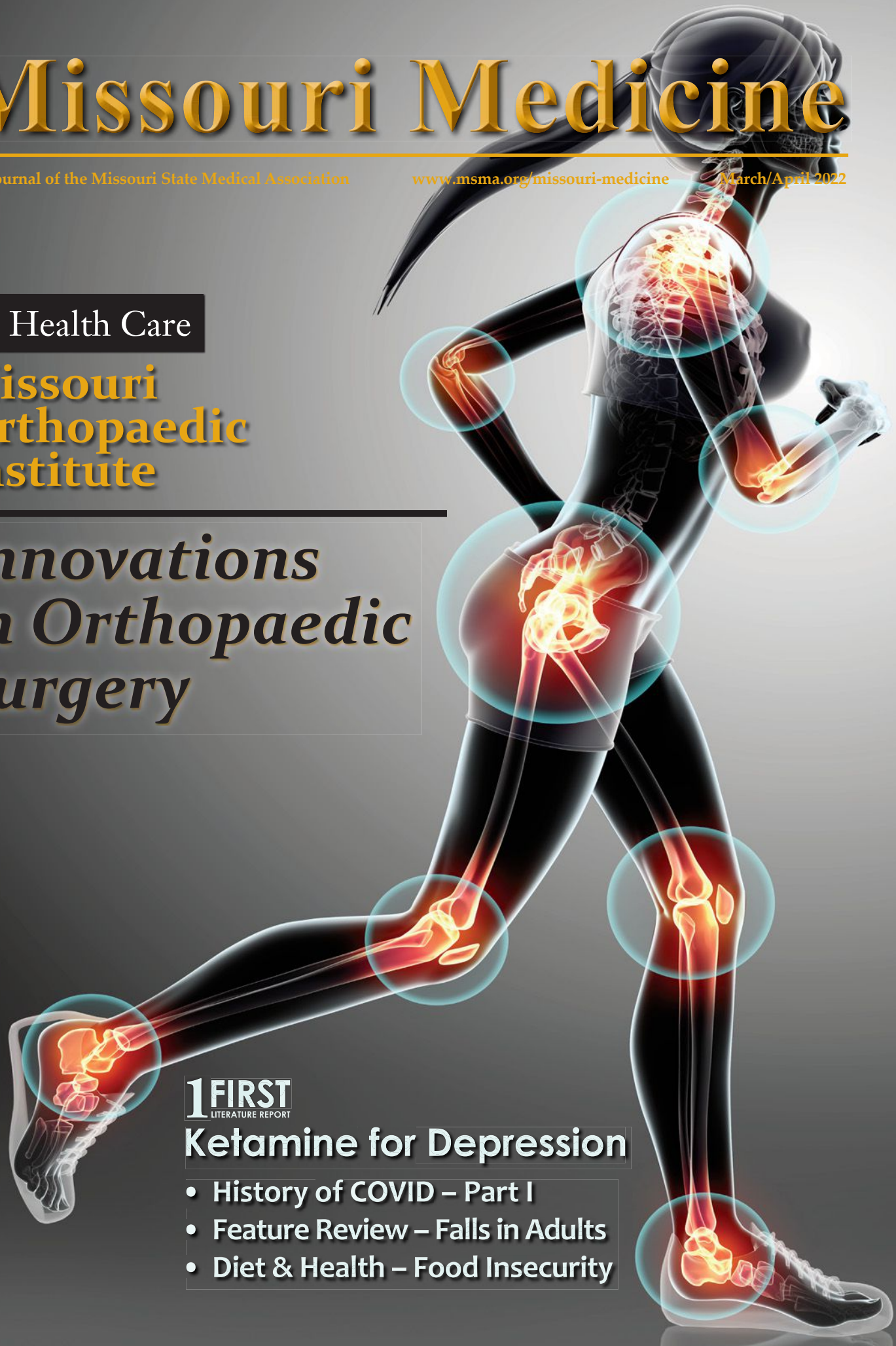
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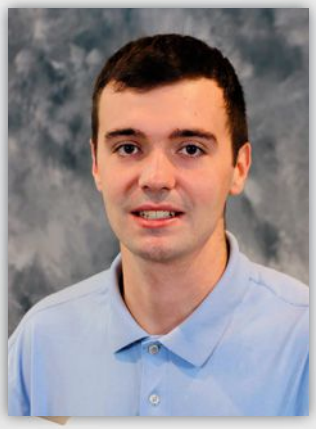
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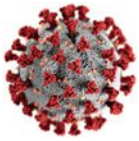
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The Doctor's Office Becomes an Assembly Line

by Devorah Goldman

Since the start of the COVID-19 pandemic, my dad's rheumatology practice has been flooded with new patients, including many from far-flung cities or out of state. This isn't thanks to a new marketing strategy or to a notable spike in arthritis sufferers. One elderly woman who had traveled from New Jersey to my father's Brooklyn, N.Y., office explained that many practices near her home had closed. Those that remained open were so overwhelmed that she would have had to wait eight months for an appointment.

Consolidation is wiping out private practices and making medical care costlier and lower quality.

This shouldn't be surprising. According to a 2020 survey by the Physicians Foundation, 12% of all U.S. doctors either closed their offices during the pandemic or were planning to do so within the year. Some 59% agreed that the pandemic would "lead to a reduction in the number of independent physician practices in their communities," and half agreed that "hospitals will exert stronger influence over the organization and delivery of healthcare as a result" of the pandemic.

But the pandemic merely accelerated a decades-long trend. In 1983, more than 75% of physicians owned their own practices, according to American Medical Association physician surveys. By 2018 that figure had dropped to 46%. Many practices have been purchased by hospitals or have merged to form larger clinics, while local hospitals have been subsumed into large health systems. Consolidation is the trend. An AMA report earlier this year found that for the first time, less than half of doctors work in private practices. This is a problem for patients like those who went in search of my father—there are simply fewer places to seek care, and many of those that are available are bureaucratic mega-facilities.

This doesn't bode well for medical care. Doctors aren't—or shouldn't be—natural subordinates. A substantial portion of their training consists in learning to make independent judgments rooted in hard-earned authority. Writing in *City Journal* in 2012, Theodore Dalrymple lamented the U.K. government's influence over medicine, which he argued "is becoming ever firmer; it now dictates conditions of work and employment, the number of hours worked, the drugs and other treatments that may be prescribed." Doctors "are less and less members of a profession; instead, they are production workers under strict bureaucratic control."

Former AMA President Barbara McAneny, who co-owns a private cancer center, echoed this idea in a 2019 article. When she and her colleagues wanted to add new services for their patients, she wrote, they "didn't have to go through 27 hospital committees



Devorah Goldman is a visiting fellow at the Ethics and Public Policy Center and a senior editor at *Mosaic* magazine. This article first appeared in the *Wall Street Journal*.

and ask permission from a bunch of vice presidents for various things." The shift from the small doctor's office to big-box medical care can be attributed to many factors. Cuts in Medicare reimbursement for private-practice services have pushed doctors out of business or into new business models. For a long time, Medicare funding mechanisms also encouraged hospitals to purchase private practices, so that the hospitals could bill Medicare for more lucrative outpatient hospital services. Medicare also reimburses hospitals at higher rates than private practices for a variety of drugs and services—and hospital systems have more administrative resources to negotiate payment from insurers and the government. More recently, rules pushing doctors to adopt onerous, time-consuming electronic health records have interfered with their capacity to attend to patients. The rise in EHRs reflects a tension between companies interested in accumulating health data, and doctors, who prefer to focus on individual needs.



For a long time, the AMA and other medical establishments such as the American Association of Medical Colleges quietly celebrated the turn away from small medicine. They assumed that larger, more consolidated health systems would also be more efficient. On the whole, this has not turned out to be the case. Kathleen Blake, AMA's vice president of healthcare quality, earlier this year cited studies showing that hospital acquisitions of private practices—which doubled from 2012 to 2018—have led to "modestly worse patient experiences and no significant changes in readmission or mortality rates."

Flawed electronic health record systems in hospitals have resulted in ghastly medical errors and millions in settlements. And while physicians in a variety of settings struggle with administrative and regulatory burdens, independent doctors are significantly more satisfied with their work than are their hospital-employed counterparts. In a 2018 survey by the Physicians Foundation, only 13% of doctors agreed that "hospital employment of physicians is likely to enhance quality of care and decrease costs." The AMA has begun to acknowledge this as a problem. In April 2021, the group launched a new initiative to support private practices. Among other things, the association is lobbying against the impending Medicare cuts that could elbow doctors out of business. While important, this doesn't address deeper problems with the evolution of medicine in recent decades.

Bureaucratic structures often suffer from inflexibility. Throughout the COVID-19 pandemic, medical bureaucracies at the national level have struggled to adapt to sudden changes in medical information in the way that frontline physicians can. Doctors must operate with a clear sense that they are serving the patients in front of them, not the government, data-collection systems, insurance companies, or hospital directors.

When Amazon took on the independent bookstore, it inspired outrage of the sort captured in the 1998 film "You've Got Mail." Unlike the book business, however, the replacement of the small doctor's office with large-scale facilities hasn't made medicine cheaper or access to it easier. It threatens to remove a core advantage of the small, privately owned practice: the sense of personal, immediate responsibility between physician and patient. **MM**

Observations on Corporatization of Healthcare Systems in America

by Alexander R. Hover, MD

This article may initially seem like a travelogue but bear with me, please. I am setting the stage to pose a thoughtful question. How was a Tuscan charitable health system, hospice, orphanage, and community service for the poor able to provide continuous service for 10 centuries? Moreover, are there lessons for us in modern healthcare governance?

I visited Siena in the Tuscany region of Italy. There I chanced upon a pilgrims' hospice from the Middle Ages. I was in awe that a pilgrim hospice evolved into a Middle Ages charitable health system continuously operating from 1093 until the 20th century. During the Middle Ages, a hospice functioned as a charitable rest stop for shelter, care, and food for religious pilgrims on their way to Rome and on to the Holy Land. A brief history will help to understand the Santa Maria della Scala organizational structure, business operations and service complexity that qualifies as a health system.

The Italian city of Siena was internationally important for commerce, art, and religion because it sat on the Via Francigena which was the Middle Ages highway from Europe to Rome.[1] Pilgrim hospices were built in many towns along this road. The Siena pilgrim hospice that became Santa Maria della Scala was originally established as a Catholic institution perhaps as early as 898 by legend or more likely in 1093 as recorded in a deed of gift.[2] In 1193 Pope Celestine III provided a Papal Bull granting Santa Maria della Scala autonomy from the church to be operated independently by the Siena community.[2,3] The hospital was operated by friars overseen by a Rector who was initially elected by the friars. The Rector was typically a wealthy community member who was obligated to give his entire wealth to the hospital and was then Rector for life.[3] As of 1404 the Rector was nominated and elected by the commune of Siena becoming a Siena city public officer.[2,] In contradistinction to the despotic rule of many large cities, some communities such as Florence, Lucca, Pisa, and Siena retained local autonomy.[1] "In those places merchant groups were usually too firmly in control to need a strong man to preserve order. They could accomplish this, for the most part, by themselves and so Republican forms of government which they could dominate were preserved."[1] As a result, Santa Maria della Scala was operated under Siena city control over the 10 centuries.

Over time, Santa Maria della Scala services offered to pilgrims went beyond hospice to include a sophisticated teaching hospital training Doctor of Medicine and surgeons, an orphanage, and staffing for wet nurses to accept babies.[2,3] Hospital staff included salaried doctors and surgeons who were obliged to "heal cheerfully and graciously."[3] Assistant doctors took the overnight shift (some things never change). Eventually, the hospital became an Italian university hospital.[3] Santa Maria della Scala flourished with generous donations from wealthy families as well as the assets from the Rectors who typically came from a wealthy family. Repeated ravages of the Black Death may also have inspired donors to help build churches and hospitals.[1]

Small hospitals were established in surrounding districts. A home health service was established to provide post discharge care. Farmlands were purchased and managed by Santa Maria della Scala to provide farm products to support the hospital either through sale or directly for the provision of patients and staff.[2,3]

As a result of the donors and presumably sensible fiscal management, a great wealth was available to support beautiful art to celebrate Christ's life and as well, documentation of the everyday work of the hospital. Apparently "nearly all" of the great Siena artists worked at some time producing art specifically



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for Santa Maria della Scala.[2] The (non-flash) photographs taken in September 2021 are beautiful 15th century murals by Domenico di Bartolo and other artists that depict the daily work. The murals depict surgery, almsgiving, care for the orphans, administration, and feeding the poor.[2] The murals adorn the Pellegrinaio, the large hall that served as pilgrims' hospice and hospital bay. Care and Healing of the Sick details the various robes and functions ascribed to the orders of the administrators and medical staff. Note the attention to hygiene for the patient about to undergo surgery. An orphanage was established that accepted newborns as well as older children. Children were educated, taught trades, and given a sum of money at discharge. Eligible girls received a dowry for their marriage.[2,3] These murals hung above bays of the patients as the care went on for ten centuries until the 1970s when a new general hospital was built in Siena. At that point, Santa Maria della Scala began to evolve into an art museum.[2] There is still ongoing excavation and restoration of incredible murals, and statuary.



Pelligrinaio Hall (Pilgrims Hospice)
The hall as it exists in the current restoration (non-flash photo permitted). Dominico di Bartolo painted in the 15th century.

Care and Healing of the Sick

A microcosm of the daily ward activities. From left to right, an aide lays an ill patient on a stretcher; two doctors confer regarding a urine specimen in a flask; hospital friars; the Rector; a surgeon observes an assistant washing a patient prior to surgery; a monk is confessing a dying patient; and two assistants are carrying a bier through the hall.



Santa Maria della Scala was a charitable organization serving the community poor with almsgiving and orphanage for foundlings and children. It was a not-for-profit teaching hospital, home health service, and hospice for pilgrims. Moreover, the Rector commissioned subsidiary hospitals throughout the district, and operated self-sustaining farming operations.[3] Certainly, that is the description of a not-for-profit health system as extensive as existing health systems within the United States today. What are the characteristics that allowed this not for profit health system to flourish for 10 centuries? Surely the community religious faith was a strong factor in sustaining the work. The Santa Maria della Scala operated in a much less complex regulatory, payor, and simpler technical environment than the healthcare environment today. However, I do think a crucial factor was likely the governance of a local philanthropic community board responsive to the Siena region. So, are there lessons for us today in healthcare? It is an important question as some would say American health care is in crisis due to corporatization.[10]



The Distribution of Alms
The scene depicts the work of clothing the naked, distributing bread to the sick, the poor, and the abandoned children.

While there are exceptions, American hospitals have evolved from local community board-operated individual hospitals to large healthcare systems with central corporate governance over the past three decades. During this time, U.S. healthcare costs have risen from 721 billion in 1990 to $4.2 trillion, almost 20% of the GDP in 2021.[11] The Centers for Medicare and Medicaid projection for national expenditures will reach 6.2 trillion in 2028.[11]

For this discussion, I define "corporatization," as consolidating previously independent parts of healthcare business into vertical and horizontal business structures with variable degrees of central corporate decision versus local autonomy. I leave it to economists to determine whether corporatization is a response or more probably the driver of rapidly escalating costs to the consumer. I also leave it to economist experts to help understand the role of public and private insurance in this mix. Despite increasing coverage, healthcare insurance and out-of-pocket expenses are both rising rapidly. Out of pocket expenses are projected to rise 10% per year through 2026.[12] Typically, there is economic rationale for business consolidation, so I would at least expect to see more benefits for patients and lower cost than what I observe. A corporate business such as Walmart relies on increasing their profit margin while lowering costs to consumers by improving worker productivity and creating business efficiencies. Certainly, U.S. healthcare "product" has miracles to be proud of and differs in many ways from commodity vendors. Still, I think it reasonable to ask if the corporatization has resulted in benefits to patients to be able to afford care.

Economy of scale, supply chain management, and standardization of some aspects of healthcare delivery, perhaps brought some improvements in service and cost early in the corporatization history. However, the per capita cost for healthcare in the U.S. is almost



The Education and Marriage of a Daughter of the Hospital

This scene depicts phases of life of the orphanage starting left to right with a tutor holding a rod and teaching reading, abandoned babies with the wet nurses, and finally a marriage celebration with the bride receiving her ring from her betrothed.

double that of most industrialized countries and without clear, discernably better health outcomes.[13,14] "No margin, no mission" is indeed a reality. The issue is not a health system or health insurers' requirement for a margin of profit. The issue is the degree of integration and effective monopolization particularly for health insurers. Health insurer merger and acquisitions such as the United Healthcare and Change Healthcare are now receiving anti-trust scrutiny that has been less common in the past.[10,12] In the past few years, my observation is that corporatization has improved health systems' and health insurers' revenue but has not reduced costs nor made great improvements in patient satisfaction. Federal policy and reimbursement control along with health insurer requirements, complex technology requirements for electronic records and required participation in complex "pay for quality" programs have also been a pressure for the evolution from community hospitals to large complex health systems. I do think electronic medical records are safer particularly for medication administration, but to date, they have not enhanced physician productivity. This all combines to reduce physician time for clinical care with patients. Requiring physicians to see more patients in less time, to me, makes as much sense as a commercial airline telling its pilots: "Yes, operating airplanes today is more complex, no we can't afford more jet fuel, but you need to get the plane from Chicago to New York an hour faster."

Not being an economist, I am going to confine my comments to my observations of how healthcare business decisions are affecting physicians and patients. My observation is that corporatization applies in similar fashion both to for profit and not for profit health systems. Many health systems have adopted central governance with subsidiary boards that vary between corporate style function and philanthropic boards. I have not seen a clear consensus on the best organization and distribution of decision making at the corporate and subsidiary board level.

An American College of Physicians position paper concerning financial profit in medicine noted as its first concern: the corporatization in the healthcare market.[4] The concerns were primarily around equity investment, but the point was missed that these recommendations also apply to not-for-profit corporatization. This is particularly so for the points made with respect to relationship with physicians such as allowing physicians sufficient time and resources to care for patients.[5]

I do not intend my remarks as a general condemnation of all central corporate governance for health systems. However, there is need to thoughtfully balance central corporate governance with strong local community board governance and decision authority. Like the longevity of Santa Maria della Scala, my

experience with major health systems over decades convinces me that a strong community board is vital whether it is primary or subsidiary. I have always been impressed with community boards incorporating dedicated, thoughtful local business leaders, physicians, along with faith and lay leaders. Strong local boards are beneficial for the hospital, the community, and the health system.

Many of the same pressures birthing corporatization over the past three decades have also adversely affected physicians providing care. Physician practice management has changed from small office independent practice to large multispecialty practice or health system employment with sophisticated, but expensive administrative resources. The American Medical Association Benchmark Survey reported that only 49.1% of physicians were in private practice as of 2020. The requirement for electronic medical records, well-intentioned but complex quality programs, increasing requirements for staff solely to perform preauthorization and revenue cycle management are all increasing pressures for physicians to seek employment.[6]

True, there is increasing desire in newly graduated physicians to find a better work life balance and to try to manage the rising debt for medical school. However, my observation is that the complexity, cost, and risk of practice management today is a major factor driving both young and mature physicians into employment. I am certainly not the first or only MSMA member to note that whether equity investors or hospitals purchase physician groups, health care costs rise.[15] Reports by young physicians are much the same.[8] Hospital Medical Staff committees that previously offered protection for hospital privileges are now dominated by health system administration. I note recent reductions in force that have included employed physicians by contracts that allow termination "without cause." That should be notice to all physicians that employment in some health systems is not a safe harbor. As one of the "mature" physicians, I am grateful to currently be in a health system with community board governance and leadership that allows me the time I need to be able to provide the best care I can. For physicians, that is consistently at the top of quality concerns for patient care.[5]

I leave a final question and its answer, to you the reader. Would today's health systems achieve the same success and service to the community over 10 centuries like that of Santa Maria della Scala? I do not think the answers are found in continued corporatization, but I must leave how to improve to another message. Policy changes and specific recommendations to consider may be found in the references that would likely improve our healthcare delivery and costs. There are many other models to consider that are not addressed in this message such as found in the Commonwealth Fund report; "Four features distinguish top performing countries from the United States: 1) they provide for universal coverage and remove cost barriers; 2) they invest in primary care systems to ensure that high-value services are equitably available in all communities to all people; 3) they reduce administrative burdens that divert time, efforts, and spending from health improvement efforts; and 4) they invest in social services, especially for children and working-age adults.[14]" I hope to hear your answers! Email me at alexhover@gmail.com.

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COVID-19 in Missouri

2020-2021

A Perspective on Origins, Spread & Controversies

Part I

by David S. McKinsey, MD, Joel P. McKinsey, MD, Neil B. Hampson, MD & Maithe Enriquez, APRN, PhD



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The onset of the COVID-19 pandemic, which has taken more lives than any other event in United States history, was unexpected and insidious. We know that certain things are inevitable: death, taxes, and influenza pandemics, the latter of which typically occur thrice a century.

However, few anticipated the first pandemic caused by a coronavirus with the notable exception of Bill Gates.[1] Further, none predicted either the pandemic's duration or the extreme societal disruption and division it would precipitate.

Introduction

In early January 2020 as Missouri health care professionals were preparing for a busy winter influenza season, rumors started circulating about an outbreak in China of an exceptionally virulent form of pneumonia of unclear etiology. A few weeks after Chinese physicians began spreading word about the new disease, reports about the rapidly escalating epidemic were grim. Wuhan, an eastern Chinese city with more than 11 million inhabitants, quickly was overwhelmed by a lethal viral illness the world would soon come to know as COVID-19.[2] It was unclear if the outbreak would be contained in Asia, as had been the case with Severe Acute Respiratory Syndrome (SARS) in 2003, or whether a new pandemic was gathering steam and threatening Missourians.

In early 2020 the United States prepared for the possible arrival and spread of the novel coronavirus. The first U.S. case, on January 18, 2020 in Orange Country, California signaled the beginning of the worst pandemic to strike the country in more than a century. Subsequent blitzkrieg spread of COVID-19 ensued in the Pacific Northwest and, shortly thereafter, in the Northeast. The duration of a major conflict often is underestimated at the onset of hostilities. In early 2020 few could have predicted that COVID-19 would become the longest-lasting respiratory viral pandemic in recorded human history, and that after two years the end would not yet be in sight.

This manuscript, first in a series, will review current knowledge regarding the origin and spread of COVID-19, discuss patterns of disease incidence in Missouri and nationwide, and address controversies regarding optimal treatment strategies. Our opinions are based on information that was available as of early January 2022

Origins and Spread

Our understanding of the onset and early spread of COVID-19 is murky, as a result of concerted efforts by Chinese authorities to obfuscate the origins and minimize the severity of the pandemic.[2] Although the first case reportedly was diagnosed in Wuhan on December 8, 2019, in real time Chinese authorities delayed announcement of the outbreak for several weeks.[2] The initial reports describing the contagiousness and lethality of the new viral illness came from whistleblower physicians in Wuhan, subsequently ostracized, who privately shared information with their colleagues. News media leaks rapidly ensued.

Chinese health authorities began notifying local health care providers about the outbreak during the last week of December 2019, and scientists determined the genomic sequence of the new coronavirus, SARS-CoV-2, on January 3, 2020. However, as the outbreak unfolded the Chinese National Health Commission "ordered institutions not to publish any information … and (to) transfer any samples they had to designated testing institutions or destroy them."[2] The World Health Organization, in an apparent attempt to avoid angering the Chinese government, minimized the potential for widespread disease transmission as late as January 14, 2020. The situation subsequently deteriorated with lightning speed as cases were reported in Korea, Japan, and the U.S. on January 20, 2020. The disease exploded worldwide in February 2020, shortly after the WHO recommended against limitations of "trade or movement" from China. The delays in early action to contain the outbreak and to determine its source have been the subject of criticism worldwide.

The questions of when, where, and how SARS-CoV-2 was introduced into the human population have prompted extensive investigation and speculation



Figure 1. Closed Wuhan Huanan Seafood Market, January 1, 2020.
Source: Alamy

but our current state of knowledge about these issues remains quite incomplete. Human coronaviruses were discovered in the mid-1960s. Four have been recognized as seasonal endemic pathogens and have been estimated to account for approximately 15% of "common colds."[3] Most cases occur in the winter months and typically are associated with relatively mild upper respiratory symptoms.[4] Prior to COVID-19, two non-endemic coronaviruses were known to have infected humans. SARS-CoV caused an epidemic for several months in 2003 resulting in almost 800 deaths in 29 Asian countries. Middle East Respiratory Syndrome coronavirus (MERS-CoV) emerged in the Middle East in 2012 and sporadic small outbreaks of this viral illness have continued.

The two coronaviruses most closely genetically related to SARS-CoV-2 (albeit with only 96.3% sequence similarity) were identified in 2013 and 2019 in bats in Yunnan Province, China, 810 miles from Wuhan.[5, 6] Of note, SARS-CoV-2 has never been identified in a bat. Multiple early SARS-CoV-2 clinical isolates lacked substantial genetic variability, a finding consistent with the notion that SARS-CoV-2 first was introduced into the human population in late 2019 shortly prior to the earliest recognized cases in Wuhan.[7] Proposed potential explanations for initial human exposure to SARS-CoV-2 include 1) direct exposure from bats; 2) transmission from bats to an intermediate host and then to humans, or 3) inadvertent or deliberate release from a laboratory where the virus had been stored and perhaps manipulated.

Ascertainment of the source of the SARS-CoV-2 outbreak has been hampered by the absence of identified viruses with direct ancestral lineage to the novel 2019 virus.[8] However, phylogenetic

dating analyses suggest that SARS-CoV-2 diverged from related bat viruses sometime between 1948 and 1982 and subsequently has circulated in bats unnoticed for several decades.[9, 10] Although all human coronaviruses identified prior to the pandemic have had intermediate animal hosts, none has yet been identified for SARS-CoV-2. The rapid adaptation of SARS-CoV-2 to minks and other animals shortly after the pandemic's onset provides strong support to the concept that transmission to humans via an intermediate host is plausible.[5,10]

Epidemiologic investigation determined that the first confirmed human case, and about two-thirds of the first 41 cases, were linked to the Wuhan Huanan Seafood Market, where 38 species of live wild animals were kept in stalls and then sold. Raccoon dogs, subsequently found to be susceptible to SARS-CoV-2 infection, were caged in the western area of the 12-acre market, a location visited by many of the initial cases.[11] Multiple other animal species including hedgehogs, badgers, deer, and raccoons, but not bats, were sold at the market.[2,11]

To borrow an analogy from trauma care, the "golden hour" for elucidation of the epidemiology of the SARS-CoV-2 outbreak was in late December 2019.[12] Unfortunately, when the Huanan Market was closed on January 1, 2020, no live mammals were screened for SARS-CoV-2, an exercise which would have provided invaluable information about the potential intermediate host or hosts; thus the golden hour was squandered (Figure 1). The possibility that SARS-CoV-2 was not introduced into humans from an animal at the crowded market, but rather that an infected visitor initiated a superspreader event there, cannot be excluded but seems less likely based on the preponderance of available evidence.

An open question is whether an intentional or unintentional laboratory leak from the Wuhan Institute of Virology, where bat coronaviruses are studied, could have been the inciting event. Multiple lines of evidence, summarized by Holmes et al., do not support this theory.[8] No evidence that SARS-CoV-2 originated in a laboratory has been identified by multiple investigators using different lines of inquiry: epidemiologic investigation of laboratory workers; evaluation of the pathogenicity of SARS-CoV-2 in laboratory animals, including mice, necessary for serial passage in virology experiments; and assessment of the feasibility of altering an existing virus to attain the characteristics of SARS-CoV-2.[8] Prior gain-of-function experiments at the Wuhan Institute of Virology used viruses with different genetic backbones than that of SARS-CoV-2 and thus the widely promoted theory that this research caused the pandemic is unfounded.[8]

Was there an unidentified smoking gun in Wuhan, either at the virology institute or across the Yangtze River at the seafood market? Many scientists have concluded that currently available evidence does not support the hypothesis that manipulation or mishandling of a virus by laboratory workers triggered the pandemic.[6,8] The aphorism that common things occur commonly is an early lesson taught to health sciences students and clinicians. Initiation of a pandemic by transmission from other species to humans has been well-documented on multiple occasions.[13] Although the mystery of how SARS-CoV-2 first entered the human population remains unsolved, it seems likely that cross-species transmission occurred, either at the market or nearby, from an as-yet unidentified intermediate host. There is scant support for the theory that COVID-19 will prove to be the first pandemic in history caused by a laboratory leak.

Incidence in Missouri and U.S.

Once the first U.S. case was documented on January 26, 2020, on the west coast, it was only a matter of time until the new coronavirus would reach Missouri. On February 5, hundreds of thousands of Missourians celebrated with the Kansas City Chiefs at their first Super Bowl victory parade in half a century. The event's timing was fortuitous: scarcely a month later public gatherings ceased. The state's first case, reported on March 7, was a college student from the suburban St. Louis area who returned home from studying in Italy and then created a furor by attending a large social event in Clayton while possibly contagious.

From March until August 2020 Missouri benefited from its central location, far from the early hotspots on the east and west coasts, as case counts remained low; incidence was about half the national average[14] (Figure 2). In particular, COVID-19 rates in rural areas in central and southern Missouri were among the lowest in the country. Unfortunately,

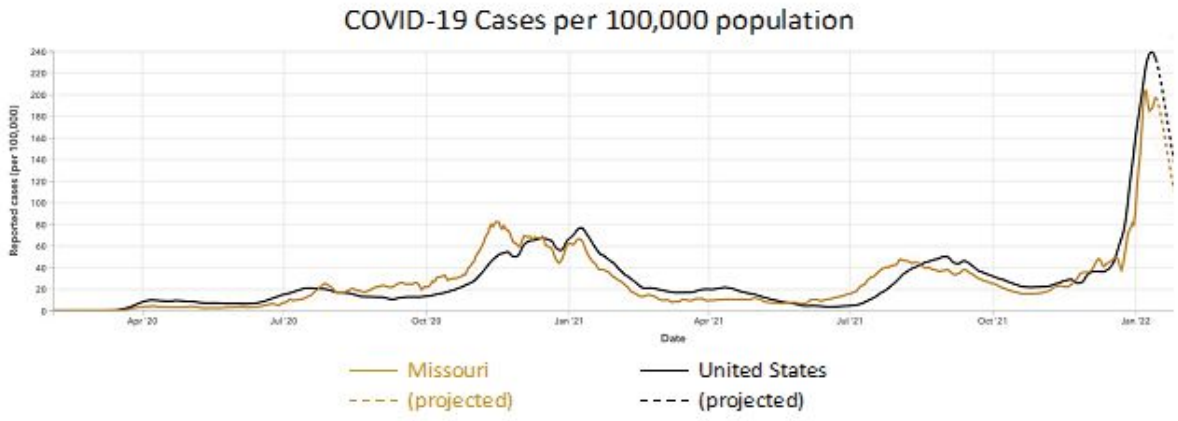


Figure 2. Epidemic Curve, Missouri and United States, 2020-21
Source: https://covid19.healthdata.org. Accessed 2/3/2022

spread of the novel coronavirus to all corners of the state soon ensued.

