitioners. However, evidence supporting the 24/7 intensivist model has been inconsistent, and most studies have demonstrated no evidence of improved patient outcomes.[8-10] Many hospitals, however, continue to move towards having ICUs covered by an intensivist for 24 hours, despite the concerns of resource utilization and cost of care.

Our academic institution consisted of a total of 42 ICU beds (14 MSTICU, 12 CCU, and 16 Neuro ICU). The old staffing model at our institution consisted of all ICUs being covered by one rounding "Pulm/CC or CC" attending with fellows and residents during the day and at night by an in-house resident, on-call "Pulm/CC or CC" attending, and continuous eICU care provided by a board-certified critical care physician. During the daytime residents and fellows gather information, formalize a plan, and then discuss it with attending before implementation. During the nighttime, residents gather information, formalize a plan, and then discuss it with the attending before implementation. eICU will usually act on emergent needs that can't wait and will be discussed with the on-call attending at times. eICU used to take care of all established patients "100%" and pick up new admissions after plan is formulated by primary team. Our academic institution then moved to a new staffing model. The new staffing model consisted of All ICUs being covered by one rounding "Pulm/CC or CC" attending with fellows, residents, and nurse practitioners during the day and at night. During the daytime and nighttime residents, fellows, and nurse practitioners gather information, formalize a plan, and then discuss it with the in-house attending before implementation. In both systems, each of the 8 "Pulm/CC" attendings used to take calls 5 weeks a year, and the single CC attending used to take 12 weeks of calls a year. In this before-and-after study, we investigated the impact of adopting the 24/7 model on patient outcomes.

## Methods

We conducted a retrospective, single-center study at Saint Luke's Hospital in Kansas City, Missouri, from 2014 to 2016, before and after adopting the new model. The ICUs included in this study were the Medical-Surgical-Trauma ICU (MSTICU) and Cardiac-ICU (CICU). Both ICUs followed the high-intensity daytime staffing model with Tele-ICU services, which will be referred to as the high-intensity staffing model. The high-intensity staffing model was followed before January 2016 for the MSTICU and CCU. The model was then changed to a 24/7 staffing model with an intensivist and advanced nurse practitioner, which will be referred to as the 24/7 staffing model.

Our study population included all adult patients (18 years and older) admitted to the MSTICU and CICU during our study period ranging from one year before to one year after adoption of the 24/7 staffing model. We collected data on all included patients through chart review using the Epic™ electronic medical record system, including demographic data (age, gender, race), admitting diagnosis, sequential organ failure assessment score (SOFA), ICU and hospital mortality ICU and hospital LOS, and days on mechanical ventilation.

We compared the two groups for baseline demographic characteristics, including age, gender, race, and SOFA. Because no other major model or quality changes in patient management protocols were made between these two time periods at our institution, we considered the two groups comparable. Our primary outcome was hospital all-cause mortality. Our secondary outcomes included ICU mortality, ICU and hospital LOS and days on mechanical ventilation.

Normally distributed continuous variables were reported as means ±standard deviation (SD). Nonparametric data were reported as medians with interquartile range (IQR). Categorical variables were reported as counts and percentages. Chi-Square was used to compare categorical variables between the two groups. Student's t-test was used to compare the continuous outcomes between the two groups for uniformly distributed variables. When data was not distributed uniformly, Mann Whitney U test was used to compare the outcomes between the two groups. All tests were two-sided with $\alpha$ level set at 0.05 for statistical significance.

With a hospital mortality rate of 10% in our institution, our sample of 5,138 (2,142 patients before and 2,996 patients after the adoption of the 24/7 staffing model) could detect a 10% change in hospital mortality with 50% power and a two-sided significance level of 0.05. All statistical analyses were performed using SPSS 23.0 (IBM Corp. Released 2015, Armonk, NY).

