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Since 1903, the *Wisconsin Medical Journal*—*WMJ* (ISSN 2379-3961)—has served as a forum for professional communication and continuing education for physicians and other health professionals. This tradition continues today, but with a broader focus that extends across the country and even around the world.

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COVER ART

Blooming Perspectives

Toan Vu

Acrylic Painting on Canvas

Artist Statement:

This acrylic painting on canvas reflects the dynamic, rich, and interconnected environment of medical education and medicine. With shared learning and open communication, collaboration between health care professionals creates a more effective health care team. Through a collaborative and interprofessional approach to medical education and medicine, many unique backgrounds, perspectives, and experiences can come together to create the "garden" of health care.

See page 204 for information about the artist.

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The mission of *WMJ* is to provide an opportunity to publish original research, case reports, review articles, and essays about current medical and public health issues. *WMJ* is published through a partnership between the Medical College of Wisconsin and the University of Wisconsin School of Medicine and Public Health.

EDITORIAL

ORIGINAL RESEARCH

The *WMJ* (ISSN 1098-1861) is published by the Medical College of Wisconsin and the University of Wisconsin School of Medicine and Public Health and is devoted to the interests of the medical profession and health care in the Midwest. The managing editor is responsible for overseeing the production, business operation and contents of the *WMJ.* The editorial board, chaired by the medical editor, solicits and peer reviews all scientific articles; it does not screen public health, socioeconomic, or organizational articles. All articles and artwork published herein, including commentaries, letters to the editor, and editorials represent the views of the authors, for which neither *WMJ* nor the publisher take responsibility, unless clearly stated. Advertising content is the responsibility of the advertiser and does not imply an endorsement or sponsorship by *WMJ* or the publsiher and its affiliates unless specified. *WMJ* is indexed in Index Medicus, Hospital Literature Index, and Cambridge Scientific Abstracts.

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Published 6 times a year, beginning in April

BRIEF REPORTS

CASE REPORTS

LIMITED SERIES

Fahad Aziz, MD, FASN

Cultivating the Next Generation of Physician-Scholars

Fahad Aziz, MD, FASN, *WMJ* Editor-in-Chief

Since its founding in 1903 by the Wisconsin Medical Society, the *Wisconsin Medical Journal* (*WMJ*) has served as a vital platform for medical and public health scholarship in Wisconsin. Yet by the late 2010s, the journal's future was uncertain, pressured by financial challenges and a rapidly changing publishing landscape.

A pivotal moment arrived in 2019 when the University of Wisconsin (UW) School of Medicine and Public Health and the Medical College of Wisconsin (MCW) jointly assumed ownership of the journal. This partnership secured *WMJ's future also launched a new era of innovation a*nd growth. Submissions surged, special themed issues gained attention, and *WMJ* reaffirmed its role as a forum for meaningful discourse on medicine and health policy in the region.

A Fellowship Rooted in Purpose

Among the most transformative developments of this new era is the *WMJ* Editorial Fellowship Program — a forward-thinking initiative designed to cultivate the next generation of physician-scholars and editorial leaders.

The *WMJ* Editorial Fellowship was conceived as an immersive experience to provide medical trainees and early career faculty with structured, mentored engagement in academic publishing. Recognizing that editorial training is rarely a part of formal medical education, *WMJ's* editorial leadership developed a curriculum that introduces fellows to the full editorial lifecycle—from peer review and decision-making to editorial writing and ethical considerations. Fellows gain a critical understanding of scientific communication and the skills to lead in academia, policy, and research.

In 2023, *WMJ* welcomed its inaugural cohort of editorial fellows. Over the course they reviewed manuscripts, participated in editorial board meetings, contributed to content strategy, and co-authored an editorial with the Editor-in-Chief. Today, having demonstrated exceptional leadership and scholarly engagement as fellows, David Mallinson, PhD, and Corlin Jewell, MD – both inaugural fellows – serve as members of the *WMJ* editorial board, exemplifying the program's goal of developing future editorial leaders.