The epidemic curve in 2020 and 2021 was characterized by recurrent surges. As SARS-CoV-2 mutated successively more contagious variants, including Delta and Omicron, evolved and spread. Incidence in Missouri surpassed the rest of the nation from September 2020 to January 2021 in concert with widespread and increasing disdain for public health best practices (Figure 2). Initial optimism that COVID-19 would be a seasonal virus, confined to the cold weather months, was quashed as new infections occurred year-round. Cases spiked with the onset of cold weather in November 2020; after the December 2020 holiday season; in July 2021 when Southwest Missouri was the national epicenter for the Delta variant surge; and in December 2021 when the Omicron variant erupted[14] (Figure 3).

As of December 2021 approximately 780,000 COVID-19 cases were confirmed in Missouri; combined with an additional 180,000 probable cases, the total count approached one million, or roughly 17% of the state's population. Of note, many cases were undocumented and the actual case count undoubtedly was far higher. The state had 12,842 confirmed and 2,896 probable deaths by the end of 2021; COVID-19 was the third-leading cause of mortality in the state. Missouri ranked 19th among the 50 states in case rate per 100,000 population and its mortality rate ranked 27th.[14]

The epidemic curves in Missouri's two largest metropolitan areas, the St. Louis and Kansas City regions, largely were superimposable during the first two years of the pandemic with the exception of a steeper spike in Kansas City during the Delta variant surge in the summer of 2021 and a more rapid decline in cases in St. Louis at that time. In contrast, Springfield had lower disease incidence than Kansas City in the first 15 months of the pandemic but then experienced an exceptionally sharp spike in cases when the Delta surge began in July 2021.[14] Epidemic curves for Kansas City and Springfield are compared to that of New York City in Figure 3. New York City sustained a severe blow at an earlier phase of the pandemic as thousands of infected travelers arrived from Europe, and then implemented lockdown measures that were implemented for a lengthier period than in either of the Missouri cities.

Missouri is comprised of 115 counties plus the independent city of St. Louis. The highest regional incidence rates in Missouri were identified in rural counties. The top three counties in cases per 100,000 persons as of the end of 2021 were Gentry, Sullivan, and Lewis, each of which rank in the lowest 20% of the state's population. In contrast, the three most populous counties in the state (St. Charles, Jackson, St. Louis), and St. Louis City ranked 23rd, 32nd, 67th and 92nd, respectively.[14]. This data suggests that low population density was not protective.

Treatment

In March 2020 when COVID-19 arrived in Missouri, health care workers found themselves, metaphorically speaking, deep in one of the state's many dark limestone caves with only the faintest

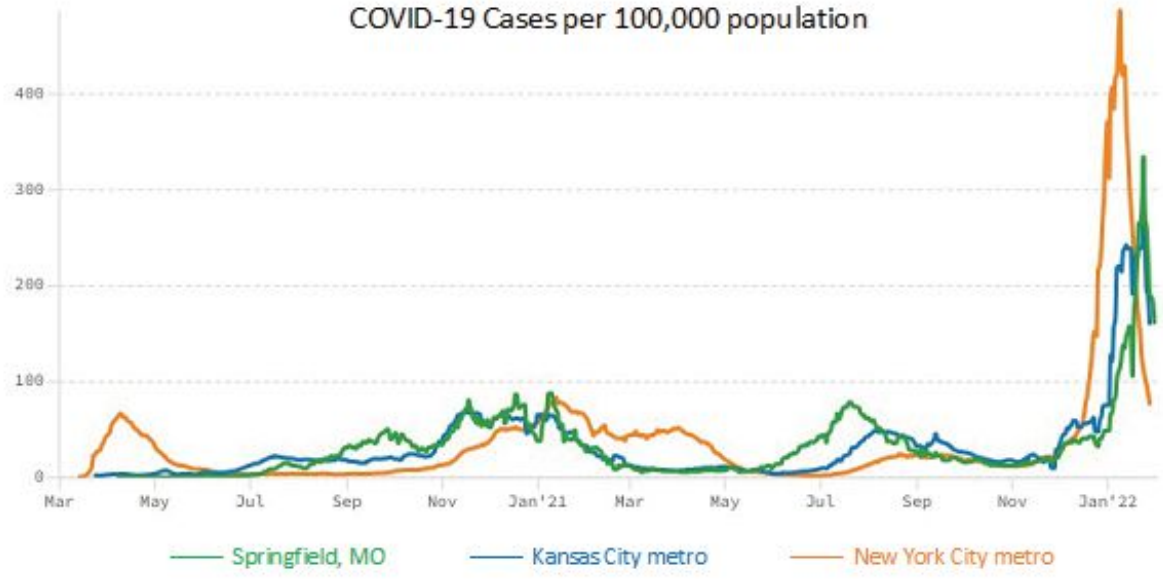


Figure 3. Epidemic Curves, Kansas City, Springfield, and New York City, 2020-21
Source: https://covid19.healthdata.org. Accessed 2/3/2022

flicker of light for illumination. There was no extant database about the formidable and unpredictable new viral adversary. As case counts inexorably increased, the evidence base regarding effective treatment options for SARS-CoV-2, and its many accompanying life-threatening inflammatory manifestations, evolved rapidly. A full discussion of treatment recommendations for COVID-19 is provided in guidelines published online by the National Institutes of Health (NIH) which are based on the highest caliber data available from clinical trials, are apolitical and unbiased, and are updated shortly after new data becomes available.[15]

Timing is a critically important factor impacting treatment decisions. During the initial phase of the illness antiviral therapies (oral paxlovid or molupiravir; intravenous remdesivir) reduce duration and severity of illness. Immune-based treatments (convalescent plasma, monoclonal antibodies) also are effective in many cases.[15,16,17] Blood banks are not currently collecting convalescent plasma, however. Steroid therapy is a double-edged sword. Although widely prescribed to outpatients, systemic corticosteroids prolong the duration of viral shedding and are not recommended.[15,18] However, for inpatients requiring supplemental oxygen dexamethasone reduces mortality and should be used routinely unless a contraindication exists. The interleukin-6 inhibitors tocilizumab and sarilumab and the JAK kinase 1 and 2 inhibitor baracitinib may be indicated for select cases in which gas exchange is deteriorating rapidly and there is evidence of systemic inflammation. Given the high risk for thromboembolic complications all inpatients should receive prophylactic anticoagulation unless contraindicated; a subset of inpatients appears to benefit from full anticoagulation.[15]

The pandemic has shined a bright light on health care workers' widely disparate perceptions about the most appropriate treatments for COVID-19. Multiple regimens not recommended in the NIH guidelines have been widely prescribed despite either the absence of quality evidence supporting their use, or even the suggestion of greater harm than benefit. The factors influencing physicians and other health care providers' treatment decisions have been studied extensively.[19] Experience during the pandemic has made it abundantly clear that discussion of certain treatments on podcasts, cable news, or social media by prominent public figures who possess a megaphone but lack scientific training or medical expertise appears to have an outsized influence on patient demand for certain medications and on prescribing practices by some providers. The apparent lack of widespread awareness

Table 1. Treatment for COVID-19: NIH Guidelines
February, 2022

Outpatient
Age > 65 or underlying medical conditions conferring high risk for severe COVID-19:
- Paxlovid
- Sotrovimab
- Remdesivir
- Molnupiravir

Inpatient
All patients:
- Prophylactic anticoagulation unless contraindicated

If requiring supplemental oxygen:
- Dexamethasone
- Remdesivir

Rapidly increasing oxygen requirement and systemic inflammation:
- tociluzumab or baricitinib
- alternatives: sarilumab or tofacitinib

Do Not Use
- Zinc
- Chloroquine or hydroxychloroquine
- Systemic steroid (outpatients)
- Azithromycin (unless bacterial infection)
- Anticoagulation/antiplatelet (outpatients)

Insufficient Evidence to Recommend For or Against Use
- Ivermectin
- Fluvoxamine
- Vitamin C
- Vitamin D

of the difference in caliber of various research studies and their applicability to practice has been striking.

In the era of instant worldwide dissemination of new information and ideas, accurate or not, rumors generated early in the pandemic often led to rapid and widespread implementation of new treatment practices. Some of these strategies should have been abandoned but their use has lingered despite evidence of potential harm. As an example, in 2020 French researchers who specialize in rickettsial infections reported favorable results of a pilot study of azithromycin and hydroxychloroquine, neither of which are antiviral drugs, for COVID-19.[20] Use of this regimen soon became commonplace. A subsequent randomized double-blind study demonstrated that azithromycin/hydroxychloroquine recipients were more likely to require mechanical ventilation or to die than those who received placebo, and a meta-analysis also found that hydroxychloroquine was associated with increased mortality. [21, 22] The senior author of the original manuscript is being investigated in France for possible disciplinary action. Nevertheless, hydroxychloroquine for COVID-19 is still advocated by some.[23]

The antiparasitic drug ivermectin has in vitro activity against SARS-CoV-2 at concentrations approximately 100-fold higher than are obtainable with standard human doses.[15] Ivermectin first received attention as a potential treatment for COVID-19 when a nonrandomized study in Egypt, subsequently retracted for inclusion of fraudulent data, reported a survival benefit.[25, 26] When this study and multiple other related publications with "significant methodological limitations" were scrutinized, the apparent benefits of the drug vanished.[15,24, 25,26] Ivermectin has not been shown to reduce viral clearance, progression to severe disease, or mortality, and its use is not recommended by the NIH or the Infectious Diseases Society of America.[26] Cases of ivermectin toxicity, manifested by gastrointestinal intolerance, ataxia, seizures, or coma, increased substantially in the U.S. during the pandemic, prompting an emergency reminder by the CDC to health care providers that the drug is not authorized by the Food and Drug Administration (FDA) for treatment of COVID-19.[27] The FDA web page states, "You are not a horse. You are not a cow. Seriously, y'all, stop it."[28] However, use of the human or veterinary formulations remains widespread. As an illustration of the highly politically charged environment surrounding ivermectin, the state health department in Missouri's eastern neighbor Illinois has threatened disciplinary action against providers who prescribe this medication whereas on our western border the Kansas House of Representatives has advanced legislation to prohibit the state's Board of Healing Arts from disciplining ivermectin advocates.[29]

Polypharmacy for COVID-19 appears to be widespread and may be associated with increased risk of adverse events.[30] Many vitamins, mineral supplements, and alternative medications which do not have antiviral activity have been used extensively for patients with SARS-CoV-2 infection. Vitamins

and alternative medicines have not been effective for treatment or prevention of COVID-19.[31] Concomitant medications have prompted extensive speculation as potential treatments for COVID-19. None have been shown either to improve or to worsen outcome.[15] Figure 4 summarizes current evidence-based management recommendations.

Conclusion

During the first two years of the historic and cataclysmic COVID-19 pandemic Missourians witnessed recurrent surges of disease that stretched our health care system almost to the breaking point on multiple occasions. Important questions remain unanswered, but dramatic advances have been made in our ability to treat COVID-19 and its complications. Although differences persist among health care providers regarding the best approach to treatment of COVID-19, these controversies are dwarfed by the highly politicized, divergent points of view about public health strategies for pandemic mitigation that will be addressed in the next article in this series.

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Disclosure

None reported.

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MSMA Members in the News





The Boone County Medical Society has new leadership for 2022 (above). **Kara Braudis, MD**, (left), will take the office of President; **John Pardalos, MD**, (center), will serve as Secretary/Treasurer; and **Albert Hsu, MD**, (right), transitions to Past President. The Board of Directors includes **Bridget Gruender, MD**; **Clay Mechlin, MD**; **Laine Young Walker, MD**; and **Amy Zguta, MD**.



The East Prairie Chamber of Commerce has honored **Jimmy Heath, MD**, with its Lifetime Achievement award. Dr. Heath, an MSMA member for over 40 years, has served the East Prairie community for several decades. In addition to providing medical care to generations of Mississippi Countians, he has stood as a pillar of his community, serving in numerous civic and leadership roles. This summer, he will close his practice to enjoy retirement – congratulations, Dr. Heath!



Farzana Hoque, MD, MRCP (UK), FACP, has been named as the President of the Society of Hospital Medicine (SHM) St. Louis Chapter. She will serve for the next three years as the only woman on this leadership board.

Dr. Hoque is an Assistant Professor of Internal Medicine in the Division of Hospital Medicine at Saint Louis University School of Medicine. She also serves as the Medical Director of Bordley Tower and current Medical Staff Treasurer at SSM Health St. Louis University Hospital.







In a January virtual meeting, the Greene County Medical Society saw a change in leadership (above) as new officers were installed by MSMA President Alexander Hover, MD. New officers are, top row: **Minh-Thu Le, MD**, (left), President; **Sanjay Havaldar, MD**, (center), President Elect; **James Rogers, MD**, (right), Secretary; and bottom row: **Jacob Thomas, MD**, (left), Treasurer. Immediate Past President **Thomas Kuich, MD**, (right), was honored for his service to GCMS.



Sam Page, MD, received the American Medical Association Award for Outstanding Government Service in the category Career Public Servant at the Local Level. The award, presented by the AMA upon the recommendation of an independent panel of judges, recognizes local, state, and federal career and elected government officials for outstanding service in the advancement of public health.

MM

Correspondence

Sacklers Sacked But Purdue Still Caused Opioid Epidemic

The role of Purdue Pharma and its blockbuster drug oxycontin in causing the opioid epidemic which has killed over 450,000 people in the past two decades has been well described in books like "The Empire of Pain" by author Patrick Keefe and in reports of investigative journalists that have appeared in leading U.S. newspapers.

From these and other sources it is estimated that in nearly one half of the cases drug addiction began with a doctor's prescription. Although other drug companies and drug distributors were involved, Purdue with its blockbuster drug oxycontin was the leading supplier of prescription opioids to patients.

Purdue used "thought leaders" in medicine like Russell Portenoy, MD, Chairman of the Department of Pain Medicine and Palliative Care at Beth Israel Hospital in New York, to promote the safety of opioids. Purdue and other pharmaceutical companies paid large sums of money to Portenoy and his department. Purdue also paid many other physicians to tout the benefits of oxycontin.

Purdue also instructed its pharmaceutical representatives all over the country to tell physicians that oxycontin was not addictive primarily because of its slow-release properties. Purdue told its representatives to tell doctors that only persons with an "addictive personality" became addicts.

Contrary to the statements of Purdue recent evidence has shown that oxycontin is addictive and has played a significant role in the devastating epidemic of opioid addiction that has gripped the U.S. in recent years.

Private parties and states attorneys general have sued Purdue. Purdue's response was to opt for a settlement and declare bankruptcy.

In the original bankruptcy proposal Purdue agreed to pay four billion dollars to plaintiffs. However, the Sackler family which privately owned Purdue, would be allowed to keep billions of dollars that it had withdrawn from the company before the bankruptcy was finalized. In December 2021 a different judge, Coleen McMahon of the District Court for the Southern District Court of New York, ruled that the previous judge's ruling on the settlement should not go forward because it released the Sackler family, the private owners of Purdue from liability. The Sackler family, she noted, had withdrawn more than 10 billion dollars from Purdue between 2008 and 2018 as the opioid epidemic was worsening. This money was mainly deposited in off-shore accounts and trusts that were not accessible to Americans. This is where the litigation stands today.

All three of the original Sackler brothers who bought Purdue and ultimately developed oxycontin were physicians. At the peak of their sales and marketing, Purdue hired 3,000 doctors to serve on their speakers bureau—a fact which certainly does not reflect well on the medical profession. Richard Sackler, the current chairman of the board of Purdue and who closely directed the firm in recent years, went to Harvard Business School—a fact which also does not reflect well on America's premier business school. At Purdue, profits trumped ethics.

The Sacklers were generous donors to universities, academic medical centers, museums, and other charitable institutions in the U.S. and all over the world. Their names adorned these venerable institutions. In almost every case their names have been removed. And with the new bankruptcy ruling the Sacklers will lose most of their vast fortune. Far more important is their tragic legacy of being a major cause of the devastating opioid epidemic which has afflicted so many American families.

Arthur Gale, MD
Retired, Internal Medicine
St. Louis, Missouri



Letters to the Editor

Submissions reflect readers' opinions and may be edited for length. Use in subject line: "Letter to Editor."

Email
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Gun Violence

In the Correspondence department of the January/February 2022 issue of *Missouri Medicine*, there is a letter titled, "Marijuana Killed My Son! Doctors, Let Me Tell You Something about the Dangers of Cannabis." Visually sandwiched in the letter's columns is a bar graph under the heading "ONE PICTURE =1000 WORDS." Intentionally or not, the graph calls attention to the epidemic of gun violence that, in contrast to the, also important, marijuana issue, has largely evaded MSMA's radar and *Missouri Medicine's* pages.

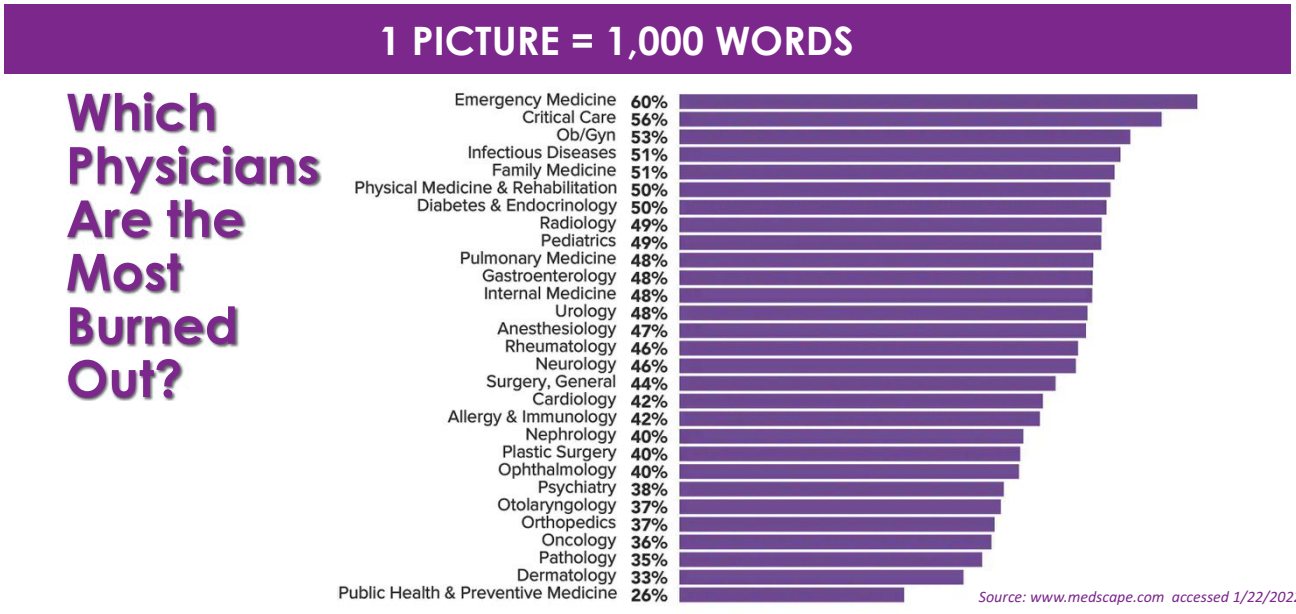
That Statista info graphic, "2020 Saw Unprecedented Murder Spike in Major U.S. Cities," shows that homicide rates for a dozen U.S. cities soared by a whopping 14% to 74% over the preceding year, making them the highest in the past quarter century! Most of those killings have of course been firearms related. Interestingly, there has not been an accompanying increase in burglaries, thefts, and other property crimes. As a Duke University crime expert observed in an Atlantic article titled, "America is Having a Violence Wave, Not a Crime Wave," what we are really experiencing is a dramatic increase in lethal violence. But what else should we expect when many states, including ours, seem intent on passing laws that make it easier to purchase and own guns, easier to use them (i.e., "stand-your-ground laws"), and harder to make them less lethal or safer (i.e. personalized/smart gun technology/magazine capacity)?

It was a profoundly sad state of affairs, three years ago, when MSMA's House of Delegates found it necessary to pass a resolution recommending that bleeding control training be instituted in our schools. Realizing now that our 2019 MSMA "tourniquet resolution" is virtually all that we have mustered the courage to do as far as gun violence is beyond disappointing—it's heartbreaking. I hope that the "1000 WORDS" conveyed by that "ONE PICTURE" is just the first thousand of many more that *Missouri Medicine* will use to create the awareness that this problem deserves. As public health advocates, we should find this epidemic of violence entirely unacceptable because it is demonstrably avoidable. We need only compare the incidence gun violence in the U.S. to that of similar countries which differ mainly in factors pertaining to guns, in order to understand that this epidemic is not by chance or misfortune, but by social and political choice.

At first glance, I expected the homicide graph, appearing alone and on the same page as the letter by Laura Stack, to be a marijuana statistic illustrating the threat that high THC products pose to our youth. That letter by the founder of Johnny's Ambassadors (along with her MSMA article) reminded me of the Sandy Hook Promise Foundation, an organization which works to prevent gun violence by training students and adults to recognize its signs. Her letter, like her article, was impactful not only because it came from a source well versed on the subject, but also because it had a personal experience perspective. It would be wonderful if *Missouri Medicine* could reach out to an organization like Sandy Hook Promise to solicit an article or letter on gun violence along the lines of the ones by Ms. Stack.

It's been over ten years since the Sandy Hook massacre claimed the lives of 20 first-graders and six educators. Yet the U.S. did not even make it to March 1 before experiencing its seventieth mass shooting of this year! I wonder how long will it take, or sadly what it will take, for Missouri's physicians, led by *Missouri Medicine* and the MSMA (hopefully assisted by the MSMA Alliance), to take on gun violence in a scientific and meaningful way.

Frank A. Cornella, DDS, MD
*Springfield, Missou*ri



MU School of Medicine Celebrates 150th Anniversary

by Steven Zweig, MD

This year we will celebrate our 150th year anniversary of the MU School of Medicine, the oldest medical school in Missouri and the school claiming the most practicing physicians in Missouri. When I graduated from MU's School of Medicine in 1979, there were only 16 women in our class of 110. Now a majority of our students are women, and in this year's entering class, 20% of our students self-designate as members of groups who are underrepresented in medicine (UIM). This class also shows the strongest indicators ever of prior academic success. Five years ago, in collaboration with health systems in Springfield, we started the Springfield Clinical Campus where close to one-fourth of our 128 students in each class spend most of their third and fourth years. The graduates of our 450-strong residency and fellowship programs in Columbia populate Missouri and the United States.

We are also striving to expand the pool of students underrepresented in medicine. Our Pathways to Success program, working in collaboration with the MU campus, started a rigorous preadmissions program for those who are UIM, first generation college students, or who come from poor financial backgrounds. Furthermore, we have one of the most successful rural pipeline programs in the country. During its 25-year history, 50% of its graduates practice in rural Missouri communities. Our students successfully compete for residency positions in all disciplines and across the country.

> **"After 150 years, we are still here – and growing. We continue to create even more opportunities to impact the health and welfare of people."**

Last year we completed the first ever joint strategic plan for the MU School of Medicine and MU Health Care. We now have shared mission and vision statements, as well as shared set of stated values. Given that we are both part of the University of Missouri, that does not seem like a great accomplishment. However, during my 40 years here as a faculty member – including 11 years as a clinical chair and almost three years as dean, we have sometime in the past lacked the alignment needed to advance as an academic health system. As our mission states, we strive to provide exemplary patient care, teach, and train within that setting, and innovate and perform research which informs both.

The MU Department of Orthopaedic surgery, under the leadership of James Stannard, MD, has gone a long way in exemplifying this mission. The department has grown in providing the full spectrum of outstanding orthopaedic care. It has collaborated with radiology, anesthesiology, internal medicine, and physical medicine and rehabilitation specialists, as well as physical and occupational therapists to provide integrated musculoskeletal care within the Missouri



Steven Zweig, MD, MSPH, is Dean of the University of Missouri - Columbia School of Medicine. He practices family, geriatric, and hospice and palliative medicine.

Orthopaedic Institute. They also support outstanding training for medical students, residents, and fellows. This issue of *Missouri Medicine* highlights some of the research advances of the department and how they are impacting the health and function of people from Missouri and beyond.

The MU School of Medicine is striving to expand our research. Our competitive federal grant expenditures grew from $28.8 million in FY19 to $45.3 million in FY21. Industry partnerships have helped our growth in clinical care and innovation. With the recent opening of the Roy Blunt NextGen Precision Health research building (245,000 square feet of space), we can perform research along the full translational continuum from basic science to implementation in populations. The Mizzou Forward initiative will fund an additional 150 research intensive faculty members across the campus. This initiative will make it possible for us to recruit more successful faculty from across the country to areas of strength and opportunity.

Our faculty are the physicians of MU Health Care, and never have we worked in a closer partnership. Furthermore, our relationships with colleagues on the MU campus in nursing, health professions, engineering, animal sciences, arts and science, and other disciplines help us become a more impactful academic health system. Each person here has stayed the course in sustaining the ambiguity, risk, and morbidity experienced during the last two years of pandemic.

Yet there are challenges ahead. Staff shortages and inflationary wages for both staff and physicians are creating rising expenses, while insurers are looking to pay less for services. Research funding is increasingly competitive. These pressures, plus increasing demands from both payers and patients, are contributing to faculty and staff burn out. Furthermore, the pandemic has again highlighted the impact of health disparities and how academic health systems can and do responsibly rise to address the needs of populations.

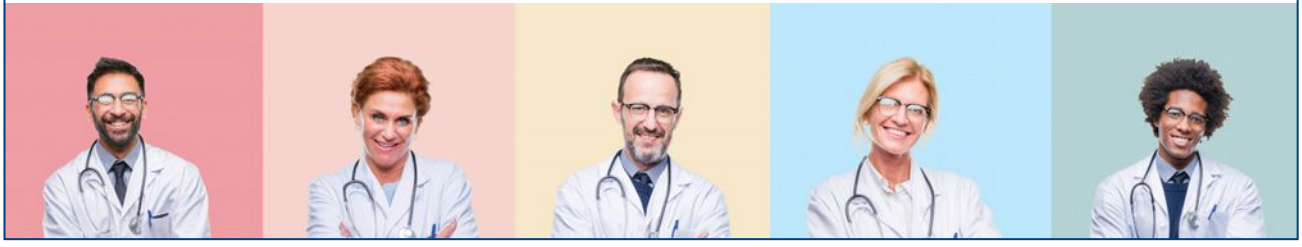
After 150 years, we are still here – and growing. We continue to create even more opportunities to impact the health and welfare of people. Having been around the MU School of Medicine for almost a third of that history, I am honored to work with such a committed, capable, and optimistic group of leaders, faculty and staff, trainees, and students. They constantly make us better, while extending our mission to save and improve lives through exemplary education, research, and patient-centered care. **MM**

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Missouri Orthopaedic Institute: A Center for Innovation and Translation

by James Stannard, MD

The Missouri Orthopaedic Institute (MOI) opened in June 2010 as the largest free standing orthopaedic hospital in the region. The goal at the time was to provide state of the art quality and comprehensive orthopaedic care combined with efficiency and compassion.

As part of the University of Missouri's Healthcare system, the institution was also established with a mission to advance knowledge by performing cutting edge research. By 2015, a second construction phase nearly doubled the size of the building and provided dedicated research space for research teams to be in close proximity to our surgeons. This combination of research and clinical talent close together has yielded translational research that really tries to solve current clinical challenges.

This edition of *Missouri Medicine* centers around the story of the MOI and how it has been used to solve current musculoskeletal problems for Missourians while also performing research that focuses on moving our knowledge and clinical practice forward.



James Stannard, MD, is chair of the Department of Orthopaedic Surgery, the Hansjörg Wyss Distinguished Chair of Orthopaedic Surgery, Medical Director of the Missouri Orthopaedic Institute, and Chief Medical Officer for Procedural Services.

The article by James Cook, DVM, PhD, et al. articulates the powerful story of putting researchers with surgeons to solve a very challenging clinical problem. This research, focusing on biologic joint restoration, has gone from bench to animal model to animal patient to human in an attempt to solve post traumatic full thickness articular cartilage loss in young and active patients. As a result of several research and clinical breakthroughs, we have treated people from 30 states and 12 foreign countries including patients from England, Saudi Arabia, and Dubai who are waiting to come as the improving pandemic begins to permit international travel once again.

As part of the MOI's spinal research and practice, Daniel Hoernschemeyer, MD, and Melanie Boeyer, PhD, a post-doctorate fellow with the Thompson Laboratory for Regenerative Orthopaedics within the MOI, have tackled the challenge of scoliosis in the pediatric population and used growth remaining in pediatric patients to allow curve correction with a new technology called 'vertebral body tethering.' When properly utilized, it allows correction while still retaining much of the normal flexibility in the spine. Dr. Hoernschemeyer's early results have been outstanding and have recently been published in one of the specialty's most prestigious journals.

Jay Bridgeman, MD, and Brett Crist, MD, lead a multidisciplinary team that takes on the difficult approaches to limb salvage. Severe trauma leads many people to experience injuries that previously resulted in amputation. The ability to combine trauma surgeons with hand microvascular surgeons has led to remarkably improved limb salvage results. This has been made far more attainable by having a facility like the MOI, which allows us to combine



The state-of-the-art Missouri Orthopaedic Institute comprises the Thompson Laboratory for Regenerative Orthopaedics, the Mizzou BioJoint Center, the Limb Preservation Center, a complete Physical Therapy Center, and the Young Adult Hip Preservation Center and chiropractic services. The four-story building offers 42 inpatient rooms, 12 operating rooms, 62 clinic exam rooms, seven X-ray rooms, EOS and DEXA scanners, two MRI scanners, a CT-scanning area, an outpatient therapy clinic, a retail pharmacy, lab services, dietician services, a café, and faculty and staff offices. Source: Architect's rendering above building looking towards the west by BSA LifeStructures.

diverse talents in a single location and tackle challenging problems as a team.