## Results

We identified a total of 5,138 patients: 2,142 (42%) patients admitted to the MSTICU and CICU before and 2,996 (58%) patients admitted after adopting the 24/7

Table 1: Baseline Characteristics

| Baseline Characteristic | High-intensity Staffing Group | 24/7 Staffing Group | p value |
|---|---|---|---|
| Age in Years Median (IQR) | 67 (53-77) | 64 (52-76) | < 0.05 |
| Age in Years Mean (SD) | 64.62 (18.1) | 62.92 (17.8) | <0.05 |
| Gender (% Females) | 51% | 51% | 0.75 |
| qSOFA Median (IQR) | 3 (1-5) | 3 (1-6) | <0.05 |
| qSOFA Mean (SD) | 3.27 (2.8) | 4.03 (3.6) | <0.05 |
| Race n (%) | African American: 469 (22%) Caucasian: 1557 (73%) Other: 116 (5%) | African American: 746 (25%) Caucasian: 2083 (70%) Other: 163 (5%) | 0.38 |

Table 2: Chi-Square Test for All-cause Mortality

| Outcome | High-Intensity Staffing Group N (%) | 24/7 Staffing Group N (%) | Effect Estimate (95% CI) | p-value |
|---|---|---|---|---|
| Hospital Mortality | 440 (21%) | 630 (21%) | OR: 1.030, 95% CI: 0.898–1.181 | p=0.67 |
| ICU Mortality | 103 (5%) | 143 (5%) | OR: 0.992, 95% CI: 0.765–1.286 | p=0.95 |

Table 3: Mean Hospital LOS, ICU LOS, and Ventilator Days

| Outcome | High Intensity Staffing Group | 24/7 Staffing Group |
|---|---|---|
| Hospital LOS | 12.53 (32.67) | 11.02 (13.01) |
| ICU LOS | 3.04 (4.43) | 2.72 (3.34) |
| Ventilator Days | 1.99 (5.00) | 1.53 (4.143) |

Table 4: Median Hospital LOS, ICU LOS, and Ventilator Days

| Outcome | High Intensity Staffing Group | 24/7 Staffing Group |
|---|---|---|
| Hospital LOS | 7 (4-13) | 7 (4-13) |
| ICU LOS | 2 (1-3) | 2 (2-3) |
| Ventilator Days | 0 (0-1) | 0 (0-2) |

Table 5: Mann Whitney Test for Hospital LOS, ICU LOS, Ventilator Days, and qSOFA

| Outcome | Mann Whitney U | Z | Asymp. Sig. (2-tailed) |
|---|---|---|---|
| Hospital LOS | 3,197,643 | -0.212 | 0.832 |
| ICU LOS | 3,149,297 | -0.438 | 0.662 |
| Ventilator Days | 3,109,554 | -2.371 | 0.018 |
| qSOFA | 3,537,871 | 6.333 | 0.000 |

staffing model. The mean age of the high-intensity staffing group was 64.62 ± 18.1 years, and the mean age of the 24/7 staffing group was 62.92 ± 17.8 years. The median (IQR) age in the high-intensity staffing group was 67 (53-77) years and the median age of the 24/7 staffing group was 64 (52-76) years. A Mann Whitney test showed that there was a significant difference between the ages of the two groups (p=0.0003). Regarding gender, 51% of the high-intensity staffing group and 51% of the 24/7 staffing group were female. A Chi-Square test showed that there was no significant difference between the genders of the two groups (p = 0.75). Further there was no significant difference between race across both groups (p=0.38). The average SOFA of the high-intensity staffing group was 3.27 (SD = 2.801) with a median of 3 (1-5) and that of the 24/7 staffing group was 4.03 (SD = 3.572) with a median of 3 (1-6) (p<0.001). Table 1 shows the baseline characteristics of the study groups.

The all-cause hospital mortality of the high-intensity staffing group was 21%, and for the 24/7 staffing group was 21% (OR: 1.030, 95% CI: 0.898–1.181, p=0.672). The all-cause ICU mortality of the high-intensity staffing group was 5%, and the value for the 24/7 staffing group was 5% (OR: 0.992, 95% CI: 0.765–1.286, p=0.953). Results are shown in Table 2.