In 2024, *WMJ* recruited its second cohort: Raul Rodriguez, MD, and Victoria Ronan, MD, who are expected to complete the program this fall. Their progress further underscores the fellowship's role in nurturing talent and embedding editorial leadership into the early stages of clinical careers.

Encouraged by this success, *WMJ* is committed to continuing and expanding the program. Recruitment is underway for a new cohort to begin this fall. The fellowship is open to MDs, DOs, or clinically oriented PhDs who are faculty members or learners at MCW, UW–Madison or one of the UW School of Medicine and Public Health's statewide clinical campuses. By broadening access, *WMJ* aims to foster a more diverse and representative editorial community—one that incorporates the breadth of voices from various regions, specialties, and training levels across Wisconsin.

> These programs reaffirm our commitment to elevating scholarship, expanding opportunity, and empowering the next generation in medicine.

New Student Editorial Internship

Building on the success of the fellowship, *WMJ* is proud to announce the development of a new Editorial Internship—an opportunity designed to introduce medical students to the world of academic publishing early in their training. Being led by *WMJ* Publishing Board members Elizabeth Petty, MD, and Jonathan Temte, MD, PhD , both esteemed leaders in academic medicine, the internship will offer medical students

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Author Affiliations: Dr Aziz is *WMJ* editor in chief; associate professor, Department of Medicine, and chief, Divsion of Nephrology, University of Wisconsin School of Medicine and Public Health (UWSMPH), Madison, Wisconsin.

a structured, hands-on editorial experience through which they will learn about manuscript review, publishing ethics, editorial decision-making, and academic writing.

The program is currently under development and once launched, it will be among the first of its kind, offering students a guided and purposeful entry into academic publishing. This initiative reflects *WMJ's* strong commitment to cultivating scholarly curiosity, mentorship, and academic excellence from the earliest stages of medical education.

Why This Work Matters

At a time when many journals face declining reviewer pools and an aging editorial workforce, *WMJ* is investing in a sustainable future by building a culture of mentorship, scholarship, and leadership development. Through the fellowship and upcoming internship, *WMJ* is helping shape a generation of clinicians who understand the value of rigorous peer review, the power of the written word, and the responsibility that comes with shaping medical knowledge.

These initiatives signal that the journal is not merely a passive repository of information, it is an active, evolving, and inclusive learning community. *WMJ* is becoming a model for how regional journals can thrive – not only through high-quality content but by nurturing the people who create, curate, and communicate it.

Looking Ahead

As *WMJ* continues to evolve, it remains steadfast in its mission to advance health care in Wisconsin and beyond. These programs reaffirm our commitment to elevating scholarship, expanding opportunity, and empowering the next generation in medicine.

We are deeply grateful to the community that makes this work possible. Our heartfelt thanks go to the authors who share their research and insights, the peer reviewers who uphold our standards with rigor and thoughtfulness, the editorial board members who offer vision and guidance, and the publishing board whose steadfast support sustains our operations and growth. Each plays a critical role in helping *WMJ* fulfill its mission. Together, we are not only publishing a journal—we are building a legacy.

"Blooming Perspectives"

About the Artist

Toan Vu was born in Vietnam and was raised in Columbia, Missouri. He is currently a medical student at the University of Wisconsin School of Medicine and Public Health. With a passion for art, he says he paints to express creativity, reflect on his identity, and capture the world around him.

WMJ names two new deputy editors

The Publishing Board for the *Wisconsin Medical Journal* (*WMJ*) has named two new deputy editors: Sanjay Bhandari, MD, MS, and Shanthi Narla, MD. They will serve three-year terms, effective immediately.

Dr Bhandari is an associate professor of medicine in the Division of Internal Medicine at the Medical College of Wisconsin. He is an academic hospitalist and also serves as director of the hospital medicine fellowship. He has extensive editorial experience, having authored two book chapters, published over 50 peer-reviewed manuscripts, and served as a peer reviewer for 10 academic journals.