Julia Nuelle, MD, a new faculty member at the Missouri Orthopaedic Institute, is working on groundbreaking research surrounding nerve preservation and regeneration. Severe damage to peripheral nerves is a problem that has eluded successful treatment for many years, leaving patients with severe impairment. Dr. Nuelle began work on this problem while serving in the United States Air Force and is bringing her novel work to Mizzou. She is combining forces with the Mizzou Biojoint Center to develop techniques to preserve live grafts and evaluate the potential of transplant in cases of deficient peripheral nerve tissue.

Richard Ma, MD, et al. have documented how a research interest in anterior cruciate ligament (ACL) graft incorporation plays a role in the post-operative treatment of our athletes. We have combined that with motion analysis to try to put the science behind our return to play decisions. State of the art science combined with a state-of-the-art facility and faculty provides major benefits to active Missourians with torn ACLs.

In the article on knee osteotomies, Mauricio Kfuri, MD, PhD, et al. present extremity alignment studies and how they are of critical importance to understand how the loads are distributed on the knee. Correction of deformities around the knee promotes a better distribution of the load among the different compartments of the joint, restoring the knee mechanical homeostasis. The goal of deformity correction is not only to shift the mechanical load to a healthier compartment of the joint, but to perform it without causing an obliquity of the joint line, or significant leg length discrepancy. Restoring knee alignment and stability may preserve the joint for many years until a joint replacement may be at consideration.

The Missouri Orthopaedic Institute is much more than a building. It is a culture of outstanding patient care and innovation that benefits our patients every day. We remain committed to pushing the boundaries of our knowledge with cutting edge research while providing compassionate and comprehensive care to Missourians and beyond.

Acknowledgment

Missouri Medicine would like to thank Adelina Colbert for her help with the preparation of this theme issue. **MM**

Biologic Joint Restoration: A Translational Research Success Story

by James L. Cook, DVM, PhD, James P. Stannard, MD, Aaron M. Stoker, PhD, Kylee Rucinski, MHA, Brett D. Crist, MD, Cristi R. Cook, DVM, Cory Crecelius, PT, Matthew J. Smith, MD & Renee Stucky, PhD

MU Health Care

Current best evidence suggests that comprehensive translational research has strong potential for further improving a valuable joint restoration technique that helps patients regain long-term function.



James L. Cook, DVM, PhD, OTSC, (above) is the William and Kathryn Allen Distinguished Chair in Orthopaedic Surgery; Director, Thompson Laboratory for Regenerative Orthopaedics (TLRO) and Mizzou BioJoint® Center; and Vice Chair, Orthopaedic Research Division. **James P. Stannard, MD**, is with the TLRO and Department of Orthopaedic Surgery (DOS); Aaron M. Stoker, PhD, is with the TLRO; Kylee Rucinski, MHA, is with the TLRO; Brett D. Crist, MD, is with the TLRO and DOS; Cristi R. Cook, DVM, MS, is with the TLRO; Cory Crecelius, PT, is with the TLRO; **Matthew J. Smith, MD**, is with the DOS; and Renee Stucky, PhD, is with the TLRO; all are with the University of Missouri - Columbia, Columbia, Missouri.

Abstract

Treatment options that result in consistently successful outcomes for young and active patients with joint disorders are needed. This article summarizes two decades of rigorous research using a bedside-to-bench-to-bedside translational approach based on the One Health – One Medicine concept that culminated in successful clinical use of biologic joint restoration options for treatment of knee, hip, ankle, and shoulder problems in this growing patient population.

Introduction

For centuries, biologic joint restoration has been one of the 'holy grails' of orthopaedics. As early as 1743, William Hunter stated in his paper, *On the structure and diseases of articulating cartilages,* that *If we consult the standard Chirurgical Writers from Hippocrates down to the present Age, we shall find, that an ulcerated Cartilage is universally allowed to be a very troublesome Disease; that it admits of a Cure with more Difficulty than carious Bone; and that, when destroyed, it is not recovered.*[1]

Current-day statistics, including that more-than 70 million adults in the United States are impacted by osteoarthritis (OA), prove Hunter's point and provide strong impetus for continuing to pursue the 'holy grail' in order to provide treatment options for these patients. While total joint arthroplasty is a reliable treatment option that is consistently successful in older, less active patients with endstage OA, younger adults and those who wish to remain highly active experience significantly higher levels of pain, complications, morbidity, dysfunction, and likelihood for revision following joint replacement surgeries.[2–5] These limitations become even more important when considering the increasing activity levels and lifespans for seniors. As such, our team set out to develop, test, and validate biologic joint restoration strategies that could provide consistently successful options for young or active patients with joint disorders who were not ideal candidates for total joint replacement. In pursuit of this goal, we implemented a bedside--to-bench-to-bedside translational approach based on the One Health – One Medicine concept (Figure 1). The objective for this article is to summarize two decades of rigorous research that culminated in successful clinical use of biologic joint restoration options for treatment of knee, hip, ankle, and shoulder problems in young and active patients.[6–32]

Starting at the Bedside: Is It Possible?

Debilitating articular cartilage loss that progresses to OA is being diagnosed more frequently and earlier in life, such that a growing number of active patients are faced with life-altering healthcare decisions at increasingly younger ages. Total joint arthroplasty is a consistently successful operation, especially for older (≥65 years), more sedentary patients, but has major limitations for younger, more active patients.[2–4,31] Nonsurgical management strategies and other surgical treatment options are often not indicated and have not proven to be consistently successful for patients who wish to remain highly active.[2–4,32–38] As such, these patients are often relegated to postpone surgery, take medications including opioids, profoundly alter their lifestyle, and live with pain and disability until total joint arthroplasty is more likely to meet their functional demands without high risk for revision. Combined, these factors result in relatively high levels of patient dissatisfaction in this large and growing patient population.[2–4,31]

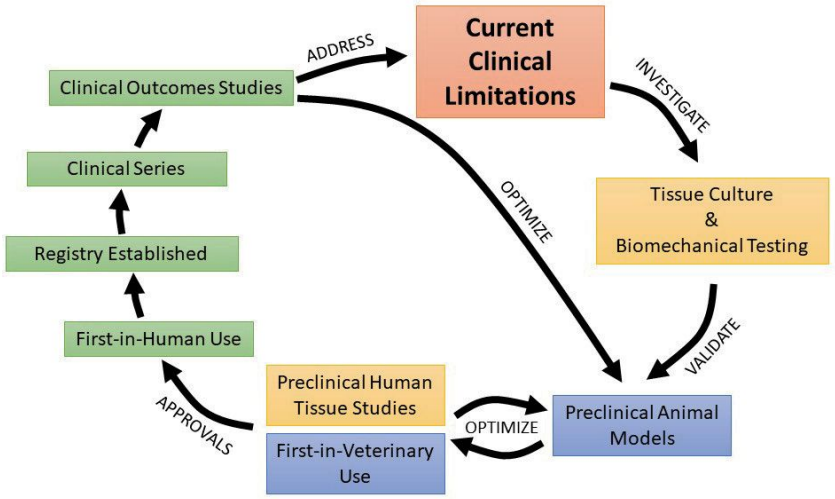


Figure 1. University of Missouri's One Health-One Medicine Translational Approach for Addressing Limitations to Successful Biologic Joint Restoration

Biologic joint restoration using osteochondral allograft (OCA) transplants has been an option for these patients for more than 50 years.[39–49] However, chondral and osteochondral defects that require transplantation of more than a single cylindrical "plug" OCA have not had consistently favorable long-term outcomes, including failure rates of 30-60% reported for extensive multisurface and bipolar OCA transplants.[39,40,43,44,50–52] Historical obstacles to these complex transplant cases include availability of OCAs with high chondrocyte viability at time of transplantation, consistent allograft bone integration, and functional allograft survival. Therefore, our multidisciplinary team focused on programmatic research aimed at innovations in donor tissue preservation, OCA pretreatment, and surgical techniques for OCA transplantation that address the primary obstacles to consistent success for biologic joint restoration surgeries that could improve outcomes for patients.

Bedside-to-Bench: The Science Behind the Surgery

A robust foundation in osteochondral allograft science from pioneers in the field including Lexer, Gross, Meyers, and Bugbee in conjunction with expansive and well-regulated tissue donation, recovery, and banking mechanisms in the United States established the methods and aims for our research. The first and most pivotal issue to address surrounded the very limited "shelf life" for preserving osteochondral tissues from time of recovery from the organ and tissue donor, through required disease testing procedures, to delivery to the surgery center for transplantation into the patient such that tissue quality, in terms of chondrocyte viability and extracellular matrix (ECM) composition and material properties, is maintained. The standard practice for tissue banks is to preserve OCAs in defined solutions at 4 degrees Celcius, which only preserves the minimally sufficient chondrocyte viability (70% of day-0 viable chondrocyte density (VCD)) for an average of 28 days after recovery.[24,25,28,29,40,53–55] After recovery from the tissue donor, mandatory disease screening protocols require at least 14 days to complete before OCAs can be released for clinical use. Based on this timeline and the strong effects that VCD has on successful outcomes, the window for surgical implantation of high-VCD OCAs is narrow, which severely limits clinical use and efficacy. Therefore, a method for OCA preservation

that maintains essential chondrocyte viability in all grafts for a longer period of time was a major unmet clinical need.

Using what we learned from our collaborative research centered on chondral and osteochondral tissue engineering, we designed a series of experiments to delineate the relevant variables that would optimize chondrocyte viability and ECM integrity during storage. These experiments resulted in development of the Missouri Osteochondral Preservation System (MOPS®), which was initially validated to preserve canine OCAs in a proprietary solution at room temperature in order to maintain sufficient chondrocyte viability, articular cartilage ECM composition, and material properties for up to 60 days after recovery.[25–29] The capabilities and importance for this maintained OCA quality were then confirmed based on comprehensive assessments of diagnostic imaging, functional, histologic, and biomechanical outcomes in preclinical canine models.[12,13,25–27] These data reaffirmed the critical importance for transplantation of OCAs with high (>70%) donor VCD, and demonstrated the superiority of MOPS over standard preservation for canine OCA transplantation surgeries, allowing for ethical use of MOPS grafts for biologic joint restoration procedures in canine patients.[56]

Based on this preclinical evidence, the Musculoskeletal Transplant Foundation (MTF) partnered with the University of Missouri to support research aimed at validating MOPS for use in preservation of human OCAs. These studies included sterility testing by a qualified external contract laboratory according to the USP 71 protocol and American Association of Tissue Banks (AATB) standards.[57] Taken together, these studies provided laboratory data to verify that MOPS® could safely preserve human osteochondral tissues from organ and tissue donors for up to 56 days after recovery, such that chondrocyte viability was maintained above the recommended threshold for success at time of implantation in all grafts.[16,17,23] The MOPS preservation duration and graft viability levels were markedly superior to those for other currently used methods of OCA storage and supported their clinical use in conformance of the tissue to the U.S. Food and Drug Administration (FDA) classification of a human cell and tissue product under section 361 of the Public Health Services Act.[11,18,19]

Bench-to-Bedside: Clinical Application of the Science

Based on the robust laboratory data in conjunction with conformance with FDA and AATB policies, guidelines, and standards, MOPS-preserved OCAs were implemented for limited use in standard-of-care OCA transplant surgeries in the knee performed at the Mizzou BioJoint® Center. Patients underwent OCA transplantation for large (> 2 cm^2) grade III or IV focal articular cartilage defects[58] of patella, trochlea, femoral condyle(s), and/or tibial plateau with or without meniscus. As part of the initial clinical use of MOPS-preserved OCAs, VCD was compared to standard preservation grafts at time of transplantation by assessing nonimplanted portions of femoral condyle OCA tissue, which were normally discarded.[19] VCD in MOPS-preserved OCAs stored for a mean of 44 days was not significantly different from normal healthy cartilage and was above the desired minimum essential level of 70% at the time of transplantation in 100% of grafts. VCD in standard preservation OCAs stored for a mean of 20 days was significantly lower than normal healthy cartilage and MOPS grafts, and only 27% were above the desired 70% threshold at the time of transplantation. Further, the combined revision and failure rate was significantly higher in the standard preservation cohort compared with the MOPS cohort. These data provided the impetus for an evidence-based shift in practice to use of only MOPS-preserved allografts at our institution, which have since been transplanted for treatment of complex articular defects in the knee, hip, ankle, and shoulder [6,8–11,14,18,19,21,22] (Figure 2).

Patients chose these biologic joint restoration options over other nonsurgical or surgical alternatives after thorough pre-operative assessments and counseling, as well as approval for coverage by their insurance provider. The decision-making and consent process for all patients included preoperative counseling with the attending surgeon and a joint restoration healthcare team to discuss risks and benefits associated with OCA transplantation, set expectations for adherence with post-operative restrictions, rehabilitation, follow-up appointments, and communication of details related to aftercare with the patient and their caregivers. With institutional

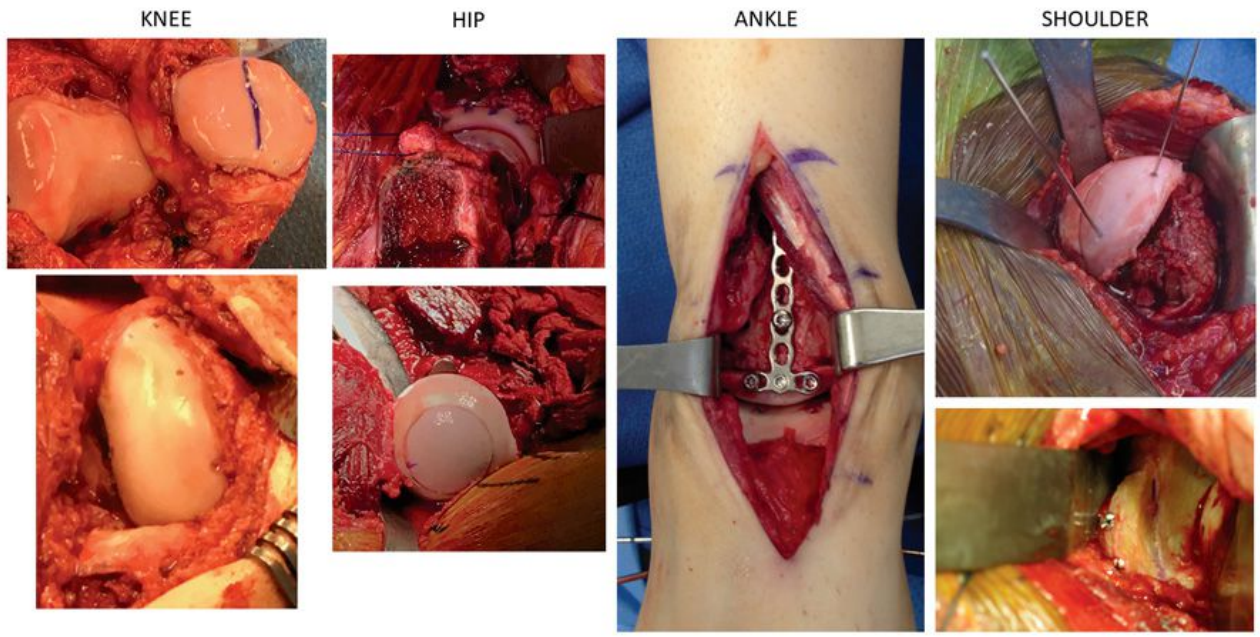


Figure 2. Representative Intraoperative Images of MOPS-preserved Osteochondral Allograft Transplantation for Complex Biologic Joint Restoration in the Knee, Hip, Ankle, and Shoulder of Patients with Large Symptomatic Articular Defects.

review board approval and documented informed consent, patients were prospectively enrolled into a dedicated registry designed to follow OCA transplantation outcomes. As we determined the critical nature of patient adherence to the postoperative rehabilitation protocol in mitigating failures, a behavioral health psychologist was added to the team to assess emotional, behavioral, and psychosocial variables related to outcomes and provide behavioral health interventions to support patients through the rigorous preoperative and postoperative processes that are paramount to optimizing successful outcomes.

By continually assessing outcomes in real-time, clinical limitations and questions can be effectively addressed by taking them back to the "bench" and providing evidence-based improvements in care through the translational process. This process has resulted in further advances in allograft science in the areas of tissue preservation, pre-implantation OCA preparation, graft immunology, transplantation techniques, postoperative imaging, rehabilitation protocols, and patient education and adherence strategies.[6–23] In the first five years of clinical implementation of these advances at the Mizzou BioJoint Center, the prospective clinical registry-based data suggest that MOPS-preserved OCA transplants are an appropriate treatment option for young or active patients with large, full-thickness articular cartilage defects. For MOPS OCA transplantation for unipolar, multisurface, and bipolar biologic joint restoration surgery in the knee, the 5% revision rate, 11% failure rate, and 82%-94% functional survival rates in conjunction with statistically significant and clinically meaningful improvements in patient-reported measures of pain and function underscore major advances in outcomes as compared with previous reports.[6,8,11,14,15] For athletes who underwent primary OCA transplantation in the knee for treatment of injury or overuse-related articular defects, large single-surface, multisurface, or bipolar shell OCA restoration surgeries resulted in two-thirds of these patients returning to sport at 16 to 24 months after transplantation with a combined revision and failure rate of 10% such that 90% of patients were considered to have successful two- to four-year outcomes with significant improvements in pain and function, even when patients did not return to their sport.[6] Elite unit military, competitive collegiate,

and competitive high school athletes returned to sport at a significantly higher proportion than did recreational athletes. The data for use of MOPS-preserved OCA transplantation in other joints for patients treated at our center include less patients over a shorter time period to date, however, the initial results for the limited number of patients with at least one-year outcomes data mimic those reported for knees.[9,22]

These encouraging results were realized with the use of MOPS preservation, autogenous bone marrow concentrate pretreatment of donor bone, and procedure-specific rehabilitation protocols, as well as evidence-based advancements in surgical techniques including graft-preparation, implantation, and stabilization. Importantly, the data suggest that revision and failure rates could be even further improved by strict patient and provider adherence.[6,8,11,15,59] These findings are especially promising in that the majority of cases treated would be considered complex cases that previously yielded higher revision and failure rates after treatment with OCA and meniscal allograft transplantation, other cartilage restoration procedures, or arthroplasty. Based on this evidence for initial success in improving outcomes after osteochondral and meniscal allograft transplantation, we continue to offer this treatment option for appropriate cases, enroll patients into the registry, and report longer-term outcomes as they become available.

What's Next?

We will continue to assess outcomes after OCA transplantation in real-time by analyzing registry data to continually improve patient care. Fortunately, funding from The U.S. Department of Defense, National Institutes of Health, and MU Health allows us to vigorously pursue innovations that can optimize clinical care. With these funding mechanisms in place, we are able use our One Health-One Medicine translational approach to target advances in the areas of OCA biomechanics, immunology, and healing. We are investigating preimplantation preparation techniques including power irrigation, compressed carbon dioxide treatment, enhanced bone marrow aspirate concentrate (BMC), and drilling of OCA subchondral bone; osteogenic, osteoinductive, angiogenic factors, and bone growth stimulators aimed at speeding and enhancing healing; and locally delivered, target-specific, anti-inflammatories, immunomodulators, and immunosuppressors to promote graft integration and joint health. Based on the safety and efficacy of OCA transplantation and its associated benefits to a large and growing patient population, continuing to pursue basic, preclinical, and clinical studies on OCA transplantation that comprehensively assess and correlate cellular, molecular, histologic, biomechanical, biomarkers, diagnostic imaging, arthroscopic, functional, and patient reported outcome measures are of high interest and importance. We also firmly advocate for implementing best practice protocols that foster individualized plans for patients, including establishing integrated care teams committed to preoperative patient assessments and education grounded in a culture of patient and care team adherence that focuses on shared decision-making to create and implement comprehensive strategies aimed at assisting patients in reaching their best possible outcomes.[6,8–11,14,15,22,59] Current best evidence suggests that comprehensive translational research in these areas has strong potential for further improving a valuable technique that helps patients regain long-term joint function.

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Innovations in Limb Salvage: A Multidisciplinary Team Approach

by Jay Bridgeman, MD & Brett Crist, MD

Health Care

The Limb Preservation Center at the University of Missouri is comprised of a multi-disciplinary team that continues to help patients with acute and chronic traumatic limb injuries to make the best possible decision regarding limb preservation versus amputation.



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Abstract

The University of Missouri's Limb Preservation Center is a multi-disciplinary team helping patients with acute and chronic traumatic limb injuries, especially when faced with the difficult decision of limb preservation versus amputation. The team focuses on acute trauma and the chronic effects of a prior failed treatment, including possible amputation. This approach results in improved care, outcomes, and a decrease in failed treatment plans for patients. New advances in amputation techniques also provides better outcomes for patients.

Introduction

Advances in trauma care over the last 20 years have resulted in improved patient survival. Surviving trauma patients often have severe limb injuries that are at risk for amputation. This has led to advances in care across disciplines in managing severe limb trauma.[1] Trauma care teams made up of surgeons who specialize in trauma surgery, orthopaedic surgery, plastic surgery, neurosurgery, and vascular surgery have made it possible to preserve damaged limbs. As surgical techniques and outcomes have improved, more damaged limbs are being saved and preserved. These include the detection of compartment syndrome, debridement procedures, temporary vascular shunts, damage control surgery, and soft tissue coverage. It is now possible to save many limbs that would have in the past met a clear indication for amputation.[2–4]

Limb Preservation versus Amputation

The decision-making process to pursue limb preserving treatment versus amputation is difficult and requires a multi-disciplinary approach. Long-term treatment plans can be expensive and can also surpass the patient's resilience. Some patients do not achieve a functional result, which may lead to permanent restrictions or a late amputation.[5–7] Many patients have better outcomes with primary amputation. The limb preservation team plays an integral role providing timely assessment and guidance in the decision-making process with a patient. This is a shared decision-making model with both patients and providers. The goal is to identify which patients with injured limbs are the best candidates for limb preservation versus those who would best benefit from amputation. We also strive

to avoid limb preservation outcomes that are non-functional, or less functional than an amputation/prosthesis.

In the past 30 years, scoring systems have been developed for the lower extremity (and applied to the upper extremity) to be able to aid in decision-making between limb preservation and amputation.[4] Some of these scoring systems include, but are not limited to, the Mangled Extremity Severity Score (MESS), Predicted Salvage Index (PSI), and the Limb Salvage Index (LSI). There is no current limb salvage or amputation score for the upper extremity. Despite the availability of these scoring systems, they have each had poor sensitivity and specificity in the lower extremity.[4,8] A low score does not reliably predict limb preservation or functional result while high scores do not reliably predict amputation in every case. Counter to the previous thought about the lack of protective sensation indicating tibial nerve transection and indication for amputation, the LEAP study,[4,8] showed that lack of foot sensation at the time of injury did not correlate with tibial nerve transection or a bad outcome in those patients who had limb preservation. According to the study, over half (56%) of patients who previously had poor foot sensation and received limb preservation had complete recovery at two years. The remainder had improved sensation. Only one patient did not recover any sensation. These findings highlight the difficult decision making that both physicians and patients face when deciding between limb preservation and amputation with severe limb injury. At the University of Missouri, we have found that a multi-disciplinary team is critical for ideal decision making and formulating a treatment plan for each patient.

Limb Preservation Center

Our multi-disciplinary team of orthopaedic trauma surgeons and microsurgeons is led by Brett Crist, MD, and Jay Bridgeman, MD, co-directors of the Limb Preservation Center at the University of Missouri. The team works closely together to help those patients who have severe limb injury and are facing possible amputation such as shown in Figure 1.

This highly skilled team works cohesively and this level of cooperation strategically improves outcomes, care communication, and makes follow-up appointments easier for patients. In addition, the team also works alongside other specialists including Infectious Disease, Interventional Radiology, Anesthesiology/Perioperative Medicine, and Health Psychology within the university's network. With this approach, the Mizzou Limb Preservation Center team possesses the ability to provide the best care and outcomes with the least burden for patients. This concerted effort was assembled as a multi-disciplinary team approach to limb preservation has been shown to have improved outcomes by other centers.[9]

Many patients that are referred to the Limb Preservation Center have had treatment for a severe limb injury that has not healed well. These patients experience long-term effects from failed treatment with ongoing pain, dysfunction, and inability to return to work and an active lifestyle. Examples include, but are not limited to, severe complex limb injuries and fractures, failed bone healing, bone deformity, limb lengthening, chronic infections, and chronic wounds. The Limb Preservation Team makes a full evaluation of the patient including their past care, current issues, advanced imaging, as well as any needed specialty referrals. The team of allied physicians and health professionals then meet with the patient to explain if limb preservation is possible. The patient is counseled on the many aspects of both the limb preservation treatment plan versus an amputation treatment plan. The goal is to create treatment plans with complete patient involvement to maximize the number of positive outcomes.

Improving Amputation

Patients that do not meet an indication for limb preservation remain a focus for the team as it has the ability to improve outcomes and function. Within the last five years, the field of orthopaedic surgery has seen new techniques and procedures that can improve the function of patients and individuals who might require amputation. An example of this advancement in the field is the Targeted Muscle Re-innervation (TMR) procedure. The TMR procedure is a nerve surgery that can be done with in conjunction with an amputation plan to improve function. The technique can be included in the early amputation surgery or for patients who have had an amputation in the past. The procedure includes finding the terminal nerve endings of the limb's major nerves. The sensory and mixed (sensory and motor) nerves are then repaired to a local nerve branch that supplies a muscle. Studies evaluating this technique have shown significantly less nerve and amputation pain. This technique can also be used to design a powered (myoelectric)

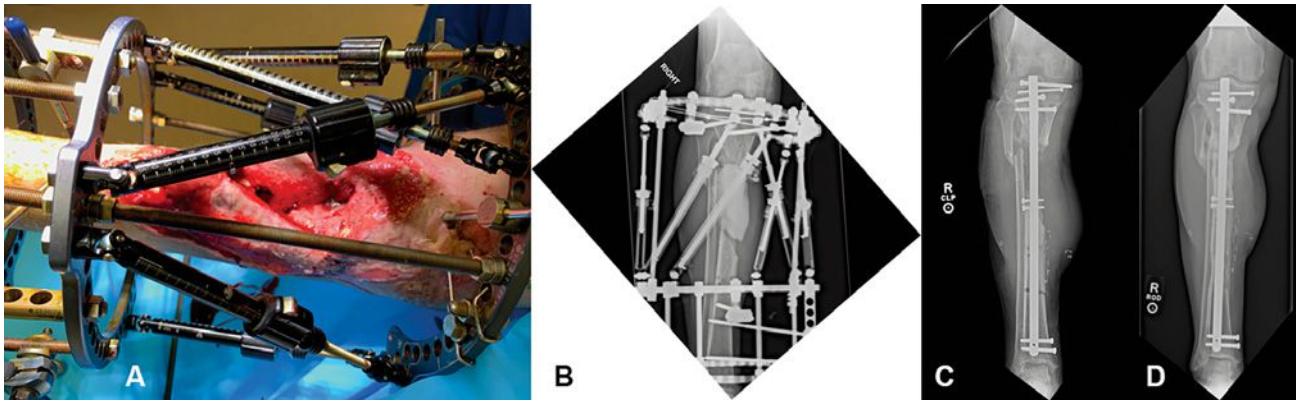


Figure 1. A) Clinical photo showing an infected open tibia fracture in a 42-year-old male status post multiple debridements, gastrocnemius flap and circular external fixator application; B) Anteroposterior tibia radiograph showing the 42-year-old male with an open tibia status post multiple debridements and healed free flap with 8cm of bone defect; C) Anteroposterior tibia radiograph status post transport tibial nail and distal tibia osteotomy for bone transport; D) Anteroposterior tibia radiograph 11 months after transport nail placement with docking site progressive healing and regenerate formation.

prosthesis.[10] The Limb Preservation Center is focused on improved outcomes for all the patients we see, including those who cannot have limb preservation.

Summary

Patients that survive trauma with severe limb injury face the difficult decision of limb preservation versus amputation. Comprehensive multi-disciplinary care is an important aspect that should be accessible to patients faced with a difficult decision making process. The Limb Preservation Center at the University of Missouri is comprised of a multi-disciplinary team that continues to help patients with acute and chronic traumatic limb injuries to make the best possible decision regarding limb preservation versus amputation. Through specialized collaboration across different specialties, patients can start to experience improved care, outcomes, and decreasing failed treatment. The team also continues to keep up with new advances in amputation techniques in order to provide better outcomes for patients who are not candidates for limb preservation.

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As Vertebral Body Tethering Impacts Missouri, New Technology Grows in the Right Direction

by Daniel G. Hoernschemeyer, MD & Melanie E. Boeyer, PhD

Health Care

If the rate of postoperative growth and maturation in any given child can be accurately predicted, physicians will be able to determine how much correction is required at the time of surgery. An accurate prediction of this type then has the possibility to decrease postoperative complications and surgical revisions, while simultaneously increasing postoperative success rates.



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Abstract

All eleven-year-old girls want to do is play and be active like every other child her age. Yet, the ability to have a normal childhood for one of our patients became a concern when she and her parents noticed an abnormal lateral curvature in her spine, which was later diagnosed as adolescent idiopathic scoliosis. In February 2014, she presented with a 45° thoracic deformity with a high risk of progression. At that time, the gold standard for the treatment of her deformity was a posterior spinal fusion – a surgical treatment she nor her parents were interested in pursuing. After their initial appointment, her parents scoured the internet and discovered a new non-fusion surgical technique, known as vertebral body tethering, that might correct their daughter's deformity without the need for titanium rods in her spine.

In April 2014, that same eleven-year-old girl underwent vertebral body tethering of her main thoracic deformity from T5 to L1 under the care and management of Dr. Daniel Hoernschemeyer, a pediatric orthopaedic surgeon, with the University of Missouri's Department of Orthopaedic Surgery. Today, she is a healthy young adult who is thinking more about prom than about her scoliosis.

A Successful Innovative Treatment

Many families confronted with a scoliosis diagnosis are concerned that life will never be the same for their child. As surgeons have been treating children for decades with posterior spinal fusions, the limitations of this procedure, including early onset osteoarthritis and adjacent segment disease,[1–3] are well understood by patients, their families, and their physicians. It is only natural, then, to want to push the surgical envelope through the development of innovative non-fusion surgical techniques that may combat the known postoperative limitations of older techniques.