The average hospital LOS of the high-intensity staffing group was 12.53 (SD = 32.67) days with a median of 7 (4-13) days, and the average LOS for the 24/7 staffing group was 11.02 (SD = 13.01) days with a median of 7 (I4-13) days. The average ICU LOS of the high-intensity staffing group was 3.04 (SD = 4.43) days with a median of 2 (1-3) days and that of the 24/7 staffing group was 2.72 (SD = 3.34) days with a median of 2 (2-3) days. The average ventilator days of the high-intensity staffing group was 1.99 (SD = 5.00) days with a median of 0 (0-1) days and that of the 24/7 staffing group was 1.53 (SD = 4.143) days with a median of 0 (0-2) days. As shown by Tables 3 and 4, the mean hospital LOS, ICU LOS, and ventilator days were larger in both groups when compared to the median hospital LOS, ICU LOS, and ventilator days. A Mann Whitney test was performed for Hospital LOS, ICU LOS, and Ventilator Days, as shown in Table 5.

## Discussion

In this retrospective, single-center study, we found similar outcomes to previous studies conducted in urban, academic hospitals with high-intensity day-time staffing.[8-10] The addition of a nighttime intensivist was not associated with statistically significant improvements in mortality (hospital and ICU), LOS (hospital and ICU). However, there was significantly higher ventilator days in the high intensity staffing group compared to the 24/7 staffing model. This could be related to higher likelihood of extubating patients even lately during day time given the availability of nighttime intensivist. Despite shorter ventilator days, such difference didn't translate into shorter ICU or hospital LOS in the 24/7 staffing model. While the SOFA between the two groups was determined to be significantly different, this was not clinically significant.

While recommendations for the high-intensity staffing model (mandatory intensivist consultation or "closed" ICUs with intensivist staffing during daytime) are universally accepted and featured in the Leapfrog Group's IPS Safety Standards, no consensus exists regarding the recommendation for 24-hour coverage. As previously reported in a prospective cohort study, a decrease in ICU complication rates and hospital LOS were observed after the addition of a nighttime intensivist in an ICU that used high-intensity day-time staffing, but no improvements in mortality and ICU LOS were noted.[12] A retrospective observational study showed that the addition of a nighttime intensivist improved hospital mortality in ICUs that use low-intensity staffing during the day, but no difference in outcomes was noted in ICUs that used high-intensity staffing during the day.[9] In a randomized control trial, no improvement in outcomes occurred for patients who had additional coverage by a nighttime in-house intensivist.[8] A systematic review that pooled data from several observational studies also reported no improvement in outcomes due to the addition of a nighttime intensivist. Mirroring these studies, our results also suggest that there is no difference in outcomes between both groups.[9]

However, the addition of a nighttime intensivist may have benefits other than traditionally measured ICU outcomes such as mortality, LOS, and ventilator days. A pilot study noted less evidence of intensivist burnout in a model in which the intensivists worked around-the-clock shifts.[11] According to another study, residents believed that nighttime intensivists had an improved educational experience.[11] Improvement in "perceptions about patient safety" have been reported among both ICU staff and patient families.[12] Improvements in some processes of care, including adherence to use of stress ulcer prophylaxis and VTE prophylaxis, have been observed.

Although, the benefits remain uncertain, implementation of the 24-hour coverage model is not without substantial costs. Although it can be argued that the cost of implementation can be made up by the cost savings associated with the decrease in the LOS associated with the 24-hour coverage model, criticism of this model is based on the lack of evidence to support reduction in LOS and on limited availability of resources, including the number of intensivists. As noted by the Leapfrog Group's 2015 hospital survey, only 44% of the responding hospitals fully met the recommended standard of mandatory high-intensity staffing in all ICUs.

The same can be potentially inferred about the Tele-ICU service model. As reported by multiple studies, Tele-ICU services are associated with substantial initial and ongoing costs, with unclear cost effectiveness or profitability.[13-15] On the other hand, other studies have shown cost effectiveness for Tele-ICU services, which would support the business case for its implementation.[16-25]

## Conclusion

Considering these conclusions, the findings at our institute suggest that no additional benefit exists in

terms of outcomes, including mortality and LOS from the addition of a nighttime intensivist. These results, which were similar to the results of previous studies, may suggest that there is likely limited room for improvement in ICUs, such as ours, that follow high-intensity daytime staffing. Although performing the study for a longer time could potentially show an improvement in outcomes, the question of cost vs benefit remains.