Dr Bhandari earned his Bachelor of Medicine and Bachelor of Surgery (MBBS) from Kathmandu University in Nepal and completed his residency in internal medicine at Chicago Medical School at Rosalind Franklin University of Medicine and Science. He also holds a master's degree in clinical and translational science from the Medical College of Wisconsin. He is board certified in internal medicine and is a member the Society of Hospital Medicine, and the American College of Physicians.

Dr Narla is an assistant professor of dermatology at the Medical College of Wisconsin, where she also serves as director of dermatology medical student research and director of adult clinical trials in the Department of Dermatology. She has published more than 60 peer-reviewed articles, abstracts, and book chapters, and has also served as a manuscript reviewer.

Dr Narla is a graduate of the Feinberg School of Medicine at Northwestern University. She completed an internship in internal medicine at the University of Illinois at Chicago and a fellowship in dermatology clinical trials at Henry Ford Health System in Detroit, prior to completing her residency in dermatology at St. Luke's University Health System in Easton, Pennsylvania. She is board certified in dermatology and is a member of the American Academy of Dermatology, Wisconsin Dermatological Society, and Women's Dermatological Society.

"Our previous deputy editor, Robert Treat, was a vital member of our editorial team. When he announced his decision to step down, we knew we had big shoes to fill. Fortunately, we had not one, but two exceptional candidates," said *WMJ* Editor-in-Chief Fahad Aziz, MD, MBA, CPE, FASN. "We were very impressed with their experience, commitment, and enthusiasm and are excited to welcome both of them to the *WMJ* team."

Dr Bhandari and Dr Narla succeed Robert Treat, PhD, who stepped down after completing two three-year terms as deputy editor. Dr Treat is an associate professor of emergency medicine and the director of measurement and evaluation in the Office of Academic Affairs at the Medical College of Wisconsin.

Cultural Competency in Short-Term Medical Missions

Isaac KS Ng, MBBS, MRCP

Cultural competency as popularized by Cross et al's seminal work in 1989 refers to a "set of congruent behaviors, attitudes, and policies that come together in a system, agency, or among professionals and enable that system, agency, or those professions to work effectively in cross-cultural situations."[1] Campinha-Bacote further developed a culturally competent model of care that comprises five core components: (1) cultural awareness – developing sensitivity and self-awareness of one's biases, (2) cultural knowledge – understanding of cross-cultural worldviews and beliefs, (3) cultural skill – being adept at making cultural assessments, (4) cultural encounter – real-world practice and exposure to different cultures, and (5) cultural desire – commitment and motivation to improve one's cultural competency.[2] Since then, over the past two decades, there has been extensive literature surrounding this concept, with more than 5000 search results in PubMed identified using the search terms cultural competence or cultural competency (title/abstract). For instance, recent articles have described cultural competency in relation to broader social justice endeavors, where there is honest introspection on discriminatory behaviors, bias, privileges, power dynamics, and resultant health inequalities across cultures.[3]