The eleven-year-old patient mentioned above, treated in our institution, was one of the first children to receive a fusionless treatment for her scoliosis in the state of Missouri (Figure 1).

To date, Dr. Hoernschemeyer has performed more than 90 vertebral body tethering procedures on children from

19 different states. His interest in the application of thoracoscopic surgery for the correction of scoliosis began after presenting on this topic at the Pediatric Orthopaedic Society of North America's Annual National Meeting in 2004 during his fellowship at Johns Hopkins Medical Center. The surgical treatment of adolescent idiopathic scoliosis with vertebral body tethering began at the University of Missouri's Health Care System in late 2013. Today, surgeons from all over the United States come to Columbia, Missouri, to learn the intricacies of the procedure from Dr. Hoernschemeyer.

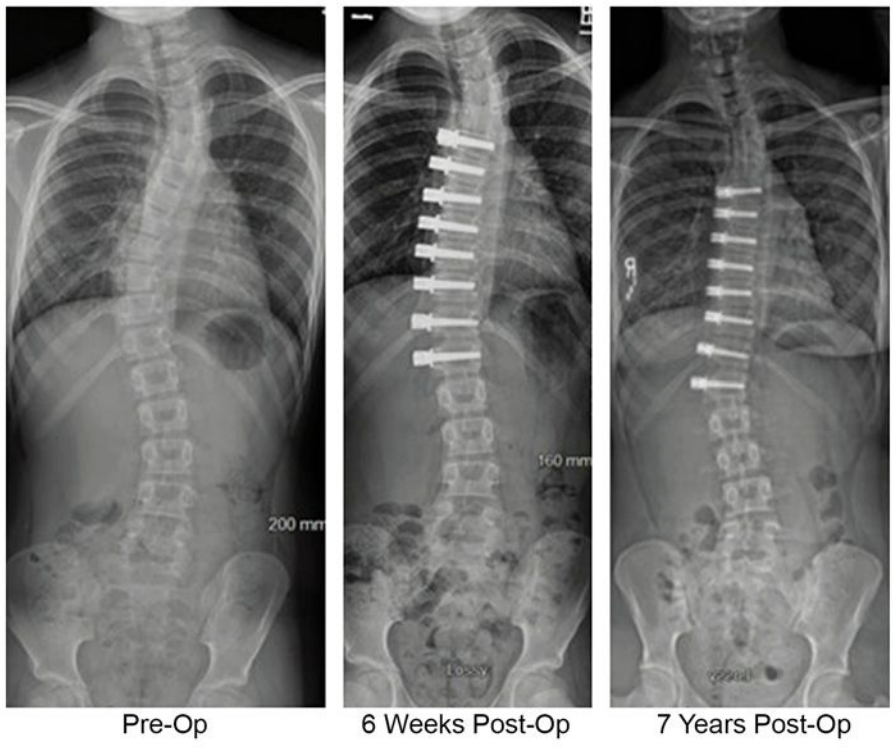


Figure 1. Preoperative and postoperative imaging of our eleven-year-old patient treated with Vertebral Body Tethering.

Since the early 2000s, fusionless treatment for adolescent idiopathic scoliosis has continued to evolve. To date, none of the techniques (eg, vertebral body stapling) have longer postoperative follow-up or higher success rates than vertebral body tethering. The first reported case in the literature was in 2010, where an eight-year-old boy was treated with vertebral body tethering for his 40° thoracic deformity.[4] Since then, numerous other retrospective studies have been published that report postoperative success rates as high as 77%, with two to five years of postoperative follow-up. Newton et al.[5] was among the first to report postoperative outcomes in patients with primary thoracic deformities who were treated with vertebral body tethering. The authors of this study noted a 51% postoperative deformity correction rate and an overall success rate of 59%, despite seven patients requiring surgical revision.[5] Similar postoperative results were reported more recently by Baker et al.[6] In 2020, Hoernschemeyer et al.[7] was the first to provide postoperative outcomes in children with a variety of deformity patterns. This retrospective series included 31 patients with two to five years of postoperative follow-up.[7] The results from Hoernschemeyer et al.[7] boasted a 74% success rate, the highest in the literature at the time. In fact, more than 93% of the patients treated in this cohort avoided a posterior spinal fusion. Later in 2020, Miyanji and colleagues[8] published their postoperative results, which included data on 57 patients from two surgical sites with minimum postoperative follow-up of two-years. Their results indicated that 77% of patients were clinically successful at their latest visit, despite a complication rate of 28%.[8] The latest prospective data from a Food and Drug Administration Investigational Device Exemption study by Samdani et al.[9] also assessed postoperative outcomes in 55 patients with an average follow-up of 4.6 years. These

authors found that 80% of patients exhibited a successful outcome at latest follow-up with only seven patients (12.3%) requiring a surgical revision.

Vertebral Body Tethering versus Posterior Spinal Fusion

In addition to these studies, many authors have begun to compare the postoperative outcomes of vertebral body tethering to posterior spinal fusion. Newton et al.[10] performed a retrospective matched cohort study of patients treated with either vertebral body tethering or posterior spinal fusion. Their data indicate that patients treated with vertebral body tethering exhibited significantly more residual deformity postoperatively and are more likely to receive a surgical revision than when compared to those who received a posterior spinal fusion.[10] Yet, no differences were observed in postoperative patient-reported outcomes.

One topic that has not been extensively published on, particularly when directly comparing vertebral body tethering to posterior spinal fusion, is the reported benefits of this fusionless technique, including the ability to preserve spinal motion while simultaneously allowing for continued spine growth. Pehlivanolglu et al.[11] assessed clinical and functional outcomes in a cohort of patients treated with either vertebral body tethering or a posterior spinal fusion who were matched based on age, sex, instrumented levels, and postoperative follow-up. The authors noted that those treated with vertebral body tethering exhibited significantly more lumbar motion in both flexion, extension, and lateral bending than when compared to their posterior spinal fusion peers. A similar study published this year by Qui et al.[12] found that deformity flexibility observed in the thoracic spine was 16% greater in patients that received vertebral body tethering than when compared to those that received a posterior spinal fusion. Taken together, these data suggest that vertebral body tethering can preserve normal motion and flexibility of the spine postoperatively.

As we consider the motion preservation benefits of this fusionless technique, it is also important to determine if the incidence of degenerative processes commonly observed in posterior spinal fusions are also reduced. One way that such degenerative process can be evaluated is through magnetic resonance imaging. Hoernschemeyer et al.[13] assessed preoperative and two-year postoperative magnetic resonance images for any indication of pathoanatomy changes (e.g., nucleus pulposus positioning and muscle atrophy) or early onset degenerative processes (e.g., Schmorl nodes, endplate edema, disc degeneration, and osteoarthritis) in nine patients treated with vertebral body tethering. The authors noted a shift of the nucleus pulposus from an eccentric position preoperatively toward midline postoperatively in 44% of patients, most of which occurred in the tethered region. Hoernschemeyer et al.[13] also observed no Schmorl nodes, endplate edema, or disc degeneration; however, one patient developed moderate facet osteoarthritis at L5-S1, which was not present preoperatively. A related study was conducted by Yucekul et al.[14] in Istanbul, Turkey, who reported no significant differences in the appearance of the intervertebral discs or the posterior facets on postoperative imaging in patients treated with vertebral body tethering. One patient did, however, exhibit degeneration of adjacent facets that was not present on preoperative imaging,[14] which was comparable to the findings presented by Hoernschemeyer et al.[13] In addition to preserving spinal motion, a patient and their family must also consider what it means to 'return to activities' postoperatively. When assessed in patients that had been treated with a posterior spinal fusion, only 60% of patients returned to their activities after instrumentation at an equal or higher level.[15] The primary reason for postoperative activity decline was a loss of spinal flexibility.[15] Conversely, more than 94% of patients treated with vertebral body tethering returned to their presurgical activities, including a subset of patients who received lumbar instrumentation.[16] As one can imagine, this is very important information for any family going into surgery.

The Future of Vertebral Body Tethering

Although initial preoperative outcome data appear promising, there is still quite a lot to be learned about vertebral body tethering. In particular, research aims include better defining preoperative patient characteristics through a more detailed understanding of the skeletal maturational



Figure 2. Our patient at her high school prom.

process. If the rate of postoperative growth and maturation in any given child can be accurately predicted, physicians will be able to determine how much correction is required at the time of surgery, which will decrease postoperative complications and surgical revisions, while simultaneously increasing postoperative success rates. As the evidence continues to grow in the right direction, vertebral body tethering will certainly make its mark in Missouri (Figure 2).

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Innovations in Peripheral Nerve Injury: Current Concepts and Emerging Techniques to Improve Recovery

by Julia A.V. Nuelle, MD, Chantelle Bozynski, DVM & Aaron Stoker, PhD

MU Health Care

Peripheral nerve injury, especially those with loss of nerve over a large gap such as those seen in trauma or after tumor resection, is a complex problem resulting in significant functional deficits for which we have not yet identified a consistently reproducible solution with high efficacy.



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Abstract

Despite the surgical advances in treatment of peripheral nerve injuries, consistent recovery of function is limited suggesting that a multimodal approach is required to optimize nerve regeneration. This approach should include advanced surgical repair techniques, as well as tissue engineering, cellular therapies, and application of local and systemic modulators of neuroregeneration. Further research is needed to advance these therapies from the laboratory to clinical practice, and to further understand how these treatments and techniques can act in concert to optimize functional nerve regeneration.

Introduction

Peripheral nerve injury or ablation, particularly those over a large segment, such as those greater than 3 cm, can result in significant functional impairment as loss of motor and sensory function occurs. Unfortunately, these injuries are not uncommon, occurring in approximately 3% of all patients admitted to Level I Trauma Centers in the United States.[1] Even with the current nerve repair and reconstruction techniques, effective treatments that result in complete motor and sensory recovery are rare.[2]

The earliest work describing nerve surgery dates back to the 7th century, but it wasn't until the 17th century that researchers investigated the possibility that neural tissue can regenerate.[3] As knowledge of the processes involved in degeneration and subsequent regeneration after nerve injury has advanced, it is now well-known that a complex amalgamation of events occurs involving the nerve cell body, the proximal and distal edges of the injury site, and the distal nerve endings either at the sensory receptors or neuromuscular junction. These events must be well orchestrated and optimized to promote regeneration and functional recovery. The regenerative process begins almost immediately after nerve injury. The axons disconnected from the cell body degenerate through a process called Wallerian Degeneration, and as early as two weeks from injury, sprouting from the more proximal axons occurs. Schwann cells, which support neurons in the peripheral nervous system, are a key component in the process as they first aid in digestion of the damaged axons. They then align in tubes called

Büngnger bands and elaborate molecules that help guide the regenerating nerve sprouts. If the sprouts reach the tube formed by the Schwann cells and continue to grow, the regenerating nerve will advance at a rate of about 1 mm per day.[4] For motor nerves, this becomes a 'race against the clock' for the nerve fibers to reach the destination of the motor end plate at the level of the muscle, before the motor end plates degenerate and functional recovery of motor function is no longer possible. Furthermore, if the nerve sprouts cannot reach the tube formed by the Schwann cells, which can be due to scar formation, the gap being too great, or there being interposed tissue, the nerve will not regenerate. Therefore, current techniques of nerve repair and reconstruction aim to improve the chances that innervation of the downstream targets occurs (Figure 1).

Current Treatment of Peripheral Nerve Injury

Primary Nerve Repair

When the ends of a lacerated nerve are in close proximity and are free from cicatrix, successful primary repair is possible. A primary nerve repair involves using a microsurgical technique to reapproximate the ends of the injured nerve by placing microsuture into the epineural layer of each end to bring them together. A primary key to success involves maintaining the native orientation of the nerve, taking care to match fascicles as accurately as possible to encourage the sprouting proximal nerve to regenerate through its native pathway to the target tissue. Additional keys to success for primary repair include debridement of nerve ends to healthy fascicles while ensuring minimal tension (Figure 2).[5]

When considering outcomes of nerve repair or reconstruction, the British Medical Research Council grading system of nerve recovery[6] or the Mackinnon-Dellon scale are often used[7] (Table 1).

A systematic review by He et al.[2] found that only 59.4% of patients undergoing primary neurorraphy achieved good to excellent sensory function (≥S3+) and 73.8% achieved good to excellent motor function (≥ M4), however, very few patients achieve full neurologic recovery.[7]

Conduit-Assisted Repair

Lacerated nerves that are unable to be repaired directly, due to high tension at the repair site, may be suitable for a conduit-assisted repair. This technique involves using microsuture to secure both ends of a lacerated nerve into a tube. The composition of the tube can include autogenous veins, collagen, polyglycolic acid (PGA), caprolactone, or a three-dimensional luminal filler made of Type I collagen and glycosaminoglycan chondroitin-6-sulfate.[8] The aims of conduit-assisted repair include: 1) to guide the newly

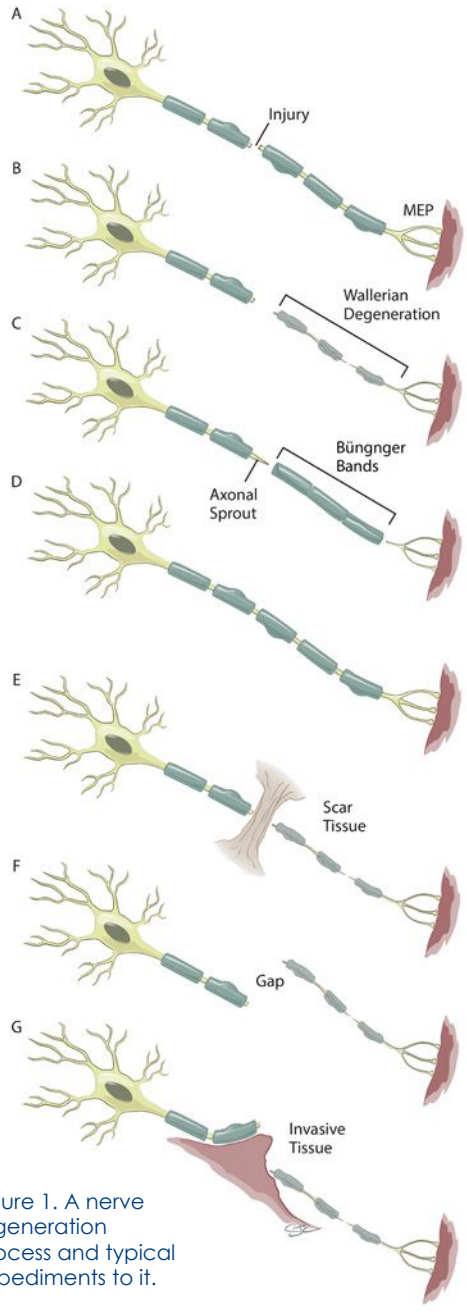


Figure 1. A nerve regeneration process and typical impediments to it.

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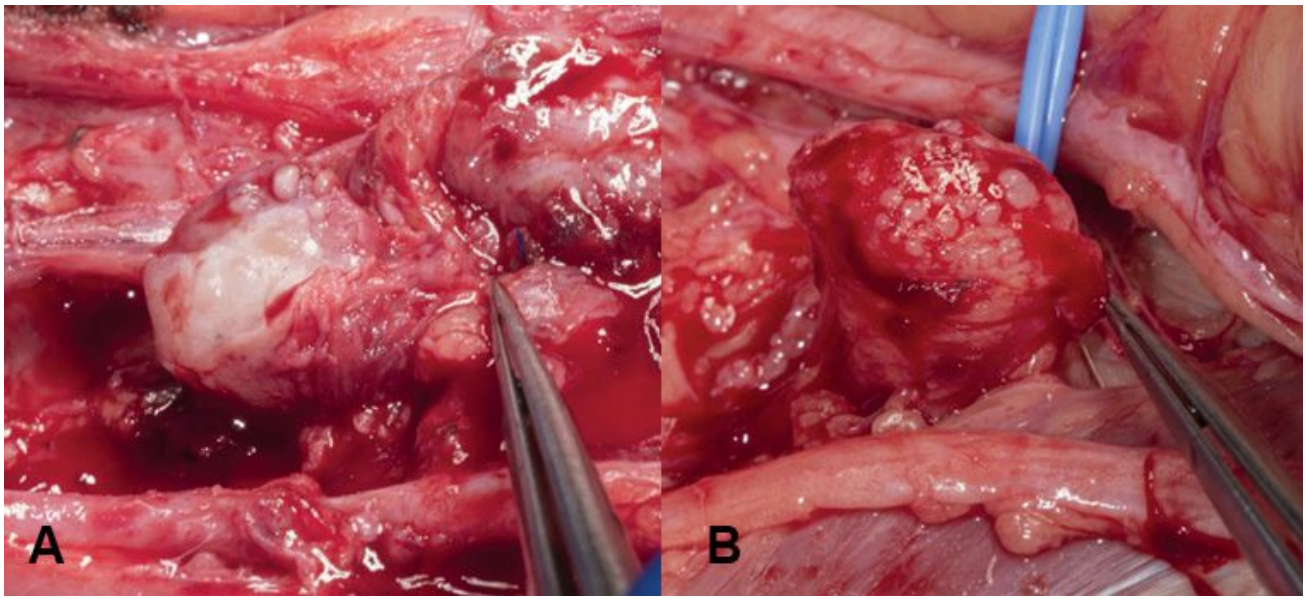


Figure 2. A) Transected nerve with inter-fascicular scar formation. B) After debridement of transected nerve back to healthy appearing fascicles.

forming sprouts to the target nerve, 2) to isolate the regenerating nerve from fibroblasts and fibrotic tissue, 3) to protect regenerating nerve from mechanical forces, and 4) to concentrate the neurotropic factors between the two nerve ends.[9]

Studies have demonstrated success with this technique when treating sensory nerve lacerations with a gap of less than 10-20mm.[10–13] Donoghoe et al.[14] reported on two patients with a median 3 cm nerve gap treated with a PGA conduit who recovered localization of two-point discrimination and function of abductor pollicis brevis. However, Moore et al.[15] concluded that for larger mixed motor sensory nerves, PGA conduits were unsuccessful.

Nerve Autograft

Nerves that have injury over a larger segment also require debridement back to healthy fascicles and thus result in a gap between the two ends greater than what can be reliably treated with currently available conduits. When this occurs, nerve grafting is required to functionally bridge the gap from the proximal nerve sprouts to target tissue. Nerve autograft has the advantage of bringing live neural tissue to the site of injury. However, related disadvantages include donor site morbidity, sensory deficits, potential for painful neuroma formation, and the limited diameter of available donor nerves. The relatively small diameter of donor nerves can necessitate "cabling" or grouping several pieces of nerve graft together to approximate the diameter of the recipient nerve. This poses associated problems including scarring at the multiple coaptation sites, difficulty in fascicular matching, and escape of the sprouting proximal axons. Any one of these events or a combination of them can result in incomplete recovery of the target function.

A systematic review of nerve autografting by He et al.[2] covering a total of 378 nerve autografts found that outcomes of nerve autografting are dependent on patient age, gender, time from injury to reconstruction, gap size, nerve location, and adjacent tissue injury. Satisfactory sensory recovery deemed S3+ or S4 was achieved in 53.8% of patients with gaps less than or equal to 30mm, 39.3% with gaps 30-50mm, and 18.2% in gaps >50mm. Satisfactory motor recovery, which was deemed to be M4 or M5 was achieved in 48% with gaps less than or equal to 30mm, 28.9% in gaps 30-50mm, and 64.9% in gaps >50mm. This demonstrates that although nerve autografting can result in meaningful recovery in some patients, others are left with permanent deficits at the recipient site as well as functional loss at the donor site.

Table 1. Grading of Nerve Recovery

Medical Research Council Grading System for Nerve Recovery	
Motor	
M0	No contraction
M1	Trace or flicker of muscle contraction seen or felt
M2	Movement with gravity eliminated
M3	Movement against gravity over almost full range
M4	Movement against resistance, but is reduced
M5	Total recovery
Sensory Nerve Recovery Grading Modified by Mackinnon and Dellon	
S0	No recovery of sensibility in the autonomous zone of the nerve
S1	Recovery of deep cutaneous pain sensibility in the autonomous zone of the nerve
S1*	Recovery of superficial pain sensibility
S2	Recovery of superficial pain and some touch sensibility
S2*	As with S2 but with overresponse
S3	Recovery of pain and touch sensibility throughout the autonomous area without hyperalgesia S2PD: > 15mm, M2PD: >7mm
S3+	As with S3, and some recovery of two point discrimination S2PD: 7-15mm, M2PD: 4-7mm
S4	Complete recovery S2PD: 2-6mm, M2PD: 2-3mm

S2PD = static 2 point discrimination; M2PD = moving 2 point discrimination (Mackinnon and Dellon, 1988)

Table 2. Key Technical Considerations for Peripheral Nerve Injury Treatment

General	• Proper nerve handling; avoid compression/crush • Debride back to healthy fascicles • Minimal tension at coaptation sites • Mitigate scar formation • Epineural microsuture technique • Use fascicular anatomy and epineural vessels to assist with rotational alignment
Hollow Conduit-Assisted Repair	• Sensory nerve gap <10-20mm
Decellularized Nerve Allograft	• Sensory only → up to 5cm nerve gap • Short segment mixed motor/sensory → up to 3cm nerve gap • Mixed motor/sensory >3cm nerve gap → data is limited
Nerve Autograft	• Considered gold standard for nerve grafting • Donor site morbidity should be considered and discussed with patient • May require cabling depending on donor and recipient diameters

Decellularized Nerve Allograft

Decellularzied nerve allografting has also shown promise in the field of reconstruction of peripheral nerve injury when gaps are present. This allograft tissue undergoes processing that removes cellular remnants and growth inhibitors, resulting in a structural scaffold to guide regenerating nerve sprouts. Due to this processing of the grafts, the need for immunosuppression is obviated. Use of allograft tissue also eliminates donor site morbidity. This tissue does require refrigeration and is thawed prior to use. A multicenter registry analysis has demonstrated meaningful recovery in 87% of peripheral nerve injuries treated with allograft with an average gap of 22mm (range 5-55mm), including 49 sensory nerves, 18 mixed motor/sensory nerves, and 9 motor nerves.[16] When considering solely mixed motor/sensory and motor nerves reconstructed with decellularized allograft, Safa et al.[17] analyzed 22 injuries and reported recovery of M3 or greater in 73%. However, this is a relatively small subset and further research is needed in this area to make meaningful comparisons to autograft and conduit-assisted repair (Table 2).

Emerging Techniques in Peripheral Nerve Injury Regeneration

PEG Fusion and Cellularized Nerve Allografts

The use of cellularized allograft is limited by the need for systemic immunosuppression, which is impractical in most cases of peripheral nerve injury.

However, there is emerging evidence that novel biomaterial processes in addition to local immune modulators may allow for use of cellularized allografts in the near future. One such novel process is known as polyethelyene glycol mediated fusion (PEG fusion). Applying the Nobel Prize-winning research by Köhler and Milstein[18] that demonstrated polyethelene glycol can be used to create monoclonal antibodies via fused hybridomas, Bitter and colleagues reported that lacerated nerves can be fused together after injury to include the use of allografts for bridging nerve gaps.[19–24] In this process, a calcium-free environment is maintained and the antioxidant methylene blue and PEG are applied. Methylene blue prevents the endogenous sealing mechanisms in cut nerve endings such that the ends of the lacerated nerves are receptive to axonal fusion.[25] When PEG is applied to these nerve ends that are closely apposed by epineural microsutures, it removes water from the area, allowing the lipid bilayers of the membranes of the axon stumps to fuse together. The plasmalemmal membranes are partially repaired as a result. A calcium-containing solution is then applied resulting in vesicular accumulation and sealing of the remaining holes at the injury site.[26] This axonal continuity at time zero after repair, has been shown to result in rapid functional recovery with Wallerian degeneration prevented or reduced.[27]

In a rodent sciatic nerve injury model, Mikesh et al.[28] demonstrated that successfully PEG fused allografted nerves maintained compound muscle action potentials at seven days and 42 days, which were comparable to unoperated nerves. These animals also had rapid and permanent behavioral recovery, more rapid than standard repair techniques. Morphologic analysis with transmission electron microscopy at 42 days postoperatively showed the morphology of successfully PEG-fused allografts appearing more similar to unoperated controls, whereas nerves reconstructed using standard microsuture technique with allograft demonstrated smaller diameter axons that further diminished distally. Furthermore, the PEG-fused allograft muscle fibers appeared similar to unoperated controls. However, muscle atrophy was noted with nerves reconstructed using the standard microsuture allograft technique. This supports the theory that Wallerian Degeneration is prevented in cases of successful PEG fusion. Finally, immunofluorescent confocal images of the neuromuscular junctions (NMJs) in soleus muscles at seven, 21, and 42 days found PEG fused NMJs to have normal structural configuration and occupied synaptic clefts whereas the standard reconstruction with allograft nerve did not closely appose the acetylcholine receptors at any timepoint. Expanding this work, Smith et al.[27] demonstrated that the PEG fusion process used in peripheral nerve allografts in a rat model resulted in attenuated innate and adaptive immune responses, providing an example of immune tolerance with cellularized peripheral nerve allograft without systemic immunosuppression. This success with allograft nerves without systemic immunosuppression opens the potential for use of viable nerve allografts for the treatment of human peripheral nerve injuries that are not amenable to direct repair.

Although this technology is yet to be used in human cellularized allograft reconstruction, there has been a report of two patients with a total of four nerves that underwent PEG fused primary repair. These were compared to six matched controls that underwent standard primary repair. There were significantly higher MRCC scores in the PEG fused nerves as compared to the standard repair at Week 1, Week 4, and Week 8. The PEG fused nerves had an average MRCC score of M4 at eight weeks, while the controls had an average just over M1.[26]

This technology has the potential to make a great impact on the field of nerve surgery and regeneration. In partnership with the RESTOR lab at the 59th Medical Wing at Lackland Air Force Base, the University of Texas at Austin, and Johns Hopkins University, we are working to further translate this technology into reproducible clinical care.

Shelf Stable Cellularized Nerve Allografts

With these emerging treatments for peripheral nerve injury, the need for a shelf-stable preservation system for allograft nerves has become apparent. One system with the potential to meet this need is the Missouri Osteochondral Preservation Solution (MOPS®). This tissue preservation solution is currently in clinical use for the preservation of fresh

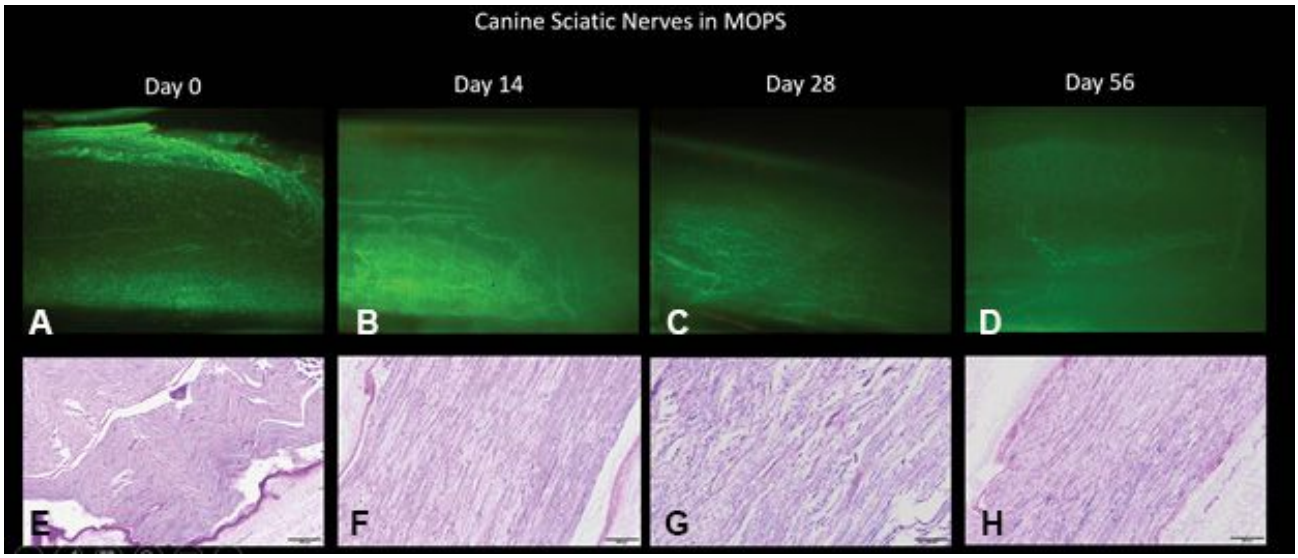


Figure 3. Panels A-D demonstrating excellent cell viability as indicated by green staining throughout the neural tissue through Day 56. Panels E-H demonstrating atrophy but limited necrosis and degeneration of neural tissue preserved in MOPS through Day 56.

osteochondral allografts, demonstrating clinically useful viable chondrocyte density for up to 56 days after recovery from tissue donors.[29] Based on its conformance with the U.S. Food and Drug Administration classification of a human cell and tissue product

under section 361 of the Public Health Services Act and its current commercial use by a tissue bank accredited by the American Association of Tissue Banks (AATB), MOPS is being explored for the preservation of nerve tissue.

In an initial study performed at the Thompson Laboratory for Regenerative Orthopaedics at the Missouri Orthopaedic Institute, sciatic nerve was recovered from skeletally mature purpose bred research hounds following humane euthanasia performed for unrelated purposes. Nerve explants were created and preserved in MOPS for a total duration of 56 days. At days 0, 14, 28, and 56, longitudinal and cross sections of each nerve were analyzed for cell viability and histology. To assess cell viability, sections of the preserved nerve at each time point were stained using the live cell stain calcein AM (1 mg/mL) and the dead cell stain SYTOX Blue (1.25 mM; Thermo Fisher Scientific). After staining, tissues were rinsed with phosphate buffered saline to remove excess stain, and full-thickness images of stained neural tissue were obtained at 4x using a BX51 fluorescence microscope (Olympus). Images were obtained using an F-View II 12-bit B&W CCD camera (Olympus). In this assay, viable cells appear green and nonviable cells appear red. Viability was assessed for cell distribution at each time point. Histologically, hematoxylin and eosin (HE) and luxol fast blue combined with the periodic acid-schiff (LFB-PAS) method was used for evaluation. Subjective analyses demonstrated well-maintained cell viability (Figure 3) and tissue architecture (Nuelle et al., unpublished data, 2021).