There were several limitations to our study. This was a retrospective study, and therefore it was subject to bias associated with such studies. Additionally, we did not investigate other outcomes for nurses, trainees (residents and fellows), and patient satisfaction; however, these factors have been shown to be improved with 24/7 coverage compared to high-intensity staffing. It has been noted that intensivists may be associated with improving care at the margins without any discernable impact on the average, such as reducing mortality for a small number of very sick patients, including those in severe shock or cardiac arrest. Measuring such factors will require large, likely multi-center studies. It is therefore advisable that hospitals wishing to invest in 24-hour intensivists should perform pilot studies to investigate not only the meaningful changes in patient outcomes but also the cost vs benefit and house staff (resident and fellow) education.

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## Disclosure

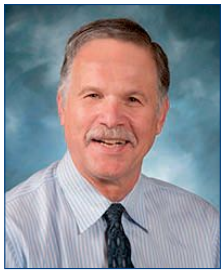
None reported. **MM**

# Correlation of Nutrition with Immune Status in Human Immunodeficiency Virus Outpatients

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**Our study shows that a significant percentage of HIV/AIDS outpatients may be at risk of malnutrition, which shows that meeting proper diet requirements is vital in this population.**



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## Abstract

**Malnutrition has been proven to cause poor outcomes in many chronic diseases. We examined the association between malnutrition and immune status in HIV patients. We used the Nutritional Risk Index to evaluate the nutrition in 812 HIV patients, and correlated this variable with viral loads and CD4 counts. We found a significant correlation between nutritional status and immune status.**

## Introduction

Human Immunodeficiency Virus (HIV) is a serious health issue that affects individuals all around the world. In 2016, 36.7 million people were living with HIV and about 1 million died from an AIDS-related illness. In the U.S. alone, it is estimated that about 1.1 million people were living with HIV at the end of 2015. HIV is an important health condition that continues to be a persistent problem globally.[1]

HIV gradually weakens a patient's immune by attacking CD4 T-cells, resulting in the development of opportunistic infections.[2] Many factors, including proper nutrition, can help decrease the severity of immunosuppression. Single or multiple nutrient deficiencies impair the cell-mediated response to a greater extent than the humoral response. Nutritional deficiencies, such as protein-energy malnutrition, have been shown to decrease the numbers of helper T-cells, cytotoxic T-cells, and natural killer cells, predisposing individuals to infections.[3] Nutritional status, immune expression, and HIV are intricate and intertwined.[4] The "vicious cycle" of HIV and malnutrition is attributed to the fact that both conditions are associated with a decreased immunity. Decreased immunity increases the risk for infections, leading to increased nutritional demand. If this nutritional demand is not met, a more severe malnourished state can ensue.[5] Malnutrition further contributes to the disease process by propagating the transition from HIV to Acquired Immunodeficiency Syndrome (AIDS).[4] In fact, most patients with AIDS develop protein deficiency and experience cachexia, diarrhea, and weight loss.[6] According to the World Health Organization, energy requirements increase by 10% in asymptomatic HIV positive adults and by 20-30% in symptomatic HIV positive adults, demonstrating the importance of proper diet in HIV/AIDS.[7]

Cooney (2015) explained that impaired CD4+ counts, beginning early after acute HIV infection, is the hallmark of HIV infection.[8] HIV patients have decreased B, CD8+, and CD4+ lymphocyte counts.[8] Additionally, it has been found that HIV patients with opportunistic infections have low CD4+ levels,[9] demonstrating the importance of analyzing nutrition and immune status to prevent the development of opportunistic infections and to improve patients' outcome. Viral load has been found to be a better

predictor of declining immune status when compared to CD4+ counts,[9] and an increase in viral load is associated with HIV infection. For this reason, we will be using CD4+ and viral load counts as an indicator of immune status when analyzing the relationship between immune and nutritional status. The goals of this study are to determine demographics, immune status, and the percentage at risk of malnutrition of HIV patients at Truman Medical Center.