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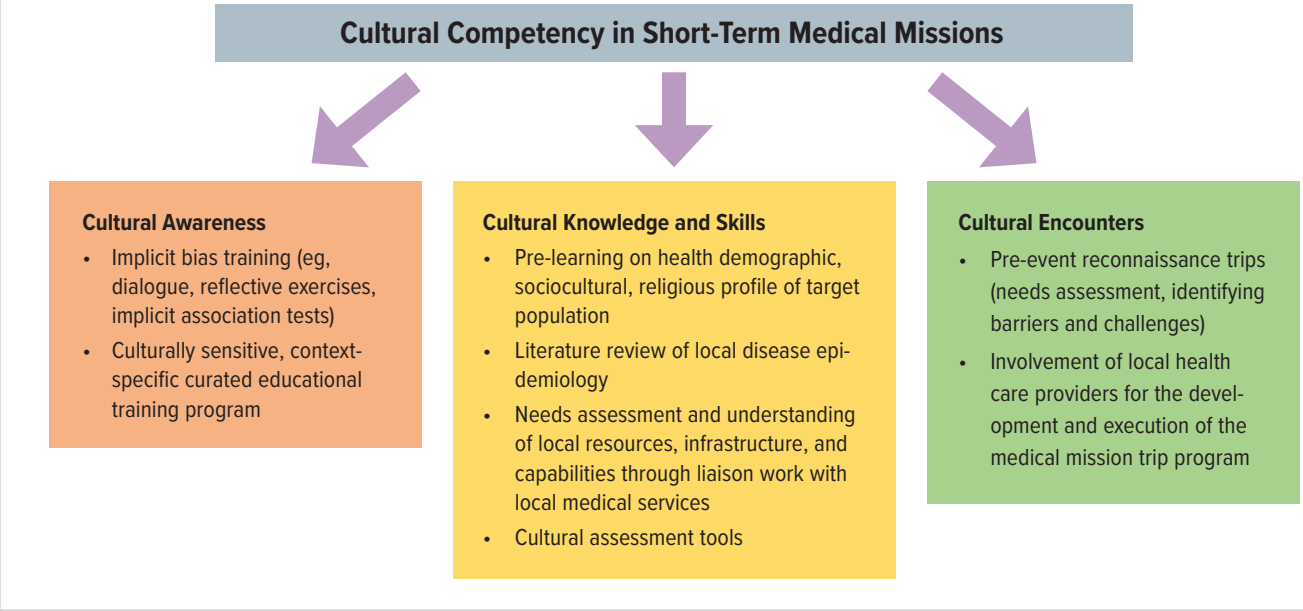
> While on the surface, short-term medical missions appear to be highly beneficial to both the providers and recipients of medical care, training, medical infrastructure and resources, there are also glaring pitfalls...

In recent years, there has been a surge in interest among members of the medical community – particularly in more affluent nations – to embark on "short-term medical missions" (STMMs) to rural, developing countries and cities for the purpose of medical volunteerism (eg, conduct health screening, diagnose and provide medical treatment, perform surgical procedures), cross-cultural exchanges, and experiential learning. The duration of these STMMs can range from 1 day to 8 weeks.[4] While on the surface, STMMs appear to be highly beneficial to both the providers and recipients of medical care, training, medical infrastructure and resources,[5] there are also glaring pitfalls related to poor quality of clinical care (eg, use of substandard medical treatments, offering services that do not address real clinical needs, unethical practices, medical errors, lack of continuity of care), cultural insensitivities, and secondary, self-serving/political agendas that have been highlighted.[5-7] In particular, most criticisms against these types of health volunteerism are directed at incompetence in dealing with cross-cultural clinical care, such as disrespect/ignorance toward local customs and practices, arrogance or presumed superiority of Western medicine/practices, undermining of local medical services, unfamiliarity with local disease prevalence and rare conditions, and inadvertent perpetuation of colonial/neocolonial relationships.[7] However, the idea of formalizing cultural competency training for medical personnel planning to embark on STMMs has hitherto only been discussed in a handful of articles.[8,9]

Therefore, herein I relate the concept of "cultural competency" in medical training/practice to STMMs by discussing multipronged practical strategies contingent to the traditional cultural competency model to improve the standards of cross-cultural clinical care provided by medical trainees and clinicians embarking on STMMs.

Figure. Cultural Competency in Short-Term Medical Missions



Adapted from Campinha-Bacote Model.[2]

Multipronged Approach to Promote Cultural Competency in STMMs

The following practical strategies are adapted from the traditional Campinha-Bacote culture competency model[2] to improve the cultural competency of medical volunteers engaging in STMMs through appropriate training and preparation in cultural awareness, knowledge, skills, and actual cross-cultural exchanges (Figure).