While further in vitro and in vivo studies are needed prior to consideration for clinical use, these initial data suggest that shelf-stable peripheral nerve allograft preservation is feasible such that viable allografts could be available for immediate transplant in a variety of settings, including far forward military operational environments.

Conclusion

Peripheral nerve injury, especially those with loss of nerve over a large gap such as those seen in trauma or after tumor resection, is a complex problem resulting in significant functional deficits for which we have not yet identified a consistently reproducible solution with high efficacy.

Continued efforts directed at developing solutions to the current limitations is vital for improving the function of patients who suffer these devastating injuries. Emerging treatments such as PEG fusion with viable allografts are demonstrating promise in preclinical investigations.

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Bench to Bedside: A Multidisciplinary Approach toward the Unknowns after ACL Injuries to Drive Individual Success

by Richard Ma, MD, Trent Guess, PhD, David Echelmeyer, DPT & James P. Stannard, MD

MU Health Care

Future development that allows one to individualize post-surgical rehabilitation that accounts for an individual's surgery (i.e., graft used) and risk factors for reinjury are likely to be more successful.



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Abstract

ACL injury and surgery are increasing in prevalence. Several challenges exist that can be obstacles to an individual achieving success after ACL surgery. A knowledge of these risk factors alongside a multidisciplinary collaborative team approach can result in a greater likelihood of achieving individual success after ACL surgery.

Introduction

The annual incidence of anterior cruciate ligament (ACL) tears in the United States (U.S.) has been estimated to be upwards of 250,000 injuries annually,[1] making it a common injury. Due to resultant knee instability and patient disability, many active individuals with ACL tears undergo surgical reconstruction to restore knee stability and function. While generally successful, there remains challenges with ACL surgery including risk of clinical failure or reinjury and post-traumatic osteoarthritis. The incidence of graft re-rupture and symptomatic post-traumatic osteoarthritis after ACL surgery has been estimated to be upwards of 11% and 35% respectively.[2,3]

These unsolved challenges are problematic when one considers the pattern of increasing prevalence of ACL surgeries in the U.S. Herzog et al. evaluated a U.S. commercial claims and encounters database between 2002 to 2014 and reported an increase of 22% for ACL surgeries during that time period.[4] When analyzed based on age segments, the greatest increase of ACL surgeries occurred amongst 13-17 year olds.[4] This trend is concerning since the youngest population theoretically has the highest risks of failure, reinjury, and future post-traumatic osteoarthritis after ACL surgery.

This article aims to review the current obstacles around achieving clinical success after ACL surgery and highlight areas where knowledge gaps exist. Finally, we will discuss the multidisciplinary approach at the University of Missouri and the Missouri Orthopaedic Institute in addressing the aforementioned knowledge gaps to optimize individual success after ACL surgery.

Risk Factors that Impact Individual Success after ACL Reconstruction

While generally successful, a notable percentage of clinical failure after ACL reconstruction

exists. Failure can be defined as resultant ACL graft laxity resulting in persistent knee instability or re-rupture/injury after ACL surgery. The risk of ACL graft failures after ACL reconstruction is estimated to be between 3.2-11% amongst individual studies and 7.9% overall, based on a recent systematic review of 10 year outcomes.[3] Established etiologies of graft failure include suboptimal surgical technique, repeat trauma, failure of biological incorporation of the graft, infection, or concomitant knee injuries that are not recognized.[5,6] Another risk factor that could contribute to failure is graft selection for reconstruction. The use of allografts has been associated with unacceptable rates of failure in the adolescent population,[7,8] despite its general use being successful in older populations.[9] The use of autografts has also been associated with higher post-surgical activity level.[10] In terms of autografts source, the literature regarding superiority of traditional autograft choices (hamstring versus patellar tendon) is controversial. While some studies, including meta-analyses, have shown a higher risk of failure with hamstring autograft reconstruction relative to patellar tendon grafts,[11–13] others have not shown that difference.[14,15] Some studies have shown a higher risk of failure with use of certain graft types in specific populations, such as hamstring autograft in the female or hyperlax populations.[16–18] Quadriceps tendon is also an emerging autograft option with early clinical outcomes demonstrating favorable outcomes relative to both hamstring and patellar tendon grafts.[19]

There is also growing attention toward identifying individual-related factors that may increase a person's risk of reinjury or failure after ACL surgery, such as younger age,[20,21] female sex,[22] greater activity level,[20] knee hyperlaxity or malalignment,[23] and inadequate neuromuscular rehabilitation after ACL surgery.[21] It has been noted that psychological or mental rehabilitation may be as critical as having knee stability or achieving neuromuscular recovery in order for an individual to reach the ultimate goal of returning to their prior level of function after ACL surgery. Contextual factors including fear of reinjury, psychological readiness, and subjective assessment of one's knee after ACL surgery have been identified as critical components to an individual's success to return to sport.[24] Depending on how return to sport is defined, a recent systematic review showed that the return to sport after ACL surgery ranged from 48.9% to 73.1%.[25]

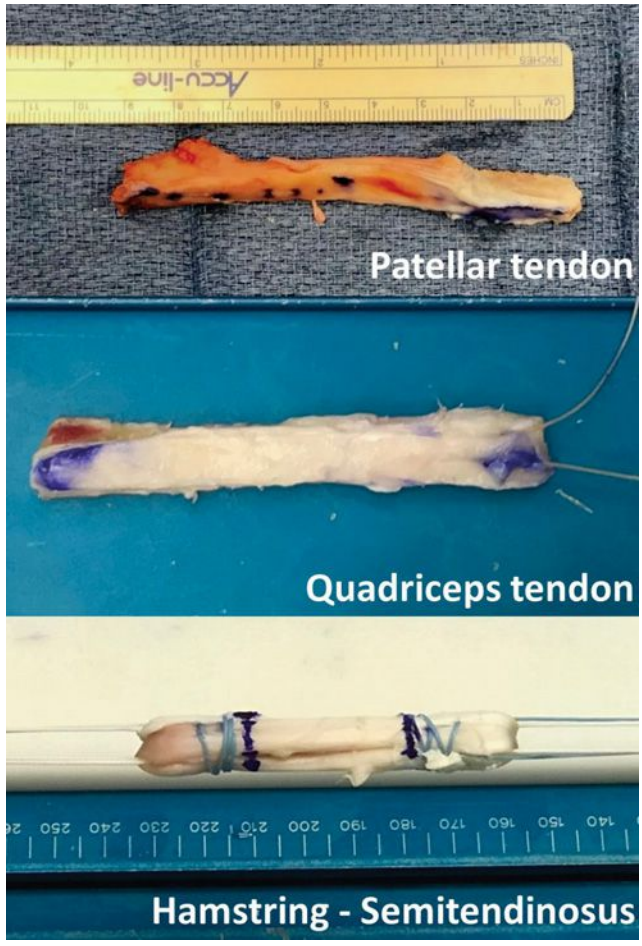


Figure 1. Three common tendon autografts used for ACL reconstruction. Patellar tendon grafts have bone plugs on either ends and therefore incorporates differently with the graft tunnel when compared to soft tissue grafts like quadriceps and semitendinosus tendon grafts.

The importance of identifying and quantifying risk factor for ACL graft failure is two-fold. If the risk factors are modifiable (i.e., graft selection based on patient characteristics or inadequate rehabilitation), there may be an opportunity to intervene to prevent or reduce the risk of graft failure. If the risk factor is nonmodifiable (i.e., patient age or sex), recognition may allow the clinician to either modify rehabilitation timelines or better counsel the patient through awareness and education on these risks.

Investigating the Unknowns Surrounding ACL Injury and Surgery

Are All ACL Autografts Created Equal?

Addressing several known knowledge gaps in ACL surgery may provide insight as to why clinical

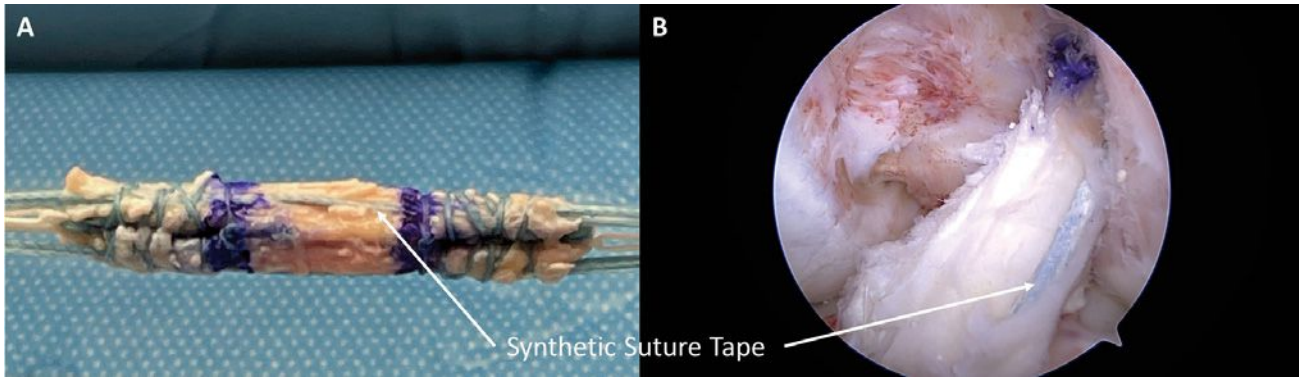


Figure 2. ACL tendon graft bracing with a synthetic suture tape. Synthetic suture tape augmentation of tendon grafts could potentially decrease strain forces on the early healing tendon graft.

failure or disparity in patient success may occur. One such area surrounds the healing biology of the tendon graft used. The intraarticular portion of the ACL graft undergoes a functional adaptation process termed "ligamentization" after it is placed. The ACL graft undergo three phases during its ligamentization process: 1) an early graft-healing phase characterized by inflammation with eventual central graft necrosis and period of graft hypocellularity; followed by 2) a phase of proliferation where the most intensive graft tissue remodeling and revascularization occurs; and finally, 3) a ligamentization phase, with characteristic restructuring of the graft toward the properties of the intact ACL, as shown by animal and human in vivo studies.[26,27] While many of the common tendon grafts (i.e., patellar, hamstring, or quadriceps tendons) used for ACL reconstruction has native biomechanical properties that approximate or exceeds the native ACL properties prior to implantation,[28–30] studies have not shown that the reconstructed ACL is capable of fully restoring the biologic and mechanical properties of the native intact ACL following the ligamentization process.[26,27]

Research efforts at the Missouri Orthopaedic Institute have been on graft-specific healing differences amongst the types of tendon grafts used. Specific fundamental healing differences exist between the bone-to-bone healing interface, which would occur with patellar tendon reconstructions where the bone ends heal to the surrounding bone tunnel, versus the tendon-to-bone interface that would occur with soft tissue grafts (i.e., quadriceps or hamstring autografts) (Figure 1).

Early high strain environments that may occur with anisometric graft placement or aggressive therapy during the early rehabilitation process could impair healing across the tendon-bone interface in soft tissue grafts.[31] High strain applied in soft tissue grafts resulted in decreased osseointegration and biomechanical properties across the tendon-bone interface.[31] Such phenomenon has not been shown to occur with bone-to-bone healing. One emerging surgical adjunct to potentially resist graft stretch or strain across the soft tissue graft tendon-to-bone interface during the early healing phases is internal ligament bracing (Figure 2).

Augmentation with a synthetic suture tape alongside the standard tendon graft during ACL reconstruction has been shown to reduce cyclic creep of the graft during cadaveric testing scenarios.[32] Early clinical results also show equivalent objective and subjective outcomes with and without tape augmentation with ACL reconstruction.[33] Long-term clinical evidence is still needed to establish superiority of such practice compared to standard ACL reconstruction.

Another area of our research is focused on understanding the biological differences amongst various autografts used in ACL surgery in response to mechanical strain. If the biomechanical properties of all tendon autografts used for ACL reconstruction meet or exceeds that of native ACL properties, then the differences that may occur in clinical outcomes based on the type of autograft used are likely not due to the lack of time-zero biomechanical properties of the tissue, but rather due to differences in the subsequent ligamentization process that exist between the various tendon autografts used. Our laboratory has shown that cellular differences exist amongst the common tendon grafts used for ACL reconstruction in terms of early production of extracellular matrix and pro-inflammatory responses.[34] These differences may result in downstream temporal differences in phases of ligamentization amongst the different autografts and could lead to

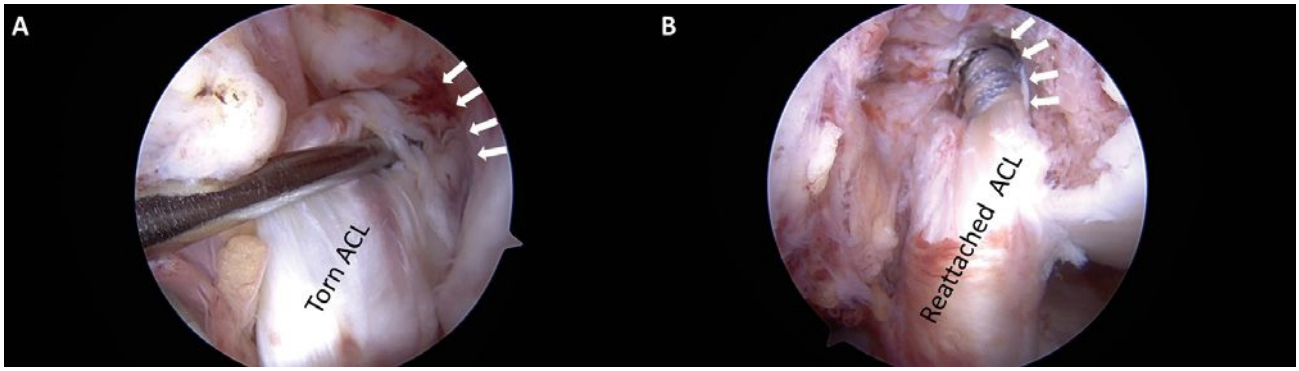


Figure 3. (A) Arthroscopic view of an ACL tear that peeled off the intercondylar notch (arrows); (B) Arthroscopic repair of the torn ACL back onto the intercondylar notch (arrows).

different periods of graft tissue vulnerability during the rehabilitation process.

One logical clinical application of this research is if post-surgical rehabilitation should be adapted based on a specific graft used for ACL reconstruction. Clinical evidence shows that specific patterns of lower limb asymmetries may develop based on the type of autograft used for ACL reconstruction. Miles et al. demonstrated that athletes who had ACL reconstruction with patellar tendon grafts showed greater impulse asymmetries than athletes with hamstring autografts during the eccentric ($P = 0.01$) and concentric ($P = 0.008$) phases of the jump.[35] The authors concluded that graft-specific loading asymmetries should be targeted during rehabilitation prior to return to play. Heijne et al. evaluated the effects of early versus late open kinetic chain (OKC) exercises following patellar tendon and hamstring ACL reconstruction.[36] The authors found that early initiation of OKC exercises (post-operative week 4) resulted in significantly greater anterior knee laxity with hamstring grafts versus patellar tendon grafts. The combined findings of graft-specific differences in biologic response to strain and specific patterns of functional deficits dependent on the graft used suggest that a tailored rehabilitation program specific to the graft type used may be more successful than using a rehabilitation paradigm that does not account for these differences.

Does an ACL Graft Recapitulate all the Native ACL Properties?

The ACL contributes to the sensorimotor function of the knee joint and it contains mechanoreceptors and nerve fibers that comprise approximately 3% of the tissue volume.[37] Our laboratory has shown that this sensory function may be as integral to the overall function of the knee joint as the structural integral of the ACL. Using a preclinical model of an ACL injury, a denervated ACL, while structurally intact, resulted in knee dysfunction similar to a partial tear of the ACL.[38] The sensory loss despite an intact ACL resulted in early osteoarthritis changes in the preclinical model similar to a partial ACL tear. It is interesting to note that a similar phenomenon is seen in humans where despite structurally intact ACL reconstructions, post-traumatic knee osteoarthritis is prevalent after ACL reconstruction.[2] The current dilemma is the fact that the ACL sensory function is likely not reestablished with current ACL reconstruction techniques. Available mitigation strategies include neuromuscular training during rehabilitation and the maintenance phase following ACL surgery. An emerging practice at our institution that may allow one to maintain the ACL sensory function is primary ACL repairs where the native ACL remnant is saved and sutured back to its native attachment (Figures 3A-B).

As arthroscopic techniques and instrumentation have improved, certain types of ACL avulsion tear off its femoral attachment have become increasingly amenable to primary repair.[39] Short-term outcomes have shown primary ACL repairs can be successful in a carefully selected patient population.[39] In theory, a successful primary ACL repair may: (1) avoid the lengthy ligamentization process following reconstruction with tendon grafts, and (2) maintain the vascularity and nerve fibers that are intrinsic to the native ACL. Still, long-term studies are needed to identify differences including post-traumatic OA amongst successful primary ACL repair versus reconstruction.

Identifying Individual Movement Risk Factors for ACL Injury and Graft Re-Tear

Movements during athletic activities are known to predispose to native ACL and ACL graft tears.

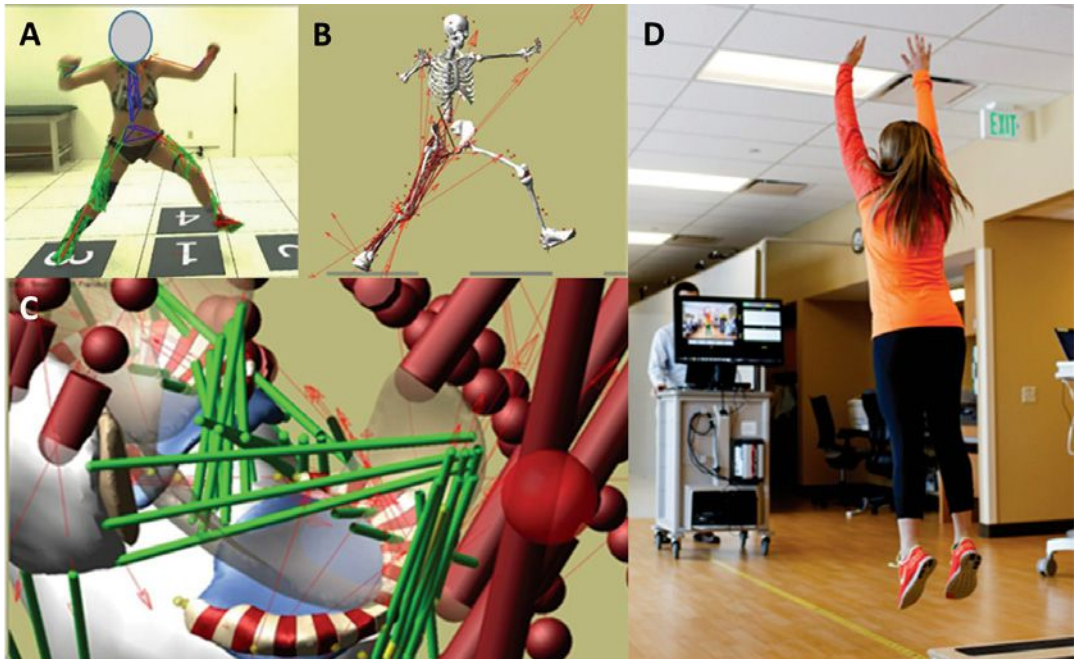


Figure 4A-C. Musculoskeletal model of a cutting task. The model combines gait analysis with medical imaging to predict loading on knee tissue, including the ACL, during movement.

Figure 4D. Depth camera assessment of movement quality during a drop vertical jumping task.

The majority of ACL tears result from non-contact mechanisms where the foot contact with the ground, and the body movement and muscle forces generate ligament loading that is sufficient to cause ACL rupture.[1] While video analysis during ACL injury can provide context for general body position and motion during the injury, the key biomechanical components that result in failure strain of the ACL fibers are not provided by video analyses, and therefore have not been fully elucidated. A more complete picture of ACL injury and reinjury mechanisms would benefit efforts in reinjury prevention and improve individual success after reconstructive surgery. Non-contact ACL tears are often associated with planting and cutting maneuvers that create transverse plane rotation and valgus moments at the knee. However, methods to directly measure ACL loading during movement do not currently exist and in vivo ligament forces during planting and cutting maneuvers are generally unknown. To address this limitation, our group also developed and validated portable and inexpensive depth camera methods to assess movement quality for ACL injury risk and prevention.[40] By combining individual knee geometries derived from medical imaging, motion capture, measured muscle activations, and ground reaction forces, our group has developed computational models that predict loading on knee tissue, including the ACL, during movement (Figures 4A-C).

Through these models, we discovered that ACL loading during a normal cutting maneuver is similar to loads found during normal daily tasks, such as walking. However, the addition of altered muscle activation patterns (i.e., increasing calf muscle activation) as well as body position (i.e., rotating the trunk outward) can result in greatly increased ACL loads and strains. These findings may explain why normal cutting athletic movements that typically generate minimal ACL strain can result in an ACL injury.

The combination of computational models and motion capture can provide insight into ACL injury mechanisms and the interplay of modifiable and non-modifiable risk factors. As modifiable movement risk factors can be potentially mitigated, they have been the subject of ACL injury prevention, intervention, and assessment for decision on return to sport. Specific movement mechanics during jump landing have been identified as movement markers associated with elevated risk of ACL injury. Typically, instrumented analyses of movement mechanics are performed in a gait lab, which limits accessibility in patient care settings. To address this limitation, our group also developed and validated portable and inexpensive depth camera methods to assess movement quality for ACL injury risk and prevention.[41] We used a common consumer product, Microsoft Kinect depth camera, to measure the knee-to-ankle separation ratio, which is a surrogate of dynamic knee valgus, during a drop vertical jump in high school athletes (Figure 4D).[41]

The use of a readily accessible objective movement assessment tool not only allows one to address movement risk factors during patient rehabilitation following ACL



Figure 5. (A) Components of a comprehensive return to sport assessment after ACL surgery including Biodex to objectively measure muscle strength recovery, and (B) functional movement screens with hop testing.

surgery, but also permits athlete screening for ACL injury prevention and establish efficacy of maintenance ACL prevention programs.

The Evidence Behind Return to Sport Assessment after ACL Reconstruction

There is a growing sentiment that the success rate with return to sport after ACL surgery may not be as high as previously thought. If one defines return to sport as returning to the exact prior levels of participation before ACL surgery, a recent systematic review showed that the rate of return to sport after ACL reconstruction was approximately 48.9%.[25] Achieving return to sport after ACL injury and surgery requires a team approach toward rehabilitation. Traditional paradigms where the criteria for return to sport after ACL surgery is predominantly time-based and knee-focused are being replaced with a more holistic biopsychosocial framework that also considers an athlete's functional progression, interaction with open uncertain environment, and psychological readiness. The return to sport decision has evolved from a singular endpoint to one that is assessed continuously between the athlete, rehabilitation team, and physician. There is currently no gold standard that exists for evaluating return-to-sport readiness after ACL reconstruction.

A comprehensive approach that considers more facets likely provides the clinician with a more complete picture of an athlete's recovery. As an example, our institution's return to sport assessment consists of both subjective and progressive objective testing algorithms centered on evidence-based guidelines. The subjective section includes a single assessment numeric evaluation (SANE) score, the ACL-RSI scale questionnaire, and a numeric pain rating. The SANE score asks the individuals to rate their current musculoskeletal illness in relation to their preinjury baseline on a scale of 0-100.[42] Patients complete the ACL-RSI questionnaire with a passing score of 65 to gauge psychological readiness to return to the previous activity level.[43] Numeric pain rating (NPR) regarding the patient's current pain level of the knee is recorded to obtain a baseline and screen for issues that would prevent testing. The objective testing algorithm was designed to increase in difficulty as the evaluation proceeds and is discontinued if the patient experiences pain greater than 2/10 or appears unsafe to continue during the process. Knee flexion and extension are measured bilaterally, with extension expected to be within 2 degrees of the uninvolved side. A modified brush test is performed to assess for the presence of knee joint effusion. Thigh girth at 15cm above the knee joint line is measured to correlate with isokinetic knee strength. Isokinetic strength testing is performed at 90, 180, and 300 deg/sec with a limb symmetry index goal of 90% for quadriceps to quadriceps and hamstring to hamstring ratio as well as a 66% for the hamstring to quadriceps ratio (Figure 5A).[43]

A lateral step-down test is observed for the presence of abnormal lower limb and trunk neuromuscular control. Y balance testing is completed with two primary goals: achieving composite reach greater than 90% of limb length and anterior reach less than 4cm difference between sides. A drop vertical jump test is then analyzed using the ACL gold software as previously described. The final testing battery includes 4 single leg hop tests consisting of single leg hop for distance, crossover hop, triple hop, and 6-meter timed hop with limb symmetry index goal

of 90% (Figure 5B).[43] In conjunction with the athlete, the therapist and physician consider the results of the tests to determine readiness to return to full, modified activity, or continue rehabilitation.

While no set standard for determination of return to play exist, the literature suggests that having an extensive battery of tests to assess readiness for return to play would be more likely to be successful than a more narrowed approach.[44–46] Kyritsis et al. studied 158 male professional athletes who returned to their prior professional level of sports.[46] Before each player returned to their sport, they underwent numerous tests including isokinetic strength testing (<10% quad deficit) at 60°, 180° and 300°/s, a running t test (<11 sec), single hop, triple hop, and triple crossover hop tests (limb symmetry index >90%). The authors found that athletes who did not pass all six criteria had a 4.1-fold increase risk of ACL reinjury. Similarly, the Delaware-Oslo ACL cohort study demonstrated that athletes returning to level 1 pivoting sports were more likely to sustain a reinjury to their ACL if they did not pass a battery of functional testing including strength and hop tests versus those who met all the criteria for return to sports (38.2% versus 5.6%, respectively).[45] The combination of both time- and criterion-based rehabilitation alongside a comprehensive functional return to sport criteria therefore has the greatest potential to minimize an athlete's reinjury risk and improve long-term success after surgery.

Conclusion

We have identified individual risk factors and knowledge gaps that can impede achieving success after ACL injury and surgery. Future development that allows one to individualize post-surgical rehabilitation that accounts for an individual's surgery (i.e., graft used) and risk factors for reinjury are likely to be more successful.

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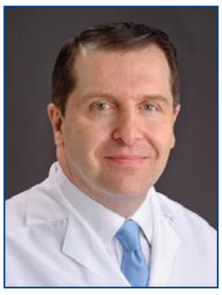
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Preoperative Planning and Preservation of the Knee with Complex Osteotomies

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Health Care

Correction of deformities around the knee promotes a better distribution of the load among the different compartments of the joint, restoring the knee mechanical homeostasis.



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Abstract

The knee is a complex structure composed of bone, cartilage, menisci, ligaments and muscles, which all work synergistically to optimize congruence, stability, and function. Osteotomies are procedures addressing an abnormal joint alignment, shifting the mechanical load from a diseased joint compartment to a healthier one. Preoperative planning is an important art of identifying the source of abnormal load distribution to the joint, enabling the surgeon to simulate a deformity correction ahead of the surgical procedure.

Osteotomies Around the Knee: A Life-Changing Procedure

John Rhea Barton performed the first documented osteotomy around the knee in 1835.[1] The patient was a physician who had a significant knee flexion contracture. The procedure was performed without anesthesia and lasted no more than five minutes. A bone wedge was removed from the anterior aspect of the distal femur, preserving the integrity of the posterior cortex. In the postoperative time, the knee was gradually straightened with serial cast changes. The surgical outcomes were so promising that the patient was able to work and ride horses again, reporting later that the procedure gave him a new life.

A Surgical Treatment for Knee Osteoarthritis

The use of osteotomies to manage degenerative disorders of the knee began in the 1950s. The concept was to correct an existing metaphyseal deformity around the knee by breaking the proximal tibia and reorienting the load pattern to the joint[2] (Figure 1).

The tibial osteotomies for the treatment of unicompartmental knee arthritis were popularized by Jackson (infra-tuberosity osteotomy), and Coventry (supra-tuberosity osteotomy).[3,4] The only implants available to fix osteotomies around the knee were staples, and therefore casting in the postoperative time was a common practice in the postoperative period of these procedures.[5] The lack of surgical standardization, fixation techniques, and postoperative protocols resulted in multiple failures. Infection, malunion, nonunion, knee stiffness, obliquity of the joint line, patella Baja, and a series of other potential complications generated a perception that osteotomies around the knee should be avoided, and knee arthroplasty should

be the alternative of choice for the management of symptomatic arthritic knees.[6–8] It was clear that a total knee arthroplasty would be a better choice especially for the elderly population.[9] The question remained open while dealing with young and active adults, as in this group of patients the outcomes of joint arthroplasty were still mixed.[10] In the last two decades, recent publications revealed favorable outcomes associated with osteotomies around the knee for the management of individuals with unstable and/or arthritic joints.[11–13] The improvement of image study modalities, the development of new technologies for preoperative and intra-operative guidance, and a new generation of implants have contributed for reproducible and remarkable outcomes.[14–16]

Understanding the Deformity and its Clinical Implications

Osteotomies around the knee are controlled fractures aiming to improve the performance of the joint. Osteotomies aim to address any sort of deformity or malalignment of the knee. The deformity may take place in the coronal plane (varus/valgus), sagittal plane (procurvatum/recurvatum), and/or axial plane (torsion). The deformity may be extra-articular (metaphysis/diaphysis) and/or intra-articular (epiphysis). The precise identification of the deformity site(s) is critical for a precise execution of an osteotomy around the knee.[17] The most typical deformities associated with arthritic knees are described in the coronal plane. Varus knees (bowed legs) are characterized by the pathological shift of the mechanical axis to the medial compartment of the joint. The opposite occurs with valgus knees (crooked legs), which tend to wear out initially on the lateral compartment. Valgus knees are also associated with patellofemoral malalignment and/or instability.[18] In the sagittal plane, the measurement of the tibial slope is of importance, especially in cases where recurrent anteroposterior instability is present. An increased tibial slope is associated with anterior translation of the tibia, which poses significant tension to the anterior cruciate ligament.[19] In the other way around, a decreased tibial slope may be detrimental to the posterior cruciate ligament function.[20] In the axial plane, torsional deformities determine patellofemoral instability and pain.[21] The three-dimensional analysis of the knee allows for a better understanding of clinical findings and optimal decision making.