Table 1. Immune Status and Viral Load

| | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Viral Load (copies/mL) | > 100,000 | 50,000 - 100,000 | Detectable < 50,000 | Undetectable |
| CD4+ count per mL | < 100 | 100 - 199 | 200 - 500 | > 500 |

## Methods

### *Study Subjects*

Eight hundred and fifty-five outpatients at Truman Medical Centers diagnosed with HIV were included in this study. Forty-three patients were excluded because the Devine formula for ideal body weight, a variable required to determine the Nutritional Risk Index (NRI), requires that a patient's height be over 60 inches, the albumin level was unavailable, or they identified as the race Native American, Pacific Islander, Asian, other, or unknown. Because there were only a small number of patients in each of those racial groups, they were excluded to protect their privacy. Our final sample size of 812 outpatients diagnosed with HIV (580 men and 219 women, ages 18-86) were further analyzed.

### *Nutritional Status*

We used the Nutritional Risk Index (NRI) to determine nutritional status of 812 HIV outpatients, which was calculated from the following well-established formula:[10]

$$NRI = (1.519*sALB) + (41.7*\text{actual weight/IBW})$$

where sALB is the serum albumin in g/L, actual weight is in kg, and IBW is the ideal body weight in kg. The IBW was determined using the Devine formula[11] for each sex:

$$\text{Male: } IBW = 50 + 2.3kg*(\text{height} - 60)$$

$$\text{Female: } IBW = 45.5 + 2.3kg*(\text{height} - 60)$$

where IBW is ideal body weight in kg and height is in inches. For the transsexual patients, we used the male IBW equation.

After calculating the IBW and NRI for each patient, they were categorized into two groups: not at risk of malnutrition (NRI $>$ 100) and at risk of malnutrition (NRI $<$ 100). The at-risk category was subdivided into borderline risk (NRI 97.5-100), mild risk (NRI 83.4 - 97.5), and severe risk (NRI $<$ 83.5) of malnutrition.

We stratified the data regarding at risk and no risk for malnutrition by age, sex, and race. With regards to age, we separated the patients into the following categories: less than 40, 40-49, 50-59, and greater than 60 years old. With regards to sex, we categorized patients into male, female, and transsexual. With regards to race, we classified patients as white, black, and Hispanic.

### *Immune Status*

We used CD4+ count and viral loads determined by PCR to assess the immune status of 812 HIV outpatients. In order to combine the CD4+ counts and viral load into one numerical value representing immune status, we ranked patients on a scale from 1 to 4 for their viral load and CD4+ count, as shown in Table 1.

The rank of the viral load category and the rank of the CD4+ count category were summed to get an overall rating of immune status. The worst possible overall rating of immune status is 2 while the best possible rating is 8. The overall immune ratings 2, 3, and 4 represent a poor immune status, ratings 5 and 6 represent a moderate immune status, and ratings 7 and 8 represent a good immune status.

### *Statistical Analysis*

For our statistical analysis, we used Statistical Packaging for the Social Sciences (SPSS) Version Stats 24. To assess the correlation between age and NRI, we performed a Pearson correlation. A 3 x 3 two-way ANOVA test was used to determine the association between race (black, white, Hispanic), sex (male, female, transsexual), and NRI. A partial Eta squared was calculated to demonstrate the strength of the relationship between NRI and our independent variables, race and sex. We performed a post-HOC test to closely analyze the groups within race and sex to determine whether these groups were statistically significant. A p-value $<$ 0.05 was considered to be statistically significant.