Cultural awareness in STMMs reflects the ability of the medical provider to accurately recognize and self-reflect on personal biases/stereotypes/assumptions towards their patients. In general, biases can be both explicit or implicit, depending on whether one is conscious about the existence of personal attitudes and stereotypes towards others. Anti-bias clinical training, including simulation experience, debriefing, group discussions, and dialogue, has been reported to be a useful pedagogical modality to improve clinicians' ability to engage and address bias and racism in clinical settings.[10] When adapted for volunteer training prior to STMMs, it is important to elicit possible areas of implicit bias towards patients given what is known about their sociocultural backgrounds.[11] This can be achieved through formal tests, such as implicit association tests, or dialogue or reflective exercises to prompt the participant to consider how their management of patients would be different if they were of a different sociodemographic status.[11] In 2014, Steinke et al reported that a 2-hour culturally sensitive education program specially curated for medical providers traveling to Haiti for STMM was able to improve cultural competency levels among the volunteers.[9]

Additionally, cultural knowledge and assessment in STMM involves attaining a holistic understanding of the health demographic and sociocultural/religious profile of the beneficiary patient population that may influence health behaviors and treatment considerations. Prior to any STMM trips, it is important for medical providers to partner closely with local health services/authorities for needs assessment of the patients, obtain health demographic information, and ascertain local resources, infrastructures, and capabilities in order to optimize the utility of the medical missions program and ensure continuity of care in the longer term.[12] In addition, it would be useful for medical volunteers to review existing literature on the typical disease profile of patients based on sociodemographic data and geographical location.[13] Ultimately, the local disease epidemiology, needs assessment, and health/volunteer resources available will affect the appropriate health services, including screening, investigations, and treatment that should be offered during the STMM.

Another fundamental aspect of cultural knowledge pertains to understanding specific health behaviors, concerns, and practices that may be influenced by sociocultural and religious beliefs. For example, in end-of-life care, patients in Asian societies generally place greater value on collective decision-making (ie, familial involvement) in terms of extent of medical treatment and life-sustaining interventions versus those in Western countries where patient autonomy is prioritized.[14] Moreover, "collusion" (ie, family hiding unfavorable or terminal diagnosis from older persons) still remains a common and accepted practice in many Asian cultures.[15,16]

In addition, health behaviors and treatment considerations may be influenced by local cultural and religious practices. For example, Muslim patients who observe Ramadan will need specific adjustments for diabetic medications, including insulin injections, and education on dietary habits, precautions, and glucose monitoring during the fasting period.[17] Vaccine hesitancy is another issue related to religious beliefs and practices, where there

is perceived moral or ethical impermissibility of receiving vaccinations or specific vaccine components.[18] For instance, religious objections to vaccinations may include objections to vaccine components (eg, presence of non-halal ingredients), production methods (eg, use of aborted fetal cells in vaccine creation), or the concept of trying to "artificially" prevent illness through man-made medicines.[18] It is important, therefore, for medical volunteers to be privy to and respectful of a patient's wishes and preferences, which may be guided by deeply held religious and cultural beliefs. At the same time, where appropriate, partnership with local religious/community leaders to educate and correct misperceptions of religious permissibility of certain medical interventions can be highly effective.[19]

Finally, cultural encounters with the target patient population prior to formal STMMs are important to improve cross-cultural health communications and interactions through real-world experiential learning. This usually can be achieved through pre-event reconnaissance trips where medical providers travel to the host country to carry out a smaller scale volunteer event. Such pilot outreach events are useful not only for direct needs assessment, but also to identify local/cultural barriers and challenges to health interventions prior to the actual STMM trip. In addition, there is also great utility in involving local health care providers in the missions' program to incorporate greater diversity of medical views and ensure that health interventions proposed are suitable and impactful for the target patient population.