Interpreting Image Studies

An extremity alignment study (EAS) is a gold standard radiograph obtained to assess the alignment of the knee in the coronal plane.[22] This image study includes a single radiograph that captures the alignment of the hip, the knee, and the ankle. The line that connects the center of the hip to the center of the ankle corresponds to the mechanical axis of the lower limb. If the alignment of the knee is neutral, this line will seat slightly medial to the medial tibial spine, close to the center of the knee. Deviations of the mechanical axis from the center of the knee to either one of the compartments of the joint determines excessive load to that compartment and, therefore, increases the likelihood of degenerative changes in that site.[23]

A tangent line to the femoral condyles, and a tangent line to the tibial plateau should intersect the mechanical axis to determine joint alignment angles. Three angles are of critical importance. The mechanical proximal tibial angle (MPTA) which is determined by a tangent to the tibial plateau and the mechanical axis on the medial side of the joint. The MPTA normally ranges from 85 to 90 degrees, and its standard value is 87 degrees.[17,22] On the lateral aspect of the knee, the angle determined by the tangent to the femoral condyles and the mechanical axis is named mechanical lateral distal femoral angle (mLDFA). The mLDFA normally ranges from 85 to 90 degrees and its standard value is 88 degrees.[17,22] Another important angle is determined by the tangent lines to the femoral condyles and to the tibial plateau. These two lines should be parallel or slightly convergent medially. These two lines determine the Joint Line Convergence Angle (JLCA) which varies from 0 to 2 degrees.[17,22] The angle determined between the mechanical axis of the femur and the mechanical axis of the tibia is named mechanical tibiofemoral angle, which normal value varies from 0 to 2 degrees (Figure 1).

Joint orientation angles are of critical importance while determining the biomechanics of the knee and how the joint is routinely loaded. Knee deformities in the coronal plane will generate bowed or crooked legs. The bowed legs are present when the knee has a varus alignment, while the crooked legs are associated with a valgus alignment of the joint. Joint orientation angles will guide the surgeon to determine if the deformity is originated at the level of the femoral metaphysis, tibial metaphysis, joint surface, or a combination of these sites.

Deformities in the axial plane will generate abnormal torsion to bone segments. They may be constitutional or inherited post-trauma. They have significant impact to the mechanics of the patellofemoral joint.

Varus Knees

A varus deformity implies in the shift of the mechanical load to the medial compartment of the knee. As a result, degenerative changes may take place in this compartment, which may cause pain and mechanical symptoms.[24] Traditionally, the deformity was meant to be originated in the upper metaphysis of the tibia and, therefore, osteotomies to correct varus knees were traditionally performed on the upper portion of the tibia. However, the systematic measurement of the joint orientation angles revealed that in some cases the deformity is not located in the proximal tibia but in the distal femur or at the level of the joint line (Figure 2).

Osteotomies should be considered as a joint preservation option in the management of symptomatic varus knees. The main goal of this procedure is to shift the mechanical load from the diseased medial compartment to a healthier lateral compartment of the joint. Medial open wedge high tibia osteotomies became the most popular method of correcting varus knees[25] (Figure 3). Sometimes, however, the deformity is not located on the tibia, but on the femur, which prompts the correction to take place at the level of the distal femur (Figure 4).

Meticulous preoperative planning helps to determine how to improve the alignment of the lower limb, as well as the distribution of loads in the joint, without generating a secondary deformity at the level of the knee. If the osteotomy is not correctly indicated or is placed at a site that does not correspond to the center of the deformity. In a few cases, we have noticed that the deformity was not located just in one of the long bones, but in both. In these cases, a double level osteotomy, which implies in performing two simultaneous osteotomies, one at the level of the femur and one at the level of the tibia should be carried out[26] (Figure 5).

Valgus Knees

The lateral compartment of the knee is the one exposed to extra loading in cases of a valgus deformity. The patellofemoral joint is also exposed to mechanical forces which pull out the patella towards the lateral aspect of the femoral trochlea. Correction of a valgus deformity offloads the lateral compartment of the knee and improves the patellofemoral tracking. The most typical site for deformity correction is the distal aspect of the femur[27] (Figure 6). Occasionally, the osteotomy should be performed at the level of the tibia or at a double level, femur, and tibia, as it has been demonstrated in the examples of varus knees.

Torsional Deformities

Deformities in the axial plane are not very intuitive as they are not easily caught by radiographs. The clinical exam with a detailed analysis of the gait, rotations of the hip, and thigh-foot angle are an essential part of the assessment of these patients. The computed tomography is the image modality that determined with precision the alignment of the limb in the axial plane. Torsional corrections are obtained when the osteotomy is performed perpendicular to the axis of the long bone allowing for detorsion of the segment[28] (Figure 7).

Conclusion

The alignment of the knee has direct implications on its mechanical performance. Knee pain could be the expression of degenerative changes caused by mechanical overloading of one of the compartments of the joint. Extremity alignment studies are of critical importance to understand how the loads are distributed on the knee. The mechanical axis of the lower limb should connect the center of the hip, the center of the knee, and the center of the ankle. A deviation of the mechanical axis in the coronal plane is present in cases of varus deformities or valgus deformities. Correction of deformities around the knee promotes a better distribution of the load among the different compartments of the joint, restoring the knee mechanical homeostasis. Deformity correction is a precise art. It requires meticulous preoperative planning based on the identification of the site(s) of deformity. The site of deformity is indicated by abnormal joint orientation angles. The location of the abnormal angle should correspond to the site of the osteotomy aiming to restore the mechanical axis. The goal of deformity correction is not only to shift the mechanical load to a healthier compartment of the joint, but to perform it without causing an obliquity of the joint line, or significant leg length discrepancy. Preoperative

planning allows for a three-dimensional understanding of the deformity and its correction in one or more spatial planes. Restoring knee alignment and stability may preserve the joint for many years until a joint replacement may be at consideration. This is especially important in young and active individuals, where the survivorship of a joint replacement is not expected to be greater than the patient's life expectancy.

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Disclosure

MK: AOTrauma board or committee member.

BDC: KCI: paid consultant; Orthopaedic Implant Company and RomTech: stock/stock options; Springer: publishing royalties, financial, or material support; AO Trauma North America: board or committee member; Globus Medical: IP royalties; International Geriatric Fracture Society: board or committee member; J*ournal of Hip Preservation*: editorial or governing board; *Journal of Orthopaedic Trauma*: editorial or governing board; Orthopaedic Trauma Association: board or committee member; Osteocentric: unpaid consultant; SLACK Incorporated: editorial or governing board; Synthes: paid consultant; research support.

JPS: DePuy, Orthopedica Designs North America, and Smith and Nephew: paid consultant; National Institutes of Health: research grant; American Orthopaedic Association: board or committee member; AO Foundation: board or committee member; AO North America: board or committee member; *Journal of Knee Surgery*: editorial or governing board; Mid-America Orthopaedic Association: board or committee member; Thieme: publishing royalties, financial, or material support; and U.S. Department of Defense: research support.

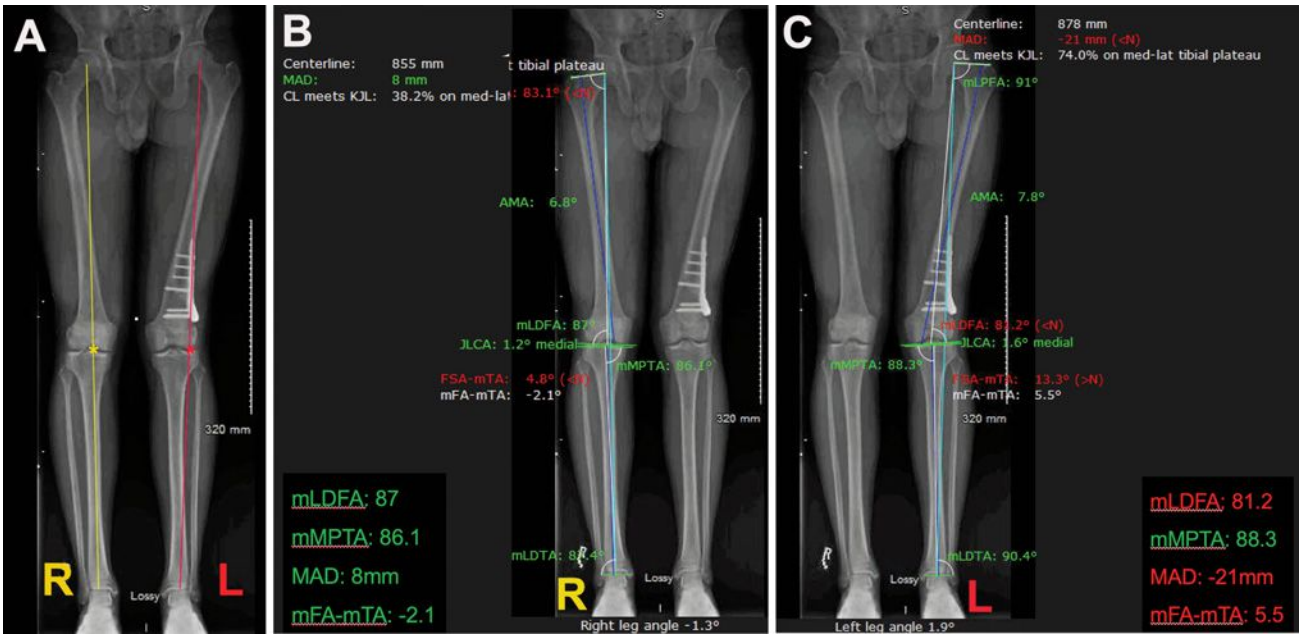


Figure 1. Assessment and interpretation of extremity alignment studies in a 21-year-old male. A: Extremity alignment revealing a right lower extremity (R) neutral mechanical axis. Observe that the yellow line (Mikulicz line) connecting the center of the hip and the center of the ankle, bisects the knee at its center (yellow asterisk). The left lower extremity (L) has a shift of the mechanical axis to the lateral compartment of the joint. Observe that the Mikulicz line (red) is bisecting the joint (asterisk) on the lateral compartment, which determines a valgus alignment of this lower extremity. B: A software is utilized to determine the joint orientation angles on each one of the lower extremities. Observe that all joint orientation angles around the right knee are marked in green, indicating that they are within normal values. In the left lower extremity, there is a valgus mechanical femoral tibial angle of 5.5 degrees. In this case the deformity is generated at the level of distal femur, as the mechanical lateral distal femur is 81.2 degrees (normal range 85 to 90 degrees). Preoperative planning using digital software provides precise quantification and location of the deformity in the lower extremity.

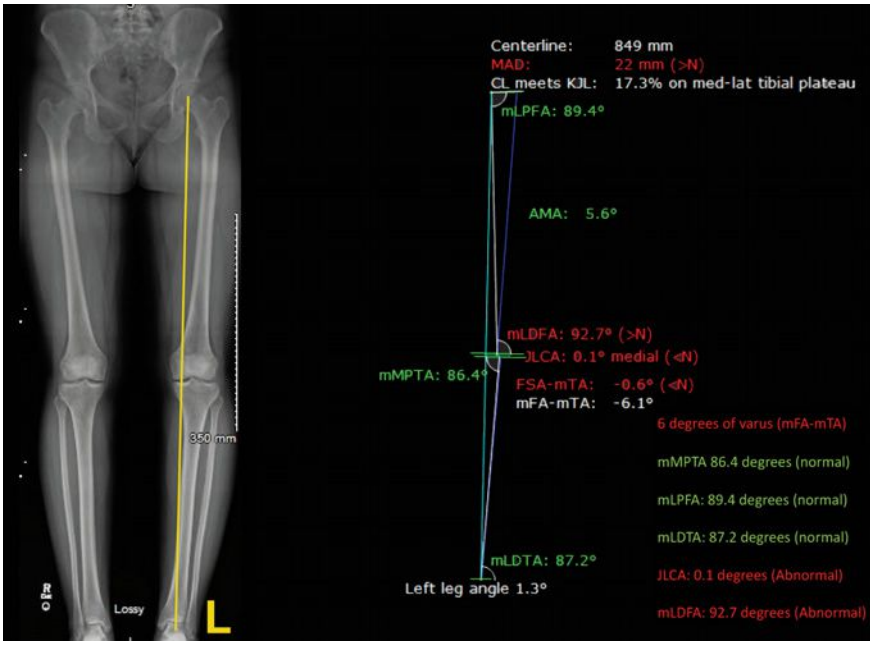


Figure 2. The importance of preoperative planning. This is an alignment study of a 25-year-old male with complaints of medial knee pain. His extremity alignment study shows varus alignment, with displacement of the mechanical axis to the medial compartment of the left knee. He was told that he would benefit of a knee arthroscopy for the management of a medial meniscal tear. The patient was also told that a possible high tibial osteotomy to correct the varus deformity would be necessary. We were asked to evaluate the patient and we confirmed that his mechanical proximal tibial angle was withing normal values (86.4 degrees), but the varus was originated on the distal femur (abnormal mLDFA superior to 90 degrees). In this case, preoperative planning was able to identify that the correct site for the osteotomy in this case would be the distal femur and not the proximal tibia.

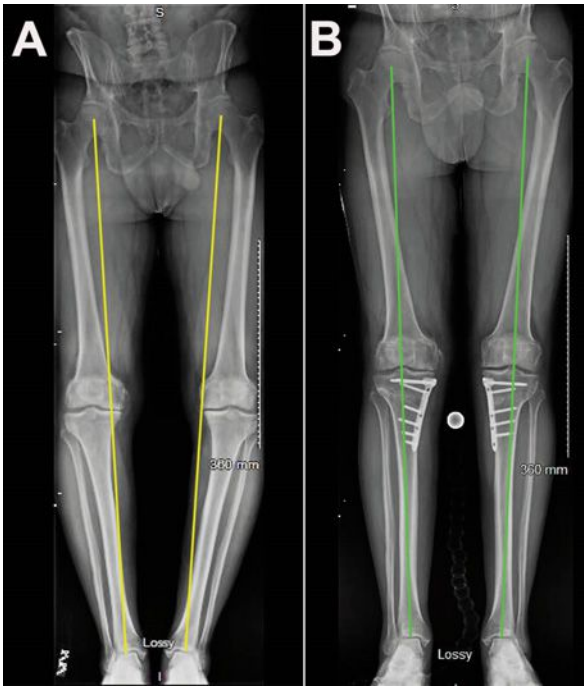


Figure 3. Medial open wedge valgus producing high tibial osteotomy. A: Extremity alignment study of a 47-year-old male with bilateral knee pain and varus deformity. He was told that the best option for his knee would be bilateral total knee replacement when he would get older. He is currently not able to stand on his feet to perform the activities of his daily living. B: Patient underwent a staged treatment for his lower extremities. Initially he was submitted to a left high tibial osteotomy. After complete recovery of this surgical procedure, he received a right high tibia osteotomy. Patient was able to resume his professional activities with minimal discomfort in his lower limbs, improved gait pattern, and improved alignment of the lower limbs.

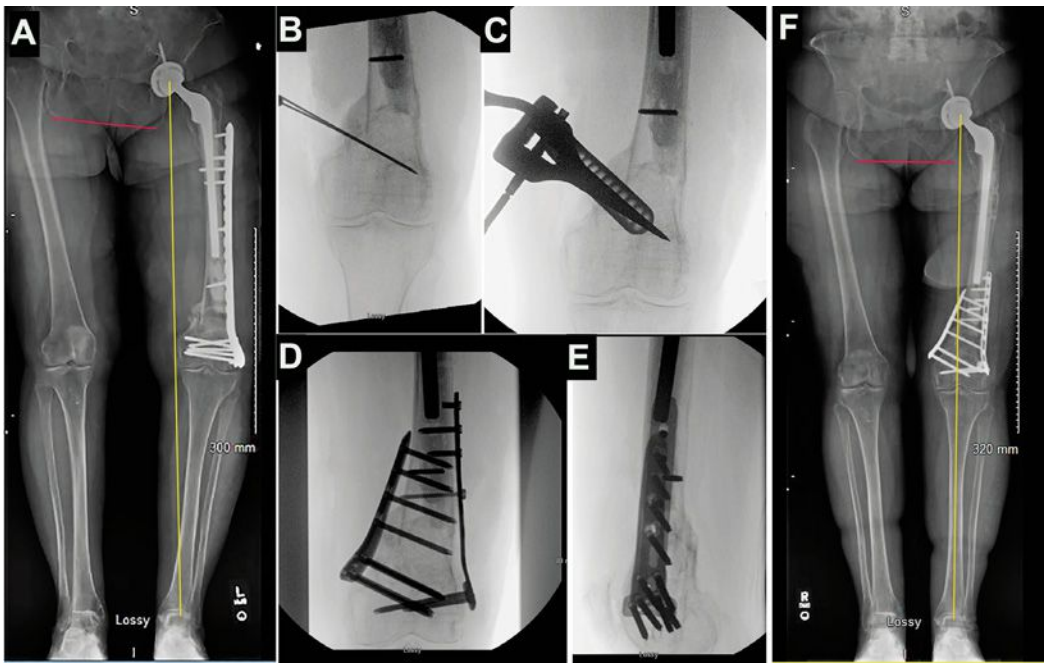


Figure 4. Status after failed left distal femur periprosthetic fracture. A: Extremity alignment study of a 62-year-old female patient 5 months after an open reduction and internal fixation of the left distal femur. Patient has varus alignment (yellow line) and shortening of the left lower limb. The leg length discrepancy may be noted by the obliquity of the pelvis (red line). The list of problems includes significant pain, disability to bear weight, osteoporosis, previous infected left total hip replacement on chronic antibiotic suppression, short distal femur segment, left knee arthritis. B: Intraoperative image illustrating the direction of an medial distal femur open wedge valgus producing osteotomy. C: A special tool is used to open a wedge of 18mm on the medial aspect of the distal femur; D: Final intraoperative aspect of the osteotomy on the anteroposterior and E: lateral projections of the knee; F: Final extremity alignment study revealing neutral alignment of the lower limb and neutral pelvis obliquity. The leg length discrepancy was improved significantly as well as patient's stability and ability to perform her activities of daily living.

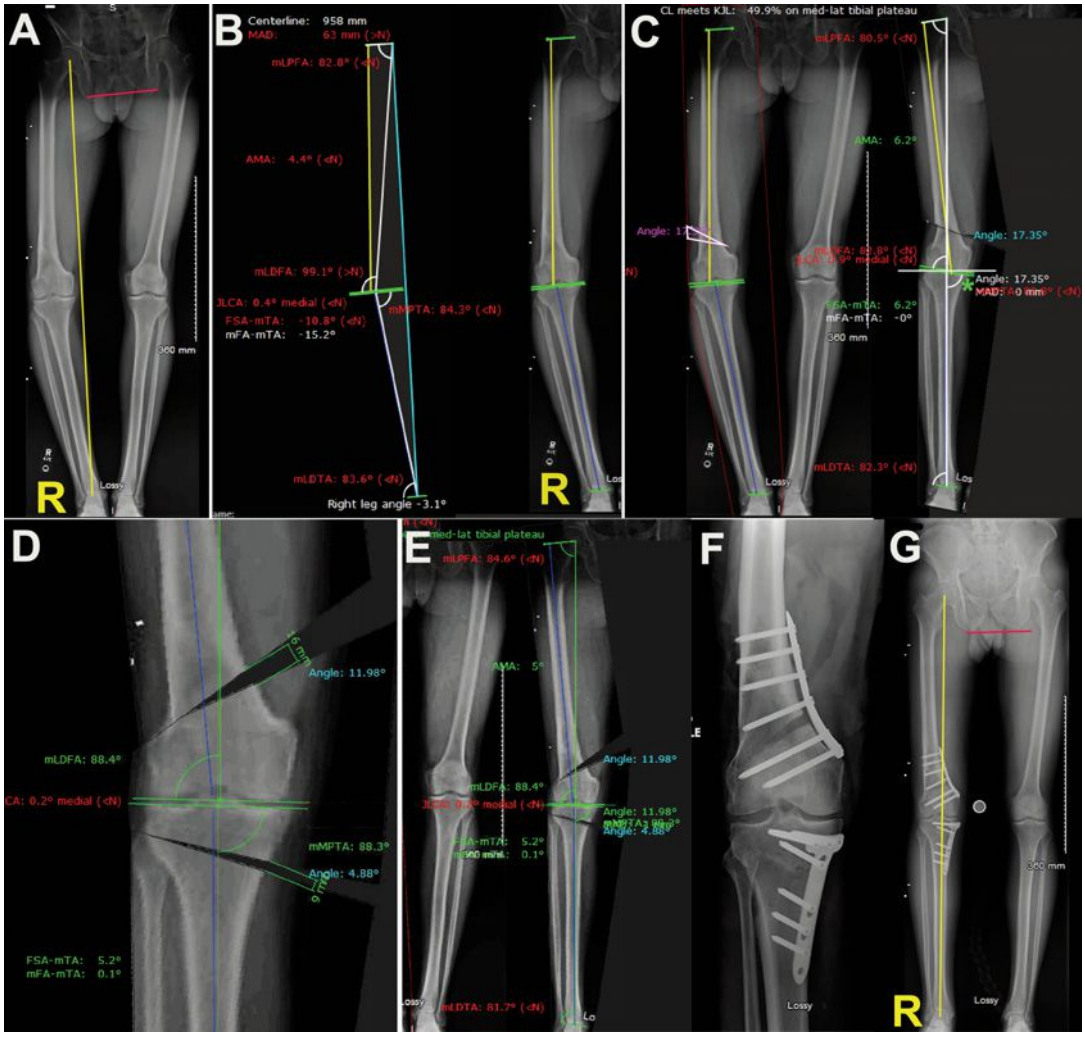


Figure 5. Illustrative case of a double level osteotomy to correct a varus alignment. A: Extremity alignment study revealing significant varus alignment in a 49-year-old male, with history of significant knee pain. Patient received an indication for a right total knee replacement and came to our office for a second opinion. Past medical history significant for a right distal femur fracture when he was 15 years of age. B: Digital preoperative planning revealing a varus deformity of 15.2 degrees and abnormal MPTA, mLDFA, and JLCA; C: A simulation to correct the varus deformity with an osteotomy performed at the level of his previous fracture resulted in correction of the mechanical axis to the expense of obliquity of the joint line (green asterisk). This indicated that the correction could not be performed just at that level; D: Considering that the patient had significant shortening of the lower limb we proposed a double level osteotomy, opening a medial wedge on the distal femur and on the proximal tibia. We were able to propose a correction superior to 2cm in length discrepancy bringing the MPTA and mLDFA to a normal range. E: Simulation of the alignment study revealing neutral mechanical axis and normal joint orientation angles; F: Postoperative radiograph on the anteroposterior projection. Bone graft was used to fill the open wedge gaps; G: Final extremity alignment study revealing neutral mechanical axis (yellow line) and normalization of the pelvic obliquity (red line). This patient has four years of follow up and has not complained of any knee pain since his lower extremity alignment has been corrected.

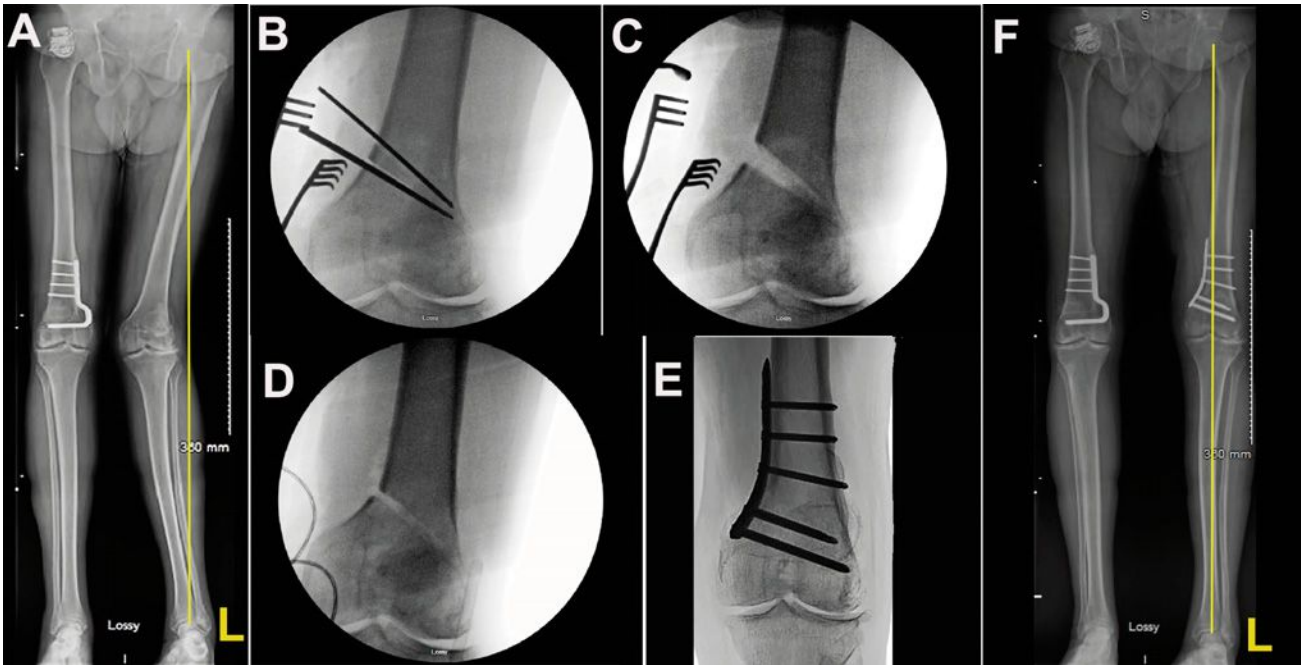


Figure 6. Illustrative case of a valgus deformity correction. A: Extremity alignment study of a 46-year-old male who complains of left knee pain and instability. He has past medical history significant for a right distal femur osteotomy to correct a similar deformity. B: Intraoperative image illustrating the resection of a medial distal femur cortical. The wedge has a base measuring 16 mm. C: Fluoroscopy pictures revealing the wedge resection, prior to correction of the deformity; D: The osteotomy gap is gently closed. Observe that the opposite hinge is intact and no translation between the distal and proximal fragments take place; E: Final radiograph depicting a good coaptation of the osteotomy. F: Final extremity alignment study revealing neutral alignment of the lower limb. This procedure was performed four years ago, and the patient has not complained of knee pain since.

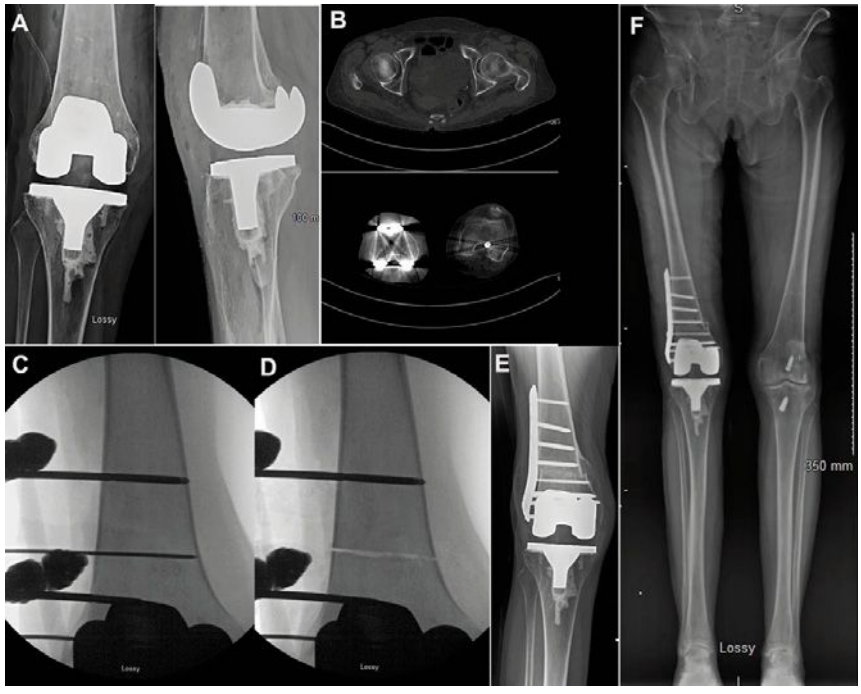


Figure 7. Illustrative case of torsional deformity. A: Radiographs of a 63-year-old female who underwent a right total knee replacement elsewhere. She had previous valgus alignment and a history of patellectomy many years ago. After her knee replacement she developed significant instability of her extensor mechanism, with recurrent dislocations. She received the indication to revise her total knee replacement. B: In our clinic a computed tomography was performed, and we noticed that she had 24 degrees of internal torsion of the distal femur. She was two months out of her total knee replacement. Instead of revising the components of the knee replacement we proposed an osteotomy to correct the torsional deformity. C: Intraoperative pictures illustrating the orientation of the osteotomy, perpendicular to the axis of the femur; D: The osteotomy has been completed. The femur does not displace because it has been provisionally fixed with an external fixator. E. Final radiograph one year after surgery with complete healing of the osteotomy. Patient has no more symptoms of extensor mechanism dislocation; F: Final alignment study depicting that the osteotomy did not introduce deformity in the coronal plane.

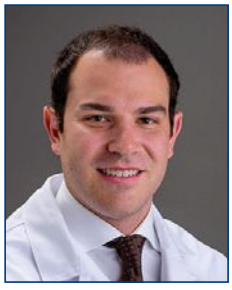
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Team Integrated Enhanced Recovery (TIGER) Protocol after Adolescent Idiopathic Scoliosis Correction Lowers Direct Cost and Length of Stay While Increasing Daily Contribution Margins

by Mark J. Lambrechts, MD, Melanie E. Boeyer, PhD, Nicole M. Tweedy, DNP-PNP, Sumit K. Gupta, MD, Eric T. Kimchi, MD & Daniel G. Hoernschemeyer, MD

Health Care

Our team-based enhanced recovery protocol after posterior spinal fusion in AIS patients resulted in a 26% decrease in hospital LOS without increasing pain scores averaging 3.5 postoperative days.



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Abstract

Introduction: Posterior spinal fusion (PSF) is the gold standard procedure for curve correction in Adolescent Idiopathic Scoliosis (AIS). Enhanced recovery protocols (ERPs) have been found to decrease pain and hospital length of stay (LOS) resulting in decreased total hospital charges.

Methods: We identified all adolescent idiopathic scoliosis patients treated with a posterior spinal fusion at our children's hospital between 2015-2019. Length of stay, pain scores, and hospital direct costs were calculated to determine the pathway's efficacy.