To assess the correlation between NRI and immune rating, we used the Spearman correlation test. To assess the correlation between NRI and the two contributors of immune status (CD4+ and viral load) separately, we used the Pearson correlation test. Regression analysis was

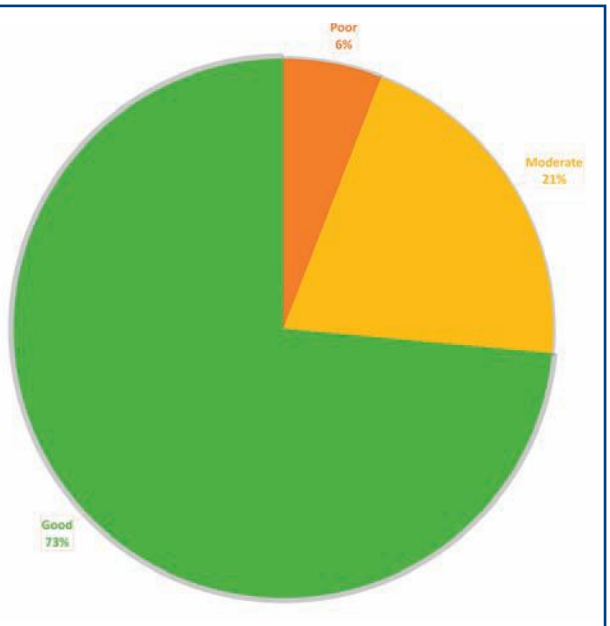



Figure 1. Immune Status in HIV Outpatients

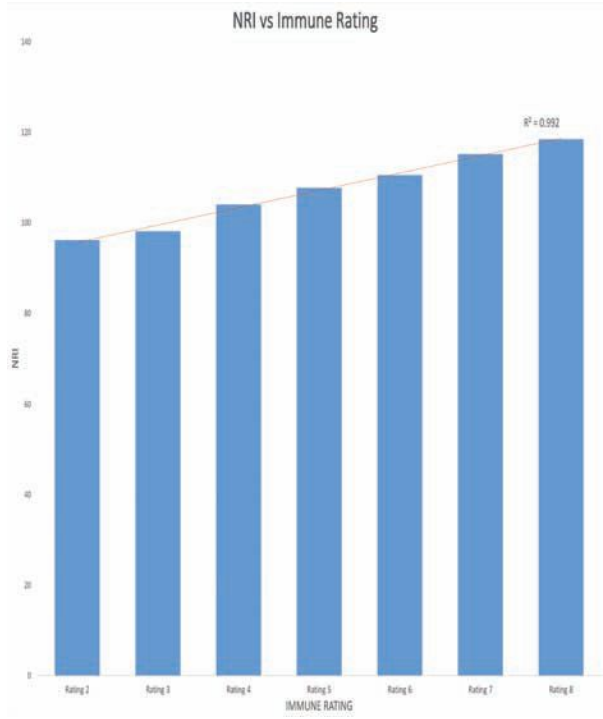



Figure 2. Immune status and Nutritional Risk Index

used to determine the extent of contribution of CD4 or viral load individually to immune status. These tests were performed for all 812 HIV outpatients as well as just the 93 malnourished HIV outpatients. For all statistical tests, a p-value of $< 0.05$ was considered statistically significant.

## Results

### *Nutritional Status in HIV/AIDS and Trends in Age, Sex, and Race*

Of the 812 HIV outpatients, 93 (11.45%) are at some degree of risk for malnutrition. 23 (2.83%) patients were at mild nutritional risk, 55 patients (6.77%) were at moderate nutritional risk, and 15 patients (1.85%) were at severe nutritional risk. Average NRI of all 812 patients is 114.81.

As age increased, NRI decreased ($r = -0.107$, $p = 0.002$). While both sex and race are independently statistically significant ($p = 0.005$, $p = 0.05$), there is no interaction between the two variables ($p = 0.246$, partial Eta squared $= 0.007$). Regarding sex, the NRI of females is greater than that of males (117.69 vs 113.71, $p = 0.001$). Regarding race, Hispanic HIV patients have greater NRI than white patients (119.72 vs 112.93, $p = 0.001$) and Hispanic patients have greater NRI than black patients (119.72 vs 114.95, $p = 0.017$). The difference in white and black patient NRIs was not statistically significant ($p = 0.090$).