Conclusion

Medical volunteerism in the form of STMMs to developing countries will continue to be prevalent in our increasingly globalized world. Those who wish to engage in such volunteer work must be committed to enhancing their cultural competencies to provide high-value and culturally appropriate clinical care.

Funding/Support: None declared.

Financial Disclosures: None declared.

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Drivers of Opioid Prescriptions for Medicare Patients at an Urban Tertiary Center

Elise A. Biesboer, MD; Abdul Hafiz Al Tannir, MD; Leonard E. Egede, MD, MS; Rebekah J. Walker, PhD; Sneha Nagavally, MS; Sarah A. Endrizzi, MD; William J. Peppard, PharmD

ABSTRACT

Introduction: Froedtert & the Medical College of Wisconsin belongs to a minority of institutions in which opioids are more frequently prescribed to non-Hispanic Black patients than their non-Hispanic White counterparts. The objective of this study was to evaluate racial and ethnic differences in prescribing practices for Medicare patients to determine areas for intervention.

Methods: This was a retrospective review of adult patients with Medicare insurance who received an ambulatory opioid prescription for pain. Outcomes included number of prescriptions, and maximum morphine milligram equivalent (MME). Unadjusted and adjusted linear regression models were used to examine associations between race and ethnicity and each outcome with and without adjustments for covariates.

Results: A total of 17105 patients were given an ambulatory opioid prescription over the study period. Although most prescriptions were provided to non-Hispanic White patients, non-Hispanic Black patients had a higher mean number of prescriptions (4.36; 95% CI, 4.08 – 4.63) and higher MMEs at 495.31 (95% CI , 445.72 – 544.91). After controlling for demographics and comorbidities, individual comorbidities emerged as independent variables associated with greater numbers of prescriptions, with sickle cell disease (β 9.86; 95% CI, 9.08-10.64; $P < 0.001$), drug abuse (β 5.22; 95% CI, 4.96-5.48; $P < 0.001$), and paralysis (β 2.20; 95% CI, 1.73-2.67; $P < 0.001$) having the strongest relationships, while after adjustment, the significance of race and ethnicity was lost.

Conclusions: Institutions should explore reasons for racially inequitable opioid receipt. Individual comorbidities were associated with differences in opioid prescribing, allowing for targeted interventions in these patient groups.

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INTRODUCTION

Evaluating opioid prescribing practices is a focus in both research and practice to combat the effects of the opioid epidemic, and interventions have extended across various levels of care. On an individual level, this has involved mandated participation in prescription drug monitoring programs.[1] Broadly, at the health system level, this has involved comprehensive evaluation of opioid prescribing and development of guidelines to reduce variation in practice.[2-5]

For decades, racial differences in pain prescribing practices have been recognized across different health care domains.[6-9] These differences are mainly regarding inequitable receipt of opioids for patients of racial and ethnic minority groups compared to their White counterparts with the same disease processes or injuries.[10,11] Potential explanations may include persistent racially based bias toward patient experiences of pain, clinician perceptions of pain, or individual preferences in pain treatment.[8,12,13]

In a recent evaluation of hospital system prescribing practices, Morden et al confirmed these findings, where Black patients received 36% fewer morphine milligram equivalents (MME) annually compared to White patients. Froedtert & the Medical College of Wisconsin (F&MCW), Milwaukee, Wisconsin, was included in this analysis, but it was found to be in a minority of systems where more opioids were prescribed to Black patients. Importantly, the authors questioned whether their findings might be due to something other than racial bias, and they called clinicians to explore root causes and remediation strategies to address

racially unequal opioid receipt.[14] This prompted an internal, pharmacist-led evaluation of prescribing practices across F&MCW's health system, which confirmed that non-Hispanic Black patients received a higher number of opioid prescriptions. However, when controlling for demographics, such as age and sex, risk score, and individual comorbidities, the individual comorbidities were identified as key predictors of prescribing practices. Moreover, there was a relationship between increased age and risk score with the comorbidities that were found to be significant.[15]