Results: Hospital LOS was reduced by 26% and post-op pain scores did not significantly change when using the Team Integrated Enhanced Recovery (TIGER) protocol (P<0.05). Total hospital costs decreased by 7.9%, daily contribution margins increased 7.9%, and daily net income increased 10.6% after TIGER protocol implementation.

Conclusion: TIGER protocol resulted in decreased hospital LOS as well as direct costs for the hospital without increasing postoperative pain scores.

Introduction

Enhanced recovery protocols (ERP) for patients undergoing posterior spinal fusion to treat adolescent idiopathic scoliosis (AIS) have become more widespread. Muhly et al.[1] was the first to demonstrate that enhanced protocols can reduce hospital length of stay (LOS) without increasing pain scores or readmission rates. ERPs rely on several avenues to enhance recovery after surgery. These include: 1) admission directly to the surgical floor rather than an intensive care unit (ICU); 2) rapid mobilization; 3) transition to a multimodal pain regimen with early weaning of patient-controlled analgesia (PCA); and 4) minimizing drains, intravenous fluid lines, and dressings.

ERPs have been shown to be effective at large pediatric spine centers in reducing hospital LOS between 31% to 48%,[2,3] and have also improved inpatient procedure costs by as much as 22%.[4] Further, Boylan et al. analyzed the New York

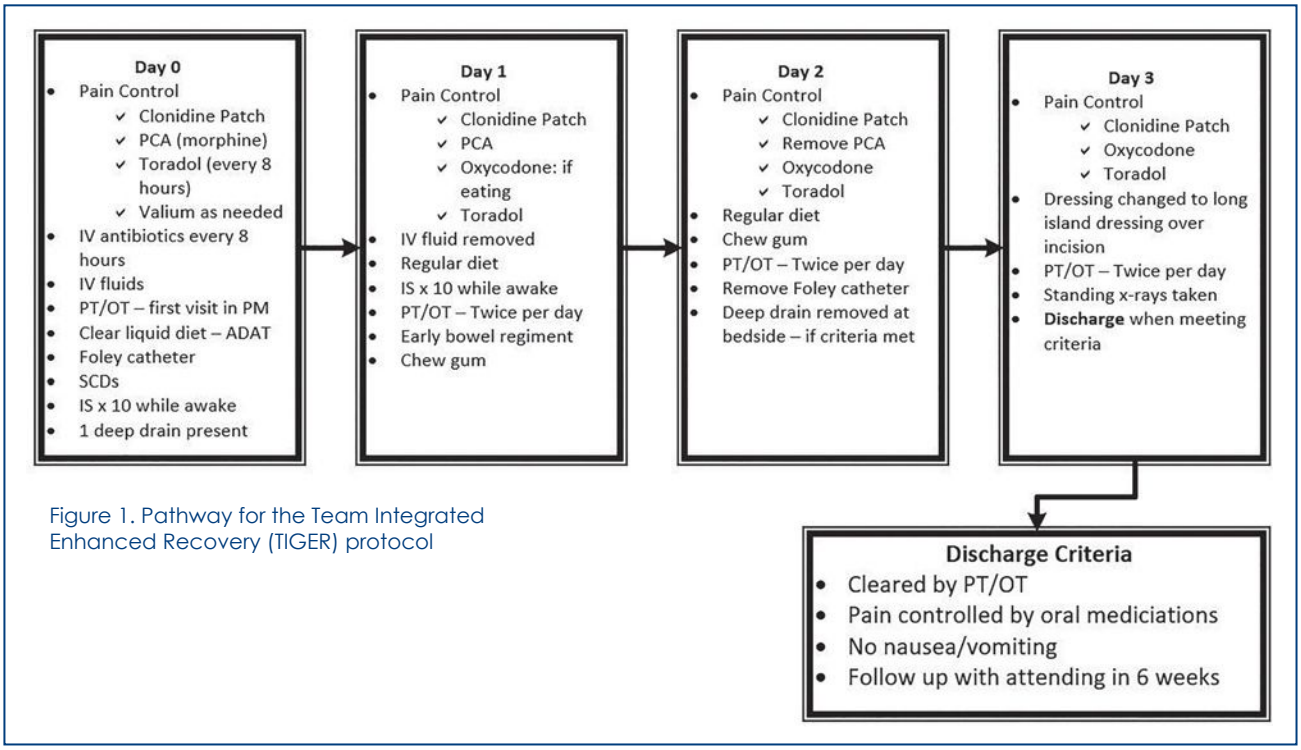


Figure 1. Pathway for the Team Integrated Enhanced Recovery (TIGER) protocol

Statewide Planning and Research Cooperative System database and determined each additional postoperative day in the hospital after posterior spinal fusion (PSF) for AIS was associated with an additional $5,198 in hospital costs, a 28% increased risk of 90-day readmission, and a 57% increased risk of returning to the operative suite within 90 days.[5] Although most previous literature has looked at direct cost savings to the hospital, we were interested in the contribution margin (total revenue of the procedure minus the direct costs of the procedure and inpatient admission) as this may give a more accurate assessment of the true impact the enhanced recovery protocol has on early discharge.

The foundation of an ERP is centered on improving patient care, but it is also economically advantageous. However, the generalizability and sustainability of implementation of an ERP is unclear. Previous ERPs have been primarily implemented at large pediatric spine centers with multiple pediatric spine surgeons and nurses accustomed to caring for AIS patients who undergo PSF. We therefore sought to determine if these protocols were generalizable to a single center with one pediatric spine surgeon. We followed the model outlined by Muhly et al.[1] to implement a quality improvement (QI) project focused on improving patient care and decreasing health care expenditure by instituting our own ERP, referred to as the Team Integrated Enhanced Recovery (TIGER) Protocol. We hypothesized that the implementation of the TIGER protocol would result in similar postoperative pain scores and a decreased hospital LOS, resulting in an increase in the contribution margin to our health care system for each patient treated with a posterior spinal fusion.

Methods

Quality Improvement (QI)

Prior to implementation of the TIGER Protocol, there was no standardized preoperative counseling for either the patient or their parents focused on post-operative expectations. Additionally: 1) dexmedetomidine was administered preoperatively as an anxiolytic requiring a post-operative stay in the pediatric intensive care unit (PICU); 2) a superficial and deep hemovac were placed during surgery; 3) physical therapy was started on postoperative day 1 and worked with patients only once per day; 4) post-operative analgesia was patient dependent with PCA administered until postoperative day three; and 5) a foley catheter was maintained until postoperative day two.

The first step in implementing the TIGER Protocol included: 1) optimization of pain management with the help of anesthesia and the pharmacy; 2) standardized physical therapy with mobilization of the patient at the side of the bed the evening of surgery; 3) engagement

Table 1. Demographics of the SP and TIGER pathways with continuous variables represented as the mean ± the standard deviation.
- SP = standard protocol
- TIGER = Team Integrated Enhanced Recovery protocol.

	SP	TIGER	P value
Number of patients	22	70	
Age (yrs.)	15 ± 2.3	14.9 ± 1.8	0.9
Sex (% female)	77	73	0.7
Fusion length	11.7 ± 1.5	9.7 ± 2.6	< 0.001

with therapy twice per day; 4) specialized nurses who managed all AIS patients; and 5) a nurse practitioner (NP) who managed all postoperative order sets and postoperative rounding (Figure 1). Perhaps the most important aspect, which we believe cannot be overstated, is having a NP or physician's assistant take ownership of this pathway to allow for continuity of care, including scheduling the same group of nurses for postoperative care. This allows for systemic buy-in from the nurses who can easily contact the same person daily with any questions regarding the post-operative protocol. This minimizes deviations from the protocol and allows for the sustainability of this model.

Although previously discussed, we believe the crux of pain management is inclusion of a regimen relying on different types of pain relief to reduce narcotic usage. Due to the high levels of evidence for the efficacy of local anesthesia, acetaminophen, and gabapentin to reduce pain and diminish narcotic usage, these are integral components of our post-operative pain protocol. Further, although the evidence is more limited, ketorolac is administered prior to the patient leaving the OR and then administered every 8 hours until the patient is discharged, or pain is minimal. Diazepam is also administered as needed to reduce muscle spasms.[6] A morphine PCA is still available for each patient, but this is limited to the first post-operative night. The effectiveness of this approach hinges on each of these medications employing a different mechanism of reducing pain.

After our NP, nursing staff, physical therapists, pharmacy, lab, and radiology technicians all felt engaged and took ownership of this ERP, we were able to achieve the following: 1) detailed patient and parent preoperative expectations; 2) improvement and acceleration of the recovery pathway by standardizing patient analgesia; 3) expedited foley catheter removal; and 4) aggressive bowel therapy (Figure 1). Once the TIGER Protocol was implemented, we continued to have biannual educational training with nursing and physical therapy staff to reinforce it.

Inclusion Criteria

All patients undergoing PSF for AIS at the University of Missouri between January 1, 2015 and December 17, 2019 were eligible for inclusion into this retrospective analysis. Any patient who underwent PSF for any diagnosis other than AIS was excluded. Our ERP (TIGER protocol) was implemented on October 31, 2016. Patients treated between January 1, 2015 to October 31, 2016 were categorized as Standard Protocol (SP) and those treated on or after November 1, 2016 were categorized as ERP. A total of 92 patients met the inclusion criteria. Retrospective review of their electronic medical record and imaging included age, sex, number of levels fused, average pain scores on postoperative day 0-4, hospital LOS, postoperative complications, and readmission rates or emergency department visits.

Healthcare Costs

All financial data was provided through our billing department, including patient insurance type, daily contribution margin, direct costs, and total costs. The data was analyzed by the billing department to determine the contribution margin of the ERP compared to the SP pathway. To have a similar number of patients in the TIGER and SP groups, only the first 26 patients in the TIGER protocol were considered for inclusion for evaluation of billing data. Further, after pooling both protocols together the contribution margin was calculated depending on patient insurance type.

Statistics

A two-tailed, unpaired, student t-test was used to evaluate the demographics, LOS, and pain scores between the TIGER and SP cohorts. Sustainability of the TIGER protocol, as determined both by LOS and pain scores on days 0-4, was calculated using an analysis of variance (ANOVA). Due to the decreased hospital LOS achieved by 2019, only two TIGER protocol patients remained hospitalized on postoperative day 4. A student t-test was used to determine if a difference existed between pain scores in 2017 and 2018. Statistical significance was set at $P < 0.05$ for all analyses.

Table 2. Length of stay, complications, and readmissions of SP versus TIGER pathway with continuous variables represented as the mean ± the standard deviation.
- SP = standard protocol
- TIGER = Team Integrated Enhanced Recovery protocol
- PICU = pediatric intensive care unit
- ED = emergency department

	SP	TIGER	P value
Length of PICU	1.7 ± 0.8	0.1 ± 0.1	<0.001
Inpatient length of stay	4.7 ± 1.0	3.5 ± 1.3	<0.001
ED visits	1	1	0.4
Complications/revisions	0	2	0.4
readmissions	0	0	1.00

Results

The demographics of the SP and TIGER pathway were not significantly different either in age or sex (P > 0.05). Both the SP and TIGER cohorts were overwhelmingly female. The number of levels fused in patients treated with the TIGER cohort was fewer than when compared with the SP group (Table 1). Importantly, when comparing the SP and ERP groups there was no significant difference in complication rate, readmissions, or emergency department visits (P < 0.05). There was also a significantly shorter LOS and PICU stay between the two cohorts. The SP group required 1.7 +/- 0.8 days in the PICU and a total hospital LOS of 4.7 +/- 1.0 days. The SP cohort had a significantly longer LOS than the TIGER pathway requiring a total hospital stay of 3.5 +/- 1.3 days (P < 0.001) (Table 2). The breakdown in LOS of the TIGER cohort was as follows: 10% of the TIGER pathway went home on day 2, 54% discharged on day 3, 24% discharged on day 4, 3% discharged on day 5, and the remaining 9% discharged after day 5 (Figure 2). Three TIGER protocol patients did require a short stay in the PICU. Two were due to intraoperative neuromonitoring changes, which resulted in no postoperative neurologic deficits. One patient had a headache raising concern for a possible dural tear. After five days of slow symptomatic improvement, the patient's headache completely resolved, and the patient was returned to floor status. Otherwise, no TIGER protocol patient was admitted to the PICU.

The TIGER protocol focuses on early weaning of PCA without a basil rate and a more aggressive physical therapy regimen. To determine if this caused any increase in pain, we recorded patient reported pain scores during postoperative days 0-4. We observed no difference in the SP or ERP pathways regarding pain scores on any postoperative day (P > 0.05). We also wanted to determine the sustainability of the TIGER protocol on a yearly basis from 2017 to 2019. We found no difference in pain scores or hospital LOS between any of the years after implementation of the TIGER protocol (Table 3). However, shorter hospital LOS did trend toward significance in 2019 compared to 2017 and 2018 (P = 0.07).

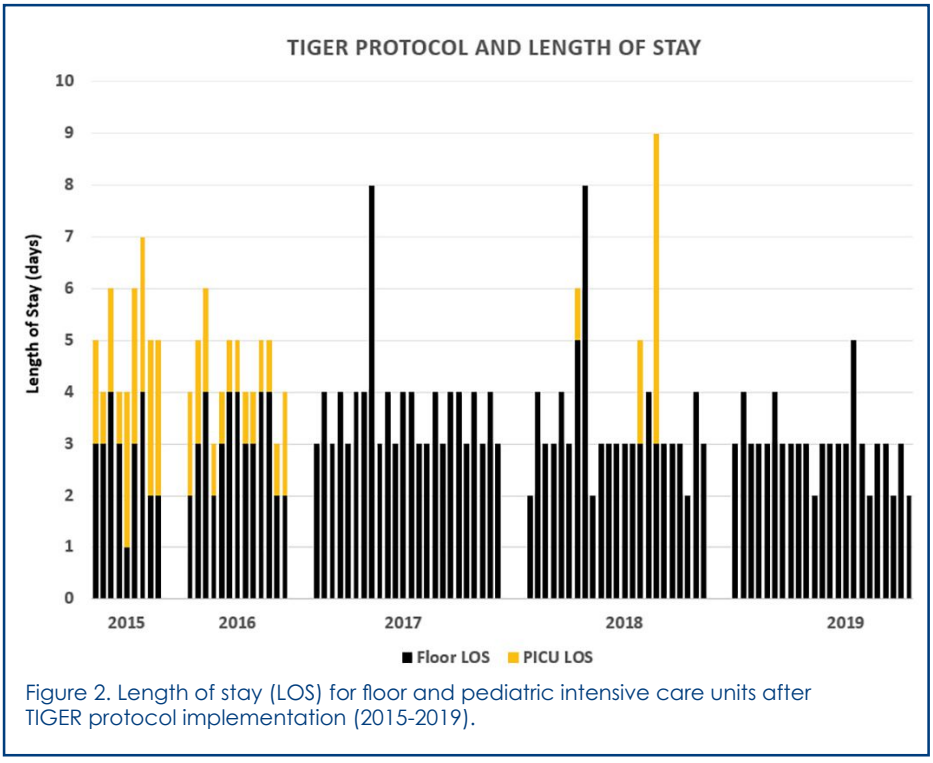


Figure 2. Length of stay (LOS) for floor and pediatric intensive care units after TIGER protocol implementation (2015-2019).

Finally, with assistance from the billing department we were able to analyze all financial data from patients undergoing PSF for AIS between January 2015 to February 2018, including all 22 SP patients and the first 26 TIGER protocol patients. The average direct cost of AIS correction in the SP cohort was $41,630.80 compared to $40,543.05 in the TIGER cohort resulting in a 2.6% cost reduction. Importantly, the average

Table 3. Sustainability of TIGER protocol as seen by LOS and postoperative pain scores during the years 2017-2019. Significance calculated using ANOVA for LOS and pain on days 0-4. Student t-test used to compare pain on postoperative day 4 between 2017 and 2018. All values are represented as the mean ± the standard deviation.

- TIGER = Team Integrated Enhanced Recovery protocol
- LOS = length of stay
- ANOVA = analysis of variance

	2017	2018	2019	P value
Length of inpatient stay	3.7 ± 1.0	3.7 ± 1.8	3.0 ± 0.7	0.07
Pain postoperative day 0	3.6 ± 1.3	3.3 ± 1.8	2.7 ± 1.6	0.14
Pain postoperative day 1	3.5 ± 1.3	3.1 ± 1.7	2.9 ± 1.6	0.4
Pain postoperative day 2	3.7 ± 1.3	3.1 ± 1.7	3.0 ± 2.2	0.4
Pain postoperative day 3	3.5 ± 1.6	2.5 ± 1.4	3.1 ± 2.6	0.2
Pain postoperative day 4	3.7 ± 2.0	2.5 ± 1.3		0.2

Table 4. Direct cost, contribution margin, and average total costs between SP and TIGER protocols pathways

- SP = standard protocol
- TIGER = Team Integrated Enhanced Recovery protocol

	SP pathway N = 22	TIGER pathway N = 26	% change
Direct cost	$41,630.80	$40,543.05	-2.6
Contribution margin	$67,033.76	$58,929.95	-12.1
Daily contribution margin	$15,127.73	$16,328.16	7.9
Total cost	$63,476.44	$58,452.27	-7.9
Net income	$45,188.11	$41,020.74	-9.2
Daily net income	$10,312.87	$11,407.60	10.6

daily contribution margin was $15,127.73 in the SP group compared to $16, 328.16 in the TIGER protocol group. This led to a 7.9% increase in the contribution margin for the TIGER protocol group. Finally, the total inpatient cost for the SP cohort was $63,46.44 compared to $58,452.27 in the TIGER cohort for a 7.9% cost savings (Table 4). When analyzing the total contribution margin between the TIGER protocol and SP cohorts, many contribution margins were in the range of $50,000 to $100,000. When broken down into contribution margins based on insurance type, regardless of protocol used, Medicaid was the only insurance that resulted in a negative contribution margin in 5 of the 48 patients. All remaining private insurances resulted in positive contribution margins with 28 of the 48 patients having a contribution margin between $50,000 to $100,000.

Discussion

The aim of our QI project was to maximize patient care and decrease total costs in patients with AIS undergoing posterior spinal fusion. Consistent with our hypothesis, LOS was decreased by 26% after implementation of TIGER protocol with no increase in postoperative pain. The 26% LOS reduction resulted in a total cost savings of 7.9%. Further, there was an increase of 7.9% to our daily contribution margin and a 10.6% increase of our daily net income after TIGER protocol implementation. Although our LOS did not approach the 2.2 days and 48% decrease found by one multi-center study,[3] it was like the 31% decrease in LOS found after implementation of an ERP by other institutions.[7-9] Additionally, our 7.9% total cost savings are consistent with the 9% cost savings found by Raudenbush et al.[9] after implementation of an ERP. Although they found minor savings using an ERP, they maximized cost savings when minimizing pedicle screws per level and bone graft.

When further analyzing hospital costs after implementation of the TIGER protocol, Medicaid insurance continued to result in a negative contribution margin even after protocol initiation; two TIGER protocol patients and all three SP patients had negative contribution margins with Medicaid insurance. Additional measures to minimize costs in scoliosis patients should be considered including the use of a low-

density pedicle screw construct design when appropriate. This has previously been demonstrated to significantly decrease implant costs, operating time, and blood loss.[10]

While results regarding decreased hospital LOS and healthcare costs have previously been identified, the sustainability of the ERP over consecutive years is less clear.[1-5,7] We found the TIGER protocol to be sustainable over a three-year period. In fact, we identified a trend toward decreased LOS (3.7 days in 2017 to 3.0 days in 2019) as the volume of patients using this pathway increased. These results are like those of Oetgen et al. that used lean process mapping to decrease hospital LOS and narcotic use while optimizing pain control in patients with AIS undergoing fusion. They found these results were sustainable over a 2.5-year period.[11] We also found the ERP to be generalizable to institutions with only a single pediatric spine surgeon. In these instances, the efficacy of the ERP may increase as volume increases.

The success of this pathway is most reliant on four core principles of this pathway: 1) systemic understanding of the enhanced recovery protocol from our therapists, nursing staff, patients, and families; 2) a regimented multimodal pain protocol implemented with the help of our anesthesia department; 3) a dedicated NP who is the direct point of contact for all patients undergoing surgery for AIS; and 4) continual biannual education meetings with staff to attempt to further improve the pathway based on new literature. If implemented, there is consistent evidence the ERP will decrease hospital LOS and hospital costs without causing an increase in pain or readmission rate to the hospital.[5,7-9]

There were multiple limitations with this study that need to be addressed. First, this was a retrospective chart review with unmatched cohorts. This limited our ability to standardize fusion length and a statistically significant longer fusion length was identified in the SP cohort. Additionally, prior to 2015 there was a lower annual volume of patients undergoing PSF at our institution. We therefore used this date as a cutoff since therapists and nurses were not accustomed to working with these patients prior to that time. Finally, we did not record patient satisfaction scores or patient-reported outcomes during this study. However, patient satisfaction has not previously been found to correlate with hospital LOS after implementation of an ERP, so there is no reason to expect a change in patient satisfaction between our two cohorts.[12]

Conclusion

Our team-based enhanced recovery protocol after posterior spinal fusion in AIS patients resulted in a 26% decrease in hospital LOS without increasing pain scores averaging 3.5 postoperative days. This resulted in a total hospital cost savings of 7.9% with a 7.9% increase to our daily contribution margin and a 10.6% increase in our daily net income. The results of our protocol were sustainable over a three-year period with a trend toward decreasing hospital LOS with an increase in patient volume and further staff education. Our study demonstrates that previous results from ERPs are generalizable to practices with only a single pediatric spine surgeon.

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Disclosure

DGH: Orthopediatrics: consultant; Zimmer Biomet: research proposal. **MM**

Falls in Senior Adults: Demographics, Cost, Risk Stratification, and Evaluation

by Stephen Luebbert, MD, William Christensen, MD, Claire Finkel, MD & Gregory Worsowicz, MD

Health Care

This Feature Review is Part I discussing falls in adults and identifying demographics, cost, risk stratification, and evaluation.



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Abstract

Falls occur at staggering rates across the country, with 25% of Americans over 65 reporting annual falls. The fall rate in Missourian older adults is 27.3%. Eighty-six percent of fall-related deaths happen over the age of 65. There are many intrinsic and extrinsic factors that contribute to falls, with some factors that can be targeted and optimized by physicians. There are nuances to the history and physical that can help physicians identify these risk factors.

Falls in Senior Adults: A Growing, Costly Problem

Every year, a growing number of senior citizens throughout the United States are negatively impacted by the life-altering, catastrophic effects of falls. Indeed, more than one out of four Americans over the age of 65 experience a fall annually.[1] According to Centers for Disease Control (CDC) data, this ultimately results to over 30 million falls, seven million injuries, three million emergency room visits, 800,000 hospitalizations, and 38,000 deaths each year. [1-3] The incidence of falls continues to escalate as the number of baby boomers advance in age. Additionally, falls place a costly economic burden on our health care system and society at large. A study conducted by the CDC in 2018 reported the direct medical costs for falls are approximately $50 billion annually, including $28.9 billion paid by Medicare, $8.7 billion paid by Medicaid, and $12 billion paid by private insurance and other payers. This collective figure is projected to rise to $100 billion annually by 2030.[4-7] In 1950, one in twelve Americans were aged 65 or older. By 2000, that proportion had grown to one in eight, and it is projected to increase to one in every five, or an estimated 88.5 million senior citizens, by 2050.[8,9]

To address falls in older adults at the state level, public health departments have made a strategic and concerted effort to quantify the magnitude of the problem and have launched a variety of initiatives to prevent falls. Each year in Missouri, the percentage of older adults that sustain a fall was roughly in-line with the national average at an estimated 27.3%.[10] Fall-related mortality in Missouri was greatly over-represented among the elderly, with 86% of fall-related deaths occurring in those over the age of 65.[2,5] To tackle this problem, the Missouri Chapter of AARP (American Association of Retired Persons), in conjunction with the Missouri Department of Health and Senior Services initiated Show Me Falls Free Missouri Coalition in late 2007.[11] This group has grown to form a coalition of over 50 stakeholder organizations seeking to provide the community with resources on fall prevention strategies.

Table 1 – Intrinsic Factors of Falling.

I. Deconditioning
- Physical inactivity
- Diminished aerobic function
- Myopathy
- Obesity

II. Sensory deficits
- Decreased visual acuity/depth perception
- Non-modifiable visual deficits
- Proprioceptive deficits
- Hearing deficits

III. Inherent
- Female gender
- Age
- Prior fall history

IV. Neurological/Neuromuscular
- Changes in gait, including reduced arm swing, decreased step length, slowed reaction time, slower movements
- Parkinson's disease (rigidity, bradykinesia and inability to correct perturbations in balance quickly)
- Stroke (visuospatial defects, impaired peripheral sensation, cerebellar dysfunction, muscle weakness, etc.)
- Normal pressure hydrocephalus
- Tremors/movement disorders
- Vertebrobasilar insufficiency
- Cerebellar dysfunction
- Vertigo
- Cognitive impairment (e.g. delirium, dementia)
- Spasticity/contractures
- Impulsivity
- Depression/anxiety/psychosis

V. Musculoskeletal
- Foot disorders
- Amputation
- Osteoarthritis/rheumatoid arthritis
- Post-orthopedic surgery

VI. Cardiovascular
- Syncope
- Orthostasis/dehydration
- Congestive heart failure
- PAD/intermittent claudication

VII. Nutritional
- Hypovitaminosis D
- B12/folate deficiency

VIII. Endocrine
- Thyroid disease
- Diabetes/insulin use

IX. Medication or Substance Use
- Polypharmacy
- Drug interactions resulting in dizziness, confusion/impaired judgement, weakness/impaired gait, sedation/slowed reaction time
- Alcohol/drug use

X. Other medical
- Incontinence
- Infection

Missed Opportunities: Identifying Patients at Risk

Physicians, particularly primary care physicians (PCPs), are optimally positioned to play a much more decisive role in mitigating fall risk through managing underlying risk factors. There are, however, several limiting dynamics that are oppositional to this idealized standard of care. Quite frequently, falls experienced by senior adults go unreported by the patient to their physician. This reporting oversight is commonplace and secondary to numerous factors, including personal embarrassment on the part of the patient, the patient not believing the fall (or near-miss) was worth mentioning to their PCP since no major injury was sustained, fear of repercussion (e.g. the patient may fear that the next step is the nursing home), or because the patient forgot the fall took place due to underlying cognitive deficits. In addition, fall risk assessment is often neglected in clinical practice due to the limited amount of time allotted to each patient visit and the fact that other competing priorities will always take precedent.

Given these barriers, a validated, systematic method of screening elderly patients for increased fall risk should be adopted and implemented in appropriate clinical settings to successfully identify

non-reporters. The Centers for Disease Control (CDC) has recommended the use of their published Stay Independent brochure, which is a quick and thorough risk assessment tool developed by the Los Angeles VA Geriatric Research Education Clinical Center.[11] This brochure provides a 12-point checklist with a weighted-scoring system whereby patients who score 4 or higher are identified as being at increased risk for falling and should therefore undergo further evaluation with more aggressive risk management. Patients who are identified as having a low fall risk (i.e. scores <4) may still benefit from basic individualized education with an emphasis on primary prevention including education regarding fall risk factors, strengthening and balance exercises, and vitamin D supplementation.

Table 2 – Extrinsic Factors of Falling.

I. Home conditions
- Environmental lighting
- Area rugs/floor runners/loose mats
- Wet floors
- Hard-to-reach personal items
- Toilet proximity to bedroom
- Low toilet seat
- Lack of handrail/grab bar supports in the bathroom
- Bed height and bed firmness
- Room/walkways free of cords and clutter
- Access to items in the kitchen
- Pets
- Unsafe shoes or slippers
- Hard-to-manage clothing
- Walk-in shower vs tub-shower combo
- Stairs vs home access ramp
- Steps inside the home vs home lift
- Flooring (slip vs non-slip)
- Exercise/diet

II. Requirement of Durable Medical Equipment
- Assistive devices (e.g. canes, walkers, wheelchairs)
- Prosthetic devices
- Incorrect wheelchair fit/inadequate wheelchair seating/broken or missing parts

III. Hospital conditions
- High patient-to-staff ratios in hospitals, rehabilitation facilities, skilled nursing facilities, and long-term care facilities
- New/novice staff
- Access to the call light
- Presence of grab bars

Root Cause Analysis of Falls

It is important to recognize that falls in the elderly rarely have a single, unifying cause. Rather, they are the result of a complex interplay of intrinsic and extrinsic risk factors as seen in Tables 1 and 2. Intrinsic risk factors are quite varied. While some elements are non-modifiable (e.g. age, gender, and prior history of falls), others can be easily changed (e.g. physical inactivity/disability, incontinence, and polypharmacy). Extrinsic risk factors that result in falls are much more amenable to modification and include elements such as environmental lighting, use of assistive devices, footwear, etc. Patients are often quick to attribute falls to underlying environmental causes (e.g. slipped on a wet floor or tripped over a pet or object) and/or social factors (e.g. being in a hurry or not paying attention). However, they fail to recognize the significant role played by intrinsic elements, where physicians can have their greatest impact. Thus, the ability to recognize and calculate the vast array of risk factors is paramount with respect to addressing the high morbidity and mortality associated with falls in the elderly.

A Comprehensive History Assessment for Increased Fall Risk

Falls, especially among the elderly, are often underreported. There are multiple explanations for this phenomenon as discussed previously.

To obtain useful information and guide further management and treatment with respect to falls in older adults, care providers should ask additional questions during the historical interview. Clinicians should investigate the cause or etiology of the fall with a goal towards prevention, which can be elucidated through an assessment of risk factors. Asking a patient about their previous fall history can help provide valuable information. If two or more falls have occurred within the past 12 months, the patient should have a comprehensive fall risk assessment. A previous history of falls can lead to a fear of falling, which is associated with

a higher risk of falls.[12] Knowing whether they live at a facility or living at home can help ascertain the level of supervision that is currently assigned to the patient, and may indicate the need for a higher level of care.