### *Immune Status*

Of the 812 HIV outpatients, 48 (5.91%) are of poor immune status, 167 (20.57%) are at moderate immune status, and 597 (73.52%) are of good immune status (Figure 1). The average overall immune rating is 6.99, average CD4+ count is 298.6 cells/uL, and average viral load is 13,019.47.

### *Immune status and Nutritional Risk Index*

Of all 812 HIV patients, there is a significant correlation between NRI and immune rating ($r = 0.302$, $p < 0.001$) (Figure 2), NRI and CD4+ ($r = 0.304$, $p < 0.001$), and NRI and viral load ($r = -0.121$, $p < 0.001$). Regression analysis shows that CD4+ and viral load are significant determinants of NRI (CD4: $r = 0.304$, $p < 0$ 0.001; viral load: $r = -0.121$, $p < 0.001$). Of the 93 patients at risk of malnutrition, 22 (23.91%) patients have poor immune status, 32 (34.78%) patients have moderate immune status, and 38 (41.30%) patients have good immune status. Of the 48 patients with poor immune status, 22 (45.83%) patients are at risk of malnutrition and broken down into individual categories, 7 (14.58%) are at mild risk of malnutrition, 10 (20.83%) patients are at moderate risk of malnutrition, and 5 (10.42%) patients are at severe risk of malnutrition. 26 (54.17%) patients are not at risk of malnutrition.

## Conclusion

Eleven point three percent of 812 HIV outpatients are at risk of malnutrition. Findings in this group include: a) with age, NRI decreased, b) NRI of female HIV patients is

greater than that of males, c) black patients have greater NRI than white patients, and d) Hispanic patients have greater NRI than black patients. Of the 812 HIV outpatients, there is a significant correlation between NRI and immune rating. The two factors that contribute to immune rating, CD4+ and viral load, also show significant correlation with NRI. CD4+, and viral load are all significant determinants of NRI in HIV outpatients.

Of the 93 patients at risk of malnutrition, 23.91% (n = 23) have poor immune status. When analyzing this subgroup, there was no significant correlation between NRI and immune rating, CD4+, and viral load.

Of the 48 patients with poor immune status, 45.83% (n = 22) are at risk of malnutrition.

There is no difference in NRI between transsexual and female patients, and transsexual and male patients. The difference in female and transsexual NRIs was not statistically significant ($p = 0.063$) and the difference in male and transsexual NRIs was not statistically significant ($p = 0.319$).

## Discussion/Future Directions

Our study shows that a significant percentage of HIV/AIDS outpatients may be at risk of malnutrition, which shows that meeting proper diet requirements is vital in this population. A study on nutritional supplementation for patients with HIV showed that oral nutritional supplements along with dietary counseling led to decreased protein catabolism and increased lean body mass.[12] Nutritional supplements also increase CD4 counts, directly reflecting an improvement in immune response.[13] Nutritional assessment and intensive dietary counseling at the time of diagnosis of HIV could prove beneficial in this population to minimize progression to the development of AIDS. Further nutritional supplement may be useful to improve the prognosis of HIV/AIDS.

The relationship between nutrition and HIV has been described in other studies as well. A study comparing HIV+ and HIV- adults found that HIV is associated with higher serum protein and lower serum albumin levels, and that HIV+ women have higher BMI and waist circumference, suggesting that nutrition is an important factor in this disease. Hillesheim et al. showed that in HIV+ children and adolescents, dietary energy intake correlates with CD4+ count and viral load. There is a significant relationship between a lower energy diet, and viral suppression and immune preservation.[14] The World Health Organization explains that improved diet may contribute to the success of antiretroviral treatment (ARTs). Some specific ARTs interfere with the metabolism of glucose and lipids, bone metabolism, and lactic acidemia, so patients on ARTs should pay special attention to maintaining a healthy, balanced diet.[7]

While nutrition is a factor affecting immune status in HIV patients, our future work will focus on additional factors such as antiretroviral therapies, other underlying conditions, and other medications contributing to immune status. We also hope to increase the sample size of our transsexual population with HIV for further research as there is limited work done in this population.