The patient's symptoms prior to the fall can help determine the etiology of the fall. "Dizziness" with "lightheadedness" can be indicative of orthostatic hypotension, which is most often due to dehydration, but could also be a sign of autonomic instability. If a patient reports being "off-balanced" or that they lean more to one side can indicate disequilibrium. Feeling like "the room is spinning" could indicate possible disorders of the inner ear (such as labyrinthitis or benign paroxysmal positional vertigo) but could also be the result of central causes, such as a vertebrobasilar stroke. Loss of consciousness can point to the need for further examination of neurologic or cardiac causes. Cardiac causes are associated with a higher risk of mortality.[13]

The location of the fall is an important factor within the fall risk assessment. Location can signal environmental factors and challenges, including lighting, flooring, throw rugs or carpets, door-to-flooring thresholds, railings, and the presence of gravel or uneven ground outside of the home, which can all contribute to poor footing and increased likelihood of falls. One Australian study found when the faller is walking, the highest rate of falls is caused by slipping on an uneven or slippery surface (29%), followed by tripping over an obstacle, such as shoes, steps, road gutters, or pets (27%).[14] A home evaluation may be warranted to further improve the patient's living situation.

Falls can be more common at certain times of the day for many reasons, such as medication effects that accumulate throughout the day (e.g. antihypertensive use at night as opposed to earlier in the day, or improper insulin management resulting in hypoglycemia and an increased chance of falls).[15]

Medication changes can significantly impact fall risk. If a patient has recently changed their anti-hypertensive or anti-hyperglycemic regimen, or recently taken another medication that can increase somnolence and/or decrease orientation (medications on the Beer's criteria), their risk of falling could increase. Polypharmacy can also increase fall risk and lead to a myriad of other adverse effects.[16]

Healthcare providers should also inquire about the type of mobility or assistive devices used by their patients. A patient's assistive device might not be appropriate for their current level of mobility, which would require further assessment. The current state of the assistive device should also be assessed, as it may need repair or replacement and could pose an additional fall risk if not addressed. Patients may also require further training for their given assistive device to ensure they can use it safely.

It can be helpful to question certain patients, especially those with foot deformities, such as diabetic patients with Charcot foot, about their footwear and other orthoses. Certain orthoses such as slip-resistant soles, shoes with a low heel height, beveled heels, fastening mechanisms, and supported heel collars can play an important role in fall prevention.

Depression can alter gait through its effect on concentration and attention, which can in turn increase the risk of falling.[17] However, conservative, non-pharmacologic measures with neuropsychology should be maximized prior to initiation of anti-depressants, as certain anti-depressants can increase the likelihood of falls.

The Physical Exam and Gait Assessment of Elderly Patients

A person's gait is a significant contributing factor to their fall risk and overall instability. However, before completing a gait assessment, it is important to evaluate other urgent etiologies, such as autonomic or cardiovascular instability. Vestibular dysfunction can also be monitored when vertiginous symptoms are involved, especially when these symptoms are associated with rapid positional changes. Once these factors have been thoroughly investigated, clinical providers should conduct a comprehensive gait assessment.

One test that can be performed in the office is the "Get-Up-and-Go Test." As an added benefit, this test does not require extensive training and can be performed with minimal materials. In this test, the individual is asked to stand up from a chair, walk three meters, turn around, walk back to the chair, and sit down without using their upper extremities. This test can grade muscle weakness, balance issues, and gait abnormalities (on a scale of 1 to 5, with 5 indicating severe impairment). If a patient must use their upper extremities to stand, they might be experiencing hip extensor weakness. This test can also be timed. If the patient is unable to complete the test within 12 seconds, they are at an increased risk of falling. Incorporating the time component tests gait velocity, which also plays an important role in fall risk.[18] A printable document is available through the CDC 's Stopping Elderly Accidents, Deaths, and Injuries (STEADI) program for ease of use in a clinical setting.[19]

The 30-Second Chair Stand Test also assesses both strength and balance. Patients are asked to cross their arms over their chest while seated in a chair. If the patient requires the use of their arms to stand, hip extensor

Table 3 – Gait Patterns		
Gait Type	Physical Gait Description	Muscles/Structures Affected
Antalgic	Limited weightbearing through painful lower extremity	Dependent upon site of injury
Steppage	Increased hip flexion for clearance of weakened ankle dorsiflexion	Ankle dorsiflexors (anterior tibialis)
Trendelenberg	Shift in weight over weakened hip	Hip abductors (gluteus medius, gluteus minimus)

weakness could be the cause. This test evaluates the patient's balance and strength, especially with respect to their hip flexors and extensors. The provider should record how many times the patient can fully stand and sit within a 30-second time interval. This test can also assess a patient's strength with transfers with the up and down movements out of the chair. For patients who are between 75-79 years of age, <11 stands within men and <10 stands within women is considered to represent an increased fall risk. A printable document is also available as part of the STEADI program from the CDC, and has grading guidelines scaled to the patient's age.[20]

A third test is the 4-Stage Balance Test, where patients are asked to stand for at least 10 seconds in the following positions: feet adjacent, semi-tandem stance, tandem stand, and on one foot. Patients unable to perform the semi-tandem test for at least 10 seconds are at an increased risk of falling. Other tests, including the Functional Reach test, Berg Balance Test, and Performance-Oriented Mobility Assessment are not commonly used in the clinic, but are utilized in research studies to better quantify neuromuscular support. Impaired performance on these tests has been linked with a higher fall risk in the elderly as well.[21, 22]

Screening tools are available, including the Morse Fall Scale and the St. Thomas' Risk Assessment Tool. The Morse Fall Scale has been shown to be useful in studies for assessing fall risk.[23] The Morse Fall Scale is composed of six items, namely a history of falling within the past three months, the presence of a secondary diagnosis, the use of an ambulatory aid, the requirement of IV therapy, an abnormal gait, and an impaired mental status. Scores range from 0 to 125. Patients who score above 45 have a higher risk of falling, with higher scores indicating an even higher risk. Another screening tool is St. Thomas's Risk Assessment Tool, or STRATIFY. A caveat with STRATIFY is that one study found it could predict fall risk in those under the age of 75, however, was unable to predict fall risk in people over the age of 75 when administered at the hospital bedside.[24] One systematic meta-analysis recommended that STRATIFY not be used in isolation, but pointed out that it could be helpful when used in conjunction with other testing.[25]

Gait patterns, with appropriate assistance either by device or staff, can help ascertain specific compensatory strategies, as seen in Table 3. Spasticity can cause leg circumduction and rigid, fixed deformities (such as equinovarus, which can be due to rigid spasticity, particularly within the posterior tibialis, lateral and medial gastrocnemius, and soleus). Patients with amputations can also exhibit an altered gait depending on the level of their amputation as well as their prosthetic device. The provider should also assess whether or not the prosthetic is properly fitted to the patient and ensure that there are no signs of skin breakdown at the amputation site. If the provider is comfortable with the design of the prosthetic, all parts of the prosthetic should be carefully inspected and monitored to ensure they are in proper working order. Should any questions arise, consultation to a physiatrist with a regular practice in lower-extremity prosthetics and gait pattern analysis as well as a prosthetist/orthotist is warranted. Another cause of an altered gait pattern is cerebellar ataxia, which can increase truncal sway to the extent that the patient requires a broad base of support when moving. Parkinsonism can lead to a shuffling gait with reduced arm swing. A significant amount of research has been conducted on freezing of gait (FOG), commonly found in parkinsonian syndromes, to better understand its underlying pathophysiology and better determine its diagnosis. Currently, certain medications have been shown to help with FOG but should be studied further.[26]

Laboratory and Diagnostic Testing: Focusing on Physiologic Determinants of Falls

To further evaluate an elderly patient who has experienced a fall, certain laboratory and diagnostic testing may be required to confirm the etiologies, especially reversible causes. Many of these reversible causes can affect the patient's mental status. These tests include

a metabolic panel for renal function assessment with serum sodium, BUN, and creatinine and a diabetic status test with glucose and hemoglobin A1c for longer glucose management assessment. A complete blood count for hemoglobin assessment for anemia can also be helpful. Further cardiovascular testing and assessment includes an echocardiogram to investigate any suspected valvular conditions with or without a bubble study to monitor for shunts as well as a Holter monitor in those with suspected paroxysmal arrhythmias. When clinically appropriate, dual-energy X-ray absorptiometry (DEXA) scans are important to further assess for bone density, especially in patients who are particularly at risk for osteoporosis. In the event of a fall, osteoporotic fragility fractures could result in long-term debility.

Falls have been an ongoing source of morbidity and mortality, especially in senior adults. As advocates of public health, there are a multitude of interventions physicians can provide to prevent falls, not only pharmacologically but also through risk identification and stratification as well as environmental modification. The follow up to this Feature Review will provide further information on treatment plans and therapy to reduce falls in senior adults.

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Disclosure

None reported. **MM**

Ketamine Infusions Administered Solely by Psychiatric Staff

by Muaid Ithman, MD, Robert Sobule PA-C, Carolyn Kundert, PA-C, Austin Campbell, Pharm D & Elizabeth Ehrhardt, MPH

Health Care

In view of the recent research on ketamine's favorable impact on mental health and the early success of the MUPC ketamine infusion team, there is a need for further research on implementing novel treatments in the psychiatric inpatient setting.





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Abstract

Even though intravenous ketamine is not an FDA-approved depression treatment, multiple studies have shown a robust antidepressant effect which has led to an increase in clinical practices implementing its use to manage treatment-resistant depression. Traditionally, this therapy has been provided in both outpatient and inpatient settings, with anesthesia specialists and psychiatrists working collaboratively on most cases. Several studies have been conducted in various psychiatric settings to study the effects of ketamine in depression, mostly in a collaborative manner. Thorough search of the literature found no published reports on the use of ketamine infusions merely for clinical purposes in a psychiatric hospital setting, implemented solely by a psychiatric-based team without collaboration from anesthesia specialists. In an effort to explore the utilization of ketamine infusions, the Missouri University Psychiatric Center (MUPC), an acute mental inpatient facility, formed a ketamine infusion team composed solely of mental health clinicians and staff to investigate the use of ketamine infusions by a psychiatric team. To our knowledge, this is the first-time ketamine infusions have been administered by a clinically based psychiatric team in a psychiatric hospital. The MUPC ketamine team has proved that ketamine infusions may provide a unique intervention safely and efficaciously without the need for collaboration with other medical specialties since initiating this pilot program.

Introduction

Ketamine is an intravenous anesthetic that has acquired acceptance as an off-label treatment for acute suicidality and treatment-resistant depression in both inpatient and outpatient settings. Ketamine, as compared to conventional antidepressants, is a quick acting agent for mood improvement in critically ill patients. With this in mind, in an effort to expand treatment options available to inpatient psychiatric teams, MUPC developed a pilot study psychiatric ketamine infusion team to evaluate utilization of ketamine infusions in the acute psychiatric hospital setting. Since implementation in 2018, the team has safely and efficiently administered over 80 infusions to severely ill patients without the assistance of other medical disciplines, with excellent results.

Ketamine's Utility in Psychiatry

Ketamine is a glutamate N-methyl-D-aspartate (NMDA) antagonist derived from phencyclidine (PCP) that has fewer negative effects and a lower potential for addiction.[1] It is a mild anesthetic with little effect on respiratory function.[2,3] Ketamine can induce an increase in blood pressure, heart rate, and cardiac output, as well as cause sensory changes, a decrease in mental sharpness, dissociation and memory problems.[1,3] Ketamine's antagonistic effect on NMDA receptors has been shown to have antidepressant effects in animal models.[4] In multiple investigations involving persons with both unipolar and bipolar depression, ketamine has shown to ameliorate depressive symptoms, notably suicidal ideation.[5,6]

The ketamine infusion team at MUPC consists of an attending psychiatrist, a psychiatric physician assistant (PA), a board-certified psychiatric pharmacist, and a mental health registered nurse (Figure 1). A strategy for adequate physical and mental health screening, inclusion and exclusion criteria, dosing, and patient monitoring for the procedure was devised in collaboration with an inpatient psychiatrist, the hospital pharmacy, and patient safety officials. To ensure therapy appropriateness, an attending psychiatrist must evaluate the patient and assess the severity of depression with either the Patient Health Questionnaire (PHQ-9) or Quick Inventory of Depressive Symptomology (QIDS) and perform a cognitive assessment using the Mini-Mental Status Examination (MMSE) prior to treatment. A urine drug screen and pregnancy test (if necessary) are also performed.

The attending psychiatrist or PA prescribed each patient a series of two or three infusions, separated by at least 48 hours, with a target dose of 0.5 mg/kg to be administered over 40 minutes. Infusions are given in a private room with blood pressure, heart rate, cardiac rhythm, respiratory rate, and oxygen saturation monitored at regular intervals throughout the treatment.



Figure 1. MUPC ketamine infusion team of all psychiatric staff (left to right): Muaid Ithman MD, Carolyn Kundert PA-C CAQ-Psychiatry, Michelle Jelinek RN, Robert Sobule PA-C CAQ-Psychiatry, Austin Campbell Pharm D BCPP.

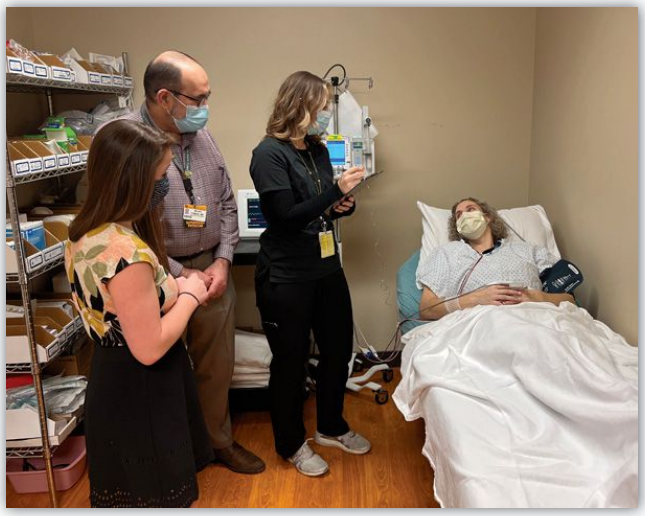


Figure 2. Between 2018 and 2021, the MUPC all psychiatric team successfully and safely delivered more than 80 ketamine infusions. No other medical specialists were present.

Efficacy of Treatment

Between 2018 and 2021, the team delivered more than 80 infusions (Figure 2). Treatment outcomes were favorable in terms of improved mood, decreased suicidal thoughts, patient tolerability, and minimal adverse effects (Table 1). The majority of individuals responded positively to the treatment, with considerable improvements in their depressive symptoms. The procedure has been well tolerated, with no patients requiring premature discontinuation of therapy. The most prevalent adverse effect was dissociation, which was addressed with a brief halt in infusion and, at times, intravenous lorazepam delivery. Other reported side effects included nausea and/or vomiting, excessive exhilaration, sedation, and an elevation in blood pressure. There were no major

Table 1. MUPC IV Ketamine Infusion Data	
Total Patients	32
Male	15
Female	17
Dosing	0.5mg/kg adjusted body weight infused over 40 minutes
Average Baseline Depression Screening (PHQ9 or QIDS)*	20.8
Average Baseline Follow Up Screening (PHQ9 or QIDS)*	7.5
Average Change in Screening Score (PHQ9 or QIDS)*	-14.1
% Change from Baseline in Screening Score (PHQ9 or QIDS)*	65.5%
Adverse Events Documented	Dissociation 5(15.6%); Nausea/Vomiting 3(9%); Extreme Euphoria 2(6%); Sedation 1(3%); BP Increase 1(3%)
* Confounders affecting accuracy of data collected. When ketamine trials began, screening questionnaires varied between patients and not all patients participated on follow up screening. The QIDS and PHQ9 questionnaires are comparable but not interchangeable.	

adverse effects that necessitated immediate life-saving measures. The data sample set revealed a 65.5 percent reduction from baseline of depressed symptoms. It should be emphasized that there were some differences in the depressed screening process, with some patients receiving the QIDS and others receiving the PHQ9. The two screenings are comparable but not interchangeable. The lack of follow-up screening after discharge complicates the analysis even more. To increase data accuracy, all patients are assessed simply with the PHQ-9 prior to infusion and again two weeks later (contacted via telephone by RN if discharged).

Conclusion

In view of the recent research on ketamine's favorable impact on mental health and the early success of the MUPC ketamine infusion team, further research on ketamine's utility in psychiatry is warranted. Results from this MUPC study, with particular respect to the robust effect and relative safety profile, indicate that intravenous ketamine can be used in an inpatient psychiatric setting under the supervision of a psychiatric team without the involvement of another specialty. This approach lays the groundwork for ongoing research into various intravenous drugs that psychiatric units can use to broaden and develop treatment modalities.

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MM

Food and Nutrition Security in Clinical Settings

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Food insecurity is a social determinant of health that has one of the largest impacts on individuals' overall health.



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Abstract

Food insecurity affects fourteen million American households. Due to the impact on health outcomes and costs of care, food insecurity is one of the leading health and nutrition issues in the U.S. In this article, we provide an overview of food and nutrition insecurity and how it is measured, followed by health consequences of food insecurity, and then discuss ways that physicians and health professionals can help address food and nutrition security in clinical setting.

Introduction

The relationship between food and health has been recognized for over 2,000 years, at least since the time of the ancient Greeks, including Hippocrates. The popular phrase ascribed to Hippocrates (400BC) "let thy food be thy medicine and medicine by thy food" is used to emphasize the importance of nutrition to prevent and cure disease, which includes access to food. Lack of access to nutritious food, referred to as food and nutrition insecurity, is still very relevant today due to the impact on health outcomes in chronic disease and costs of care. In 2019, almost 14 million households in the U.S. (10.5%) were food insecure.[1] Among those, more than five million households were at a more serious level known as very low food insecurity.[1]

Among various social determinants of health, food insecurity has one of the largest impacts on individuals' overall health. It can have significant short- and long-term consequences, such as malnutrition, obesity, and chronic diseases. Individuals who report being food insecure are at higher risk of developing obesity, diabetes, hypertension, cardiovascular disease, stroke, cancer, and associated conditions. The burden of food insecurity is not borne equally across all populations. Within the U.S. population, food insecurity is more likely to occur in households with income near or below the federal poverty line, low education levels (less than high school), in households with children, and in Black and Hispanic households.[1]

Individuals with food insecurity experience higher health care costs than food secure individuals. In the U.S., annual health care expenditures of adults with food insecurity were almost $2,000 higher than the costs of food secure adults.[2] For older adults, on average, food insecurity adds approximately 11% to the health care costs, with or without a specific chronic condition.[3] In addition, food insecurity has been associated with delaying medical care, the timely and adequate intake of medications, and higher levels of service use such as emergency department visits and hospitalizations.[4] It is therefore important for health professionals

to understand negative health and nutrition outcomes resulting from food insecurity and the challenges experienced by food insecure individuals, in order to become more sensitive to patients' needs and adapt the treatment and services accordingly.

Food and Nutrition Security

The Food and Agriculture Organization (FAO) defines food security as "when all people, at all times, have physical, social, and economic access to sufficient, safe and nutritious food that meets their dietary needs and food preferences for an active and healthy life".[5] In the contrast, a person is food insecure when they lack regular access to enough safe and nutritious foods for normal growth and development and an active and healthy life. This definition is the current widely accepted definition of food security and embraces both food security and nutrition security, which emphasizes access, availability and affordability of nutritious foods, coupled with a sanitary environment and adequate health services and care to promote well-being, prevent or treat disease, not just foods that provide calories.

Based on this definition from FAO, food security comprises four key elements: availability, accessibility, utilization, and stability. Availability refers to the physical existence of food, which includes food production, commercial food imports and exports, food aid, and domestic food stocks. Food access is ensured when all households have enough resources to obtain food in sufficient quantity, quality, and diversity for a nutritious diet. In other words, it depends on whether consumers have adequate resources to purchase the food they require, which depends upon factors such as household income, food prices, employment opportunity and working resources. Adequate food supply does not guarantee food security at the household or individual level because lack of access to food is often more problematic than availability. Utilization refers to the capacity of the human body to absorb or utilize safe and nutritious food, which depends on the quantity, quality, and diversity of food consumed as well as adequate health care and sanitation services. Food utilization also includes good practices on food processing, storage, preparation, and distribution. Finally, stability is linked to the vulnerability context and risk factors that can negatively impact food availability or accessibility. It is given when food supply remains constant during the year or in the long-term and households have income and economic resources to purchase the food they require. To achieve food security, all four elements must be fulfilled simultaneously.

Food security also cannot be achieved without nutrition security, and vice versa. Sound nutrition requires not only enough energy for everyone, but also a diversity of macronutrients and micronutrients to ensure good health and prevention from diseases. On the other hand, food insecurity can be linked with nutrition security, as food insecure households may sacrifice food quality or variety in favor of food quantity, such as consuming low-cost, energy-dense foods in substitution of nutrient-dense foods.[6] This results in nutrition insecurity in presence of excess calories and lack of essential nutrients. It has been recommended by experts to use the term "food and nutrition security" which embraces both concepts to emphasize the food and health requirements for individuals.[7] In this paper, the term "food insecurity" that we use in our discussion below refers to both food and nutrition security.

Food Insecurity, Health, and Nutrition Outcomes

Dietary Behaviors and Overweight/Obesity

Several studies have shown that food insecure individuals have lower nutrient intakes, and diet quality while having increased fat and sugar intakes. For example, American adults experiencing food insecurity eat fewer vegetables, fruit, and dairy products and have lower intake of vitamins A and B6, calcium, magnesium, and zinc.[8] Among children, an adverse association between food insecurity and fruit consumption was consistently observed.[8] In addition, food insecure children consume more cheaper foods with high fat or sugar, compared to food secure children.[9] Quality of diet is also reported to be low among young adult population. For example, food insecure college students have significantly lower intakes of fruit, vegetables, and fiber while having higher intake of total added sugar than food secure students.[10]

A reason to explain the relationship between food insecurity and poor quality diet is that healthy food is perceived to be higher cost whereas refined grains, added sugars, and fats are generally inexpensive, palatable, and readily available in low-income communities.[11,12] Food insecure households and individuals often try to stretch their food budgets by purchasing cheap, energy-dense foods, which typically have lower nutritional quality.[13] Moreover, low-income communities may be limited to shopping at small

neighborhood convenience and corner stores where fresh produce and low-fat products are limited; whereas fast food restaurants, which serve many energy-dense, nutrient poor foods at relatively low costs, are largely available in these communities.[14-16] In addition, healthy food, especially fresh fruits and vegetables when available in low-income neighborhoods, was often of poorer quality and was not appealing to customers.[17] Thus, individuals in these neighborhoods were less likely to buy the healthier food.

As a consequence of poor-quality diet, overweight and/or obesity is prevalent among food insecure individuals. In fact, researchers have demonstrated the coexistence of food insecurity and obesity in the same individual, family, or community. One in three American adults with food insecurity are obese, especially among women.[18] For children, research studies show mixed results about the association between food insecurity and obesity. For example, a review of 20 cross-sectional and longitudinal studies was conducted to examine the relationship between food security and weight status among children and adolescents in the U.S.[19] Findings of this review showed that majority of the studies (nine out of 20 studies) included in the review did not show significant association, while six studies showed more weight gain and higher body mass index among food-insecure children. A small number of studies in this review (n = 5) even suggested that food-insecure children were less likely to have obesity compared to food-secure peers. Additional studies are encouraged to fully understand the relationship between food insecurity and weight gain and obesity among children.

Food Insecurity and Chronic Diseases

Research has demonstrated that individuals with low and very low food security are more likely to have chronic diseases and conditions, such as diabetes and high blood pressure. For instance, the prevalence of diabetes mellitus among American adults with low and very low food security is approximately two times higher than the rate among food secure adults.[20] In addition, individuals with food insecurity are two times more likely to have higher diastolic blood pressure, compared to those without food insecurity.[20] Older adults experiencing food insecurity are more likely to have multiple chronic conditions, including asthma, chronic bronchitis or COPD, chronic pain, diabetes, kidney disease, and a sleep disorder than food secure counterparts.[20] The association between food insecurity and multiple chronic conditions among these older adults was significant even after adjusting for educational level, household income, employment status, and other socio-demographic factors.[21]

Among children, food insecurity might negatively affect their acute and chronic health conditions in both direct and indirect ways. As mentioned previously, food insecure individuals and households are likely to have poor diets or disrupted eating patterns, which may lead to poor weight outcomes and increased risk of chronic conditions, such as diabetes and heart diseases.[22,23] Moreover, children living in food-insecure households are at higher risk for mental stress and depression, which might impact immune functioning, thus leading to more acute and chronic health conditions.[24] An analysis of data from the 2007-2014 National Health and Nutrition Examination Survey (NHANES) showed that children and adolescents living in food insecure households had 1.26 times higher risk of having high blood pressure than those who are food secure.[25] Assistance programs and policies are needed to address food insecurity among children and adults to protect health and prevent health issues and diseases.

Supporting Food Insecure Patients in Clinical Settings

Physicians and other health professionals can help improve the health and nutritional status of patients who experience food insecurity, by applying the SEARCH mnemonic (Screen, Educate, Adjust, Recognize, Connect, and Help).[26]

Screen

Screening for food insecurity among patients helps health professionals improve patient care and develop approaches to support patients manage their conditions well. Screening for food insecurity in health care setting is highly accepted among patients. For example, most patients (~84%) in a study reported high levels of acceptability about food insecurity screening and stated that it was valuable in the primary care setting.[26] However, few physician practices and hospitals screen for food insecurity. In a cross-sectional study with approximately 3,000 physician practices and hospitals in the U.S., Fraze and colleagues found that the majority of the physician practices and hospitals (70.4%) did not report screening patients for food insecurity.[27]

The USDA developed an 18-item survey to measure food insecurity during the previous 12



New situations may arise and affect food security, such as loss of employment or the current coronavirus pandemic that affect income and food access.

months.[28] Even though the 18-item survey was preferred to screen for food insecurity, a two-item screening tool was used to quickly assess food security status.[29] Individuals have food insecurity if they answer "often true" or "sometimes true" to either of the two following statements: 1) Within the past 12 months, I/we worried whether my/our food would run out before I/we got money to buy more; 2) within the past 12 months, the food I/we bought just didn't last and I/we didn't have money to get more. Patients should be screened for food security during the intake process so that health professionals and physicians can tailor their treatment to improve the health of patients.

Education

Food insecure individuals and households used several ways to cope with their food insecurity. Many food insecure individuals used food-based coping strategies, such as eating less preferred foods or cutting down portion size, stretching or diluting food and beverages, fasting or skipping meals, eating excessive amounts of high-calorie foods when food is available.[30,31] In addition to food-based strategies, individuals and families utilize money-saving and trade-off techniques to cope with their food insecurity situation. These techniques include purchasing only very basic necessities, forgoing purchases of clothes and shoes, not going out for entertainment, dispensing with phone services, using less electricity for light and air conditioning, and cutting down on food consumption.[6] Some families receive donations such as non-perishable foods, clothing, and monetary assistance from relatives and community organizations.[6] Moreover, approximately one in three food insecure individuals are often faced with a difficult choice to pay for food or medication; they often skip food for medications or deny to purchase/refill medications to be able to buy foods.[32] This strategy greatly challenges the success of chronic disease management.

Understanding strategies used by food insecure patients help clinicians in educating the patients on appropriate coping strategies. However, in clinical setting, much of the counseling on dietary changes is to increase healthy and nutrient-dense foods like fresh fruit and vegetables, which is implausible as these foods are the least affordable foods for patients with food insecurity.[33] Instead, providers should counsel patients to eat healthy foods on a limited budget and learn portion sizes like minimizing large amounts of energy-dense foods in favor of smaller portions of nutrient-

dense foods. For patients with diabetes, it is important that physicians teach the patients mindful eating, avoid eating excessive amounts of foods when food is available and then prolonged fasting because this behavior can cause hyper- or hypo-glycemia.[34] For patients with hypertension, physicians should educate about sodium restriction because sodium is often high in prepacked food or low-cost fast foods. In addition, physicians and other health professionals can educate and help engage the patients to state and local benefit programs to help reduce the burden of food insecurity and their competing choices between foods and medications or treatment.

Adjust

Identifying patients with food insecurity helps physicians adjust the patients' use of medication if it should be taken with food. For example, as food insecure patients are likely to skip meals, physicians can prescribe medications that are less likely to cause hypoglycemia, such as metformin, and schedule medication taking with meals instead of time of day.[34] In addition, physicians can teach patients to alter medications when dietary intake is low or absent.[35] Prescribing medications that are effective yet affordable is of the essence for food insecure patients.

Recognize

Physicians need to understand that food insecurity is a recurrent condition – it can be long term or temporary;[36] therefore, patients should be screened at every visit to help ensure appropriate evaluation of food insecurity. New situations may arise, such as loss of employment or the current coronavirus pandemic that affect income and food access. In addition, screening for food insecurity and recording into the medical record would enable physicians and other health professionals to address food insecurity as an ongoing issue in medical care.

Connect

Connect patients with healthy food access by referring resources that are available in the clinic, community, or federal assistance programs. These resources might include:

- Local food banks and food pantries
- Social assistance programs: Supplemental Nutrition Assistance Program (SNAP); Temporary Assistance for Needy Families (TANF); Women, Infants, and Children (WIC)
- Home-delivered meals: Meals on Wheels
- Organizations providing free or low-cost meals and other supplemental food programs: summer, afterschool, and weekend meal and supplemental food programs
- Find Food Support site (https://findfoodsupport.withgoogle.com/) includes a Google Maps locator for finding the nearest food bank, food pantry or school lunch program pickup site. The site also includes a SNAP benefits search feature that provides information on national and state eligibility requirements and additional food support resources for specific populations, such as seniors, families with children, and military families.

Connecting patients with these programs and resources not only enables food access but also help patients reduce their competing choices between foods and medications or treatment. To make it sustainable, hospitals should develop an accessible and reliable database of the local resources to share with their patients.

Help

Many health professionals perceived food insecurity as "normal" for some patients and not something they need to change their clinical practice to address.[37] They are also uncertain to raise the food insecurity issue with their patients due to the fear of offense. This suggests a need for support to help health professionals recognize the relationship between poor health and food insecurity and better understand the challenges of food insecurity experienced by their patients, especially those with long-term health conditions. Programs for research and development should also be implemented to ensure health systems foster good professional practice in food insecurity area.

Conclusion

Food insecurity is a social determinant of health that has one of the largest impacts on individuals' overall health. It affects one in 10 American households and should be considered in any population health strategy and in treating individuals with chronic disease. Health professionals need to understand the relationship between food insecurity and poor health outcomes and the challenges experienced by food insecure individuals. This helps health professionals become more sensitive to patients' needs and adapt the treatment and services accordingly, in order to improve the control and management of health conditions of

patients. This relationship between food and health was recognized in the ancient practice of medicine and is still just as true and relevant in modern medicine.

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