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## Disclosure

None reported.

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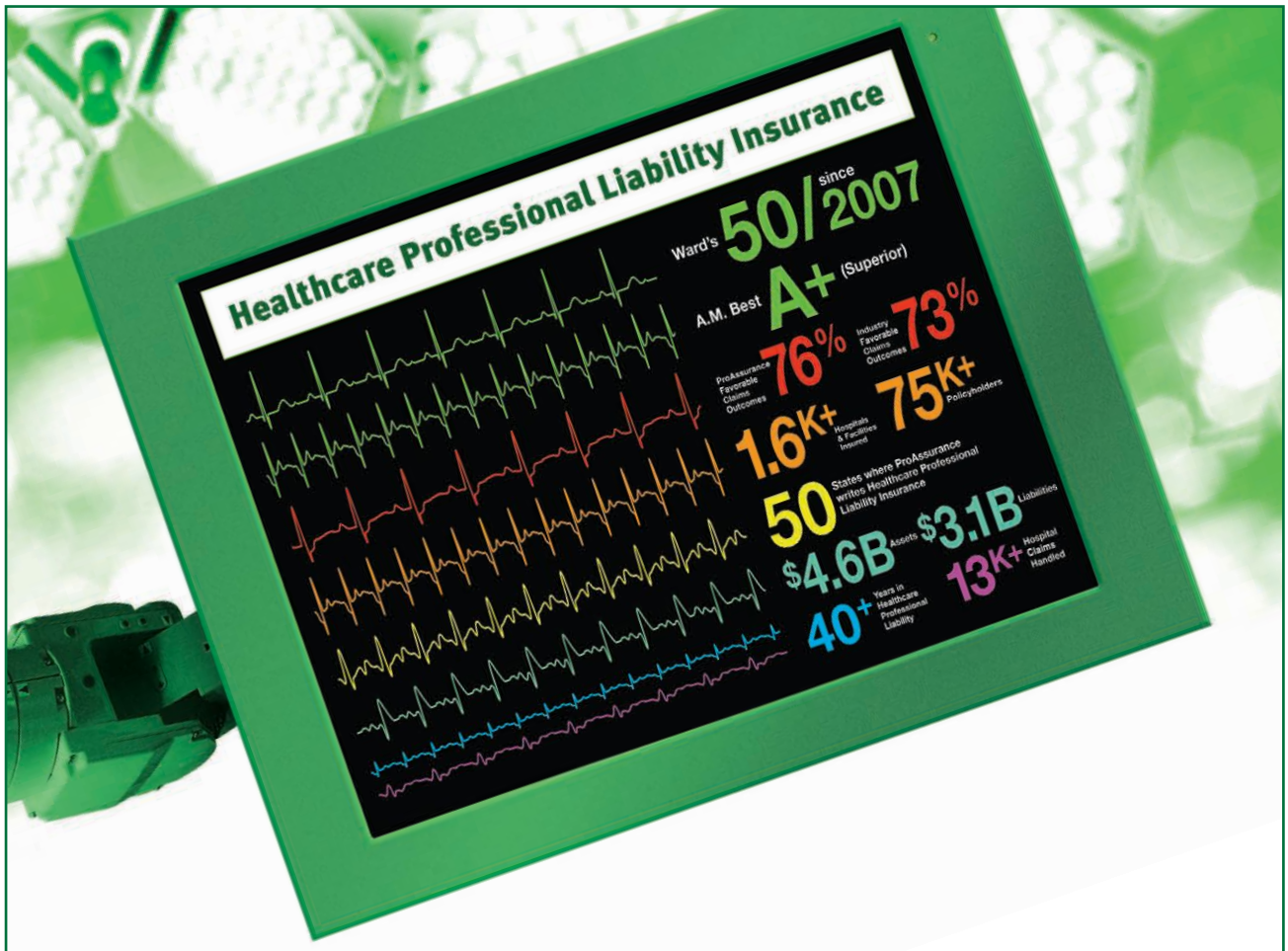
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