The original Morden et al analysis was performed on Medicare-insured patients utilizing Medicare claims data,[14] but the initial institutional analysis was performed on all patients. In the United States, approximately 62.5 million people are enrolled in Medicare. The majority of patients are aged 65 or older,[16] have a high prevalence of comorbidities, and greater illness severity.[17,18] After implementation of Medicare Part D in 2006, studies have shown increased access to prescription medications – especially for older adults.[19,20] Despite increased access, prescribing practices still may differ for Medicare patients.[21,22] The objective of this study was to determine if the racial and ethnic variations in opioid prescribing practices reported by Morden et al[14] and seen on the initial health system evaluation[15] persisted for Medicare-insured patients.

METHODS

This was a retrospective review of adult (≥ 18 years old) patients with Medicare insurance who received an ambulatory opioid prescription for pain from July 2020 to June 2021 at F&MCW health system. At time of analysis, the health system included 5 hospitals and over 45 health centers in Wisconsin. The principal hospital is an urban, tertiary referral center in Milwaukee, Wisconsin, which has a diverse patient population and serves a large catchment area. The project received approval as a quality improvement initiative from the Medical College of Wisconsin Human Research Protection Program and was exempt from full institutional review board review (PRO#00042098).

Patients who received a prescription not due to pain were excluded (for example, methadone or buprenorphine for the treatment of opioid use disorder). Those who received buprenorphine prescriptions for pain treatment also were excluded, as buprenorphine does not have a reliable MME conversion factor.[23] Prescription data also were excluded if the associated patient's race and ethnicity was absent in the medical record.

Patient data were abstracted from the electronic health record. Race and ethnicity were self-reported and categorized as non-Hispanic White (White), non-Hispanic Black (Black), Hispanic, and non-Hispanic Other (Other). Comorbidities were obtained via *International Classification of Diseases, Ninth Revision* (ICD-9) and *Tenth Revision* (ICD-10) codes and were determined by the Elixhauser Comorbidity Index.[24,25] Comorbidities were evaluated as both counts (0, 1, 2, 3+) and individually. Primary outcomes were chosen based on those in the Morden et al paper[14] and included number of opioid prescriptions and MMEs.

Of note, the term "drug abuse" is no longer accepted as a patient-centered term for describing the disease process of addiction or drug misuse. ICD-10 codes are still reflective of outdated terminology; therefore, drug abuse is used in this report to accurately describe the ICD codes used to assess this patient cohort. For a more patient-centered approach, the terminology "opioid use disorder" or "substance use disorder" is used when not specifically referring to the code.

Statistical Analysis

Descriptive statistics were used to describe opioid prescribing patterns for the sample. Continuous variables were reported by mean and standard deviation, and categorical variables were reported by counts and percentages. Unadjusted and adjusted linear regression models were used to examine associations between race and ethnicity and each outcome (number of prescriptions, MME) with and without adjustments for covariates. Covariates included age, sex, readmission risk score,[26] and comorbidities. The first model was unadjusted; the second model was adjusted for demographics (age and sex) and total comorbidity count (0, 1, 2, 3+); the third model was adjusted for demographics and individual comorbidities rather than comorbidity count. Unstandardized betas (β) are reported with the 95% confidence interval and respective *P* values, with β indicating the change in outcomes for each unit increase (for continuous variables) or compared with a reference group (for categorical variables). All statistical analyses were performed in R using R version 4.1.3 (R Core Team). Statistical significance was set at $P < 0.05$.

RESULTS

Over the study period, there were 53 630 ambulatory opioid prescriptions given to 17 146 Medicare patients. Race and ethnicity data were missing from 41 patients associated with 112 prescriptions; therefore, 17 105 patients and 53 518 prescriptions were analyzed. Of these, 14 016 (82%) patients were White. In each race and ethnicity category, the majority of patients were female (White 58%, Black 65%, Hispanic 60%, Other 55%; total cohort 59%), had an average age over 60 years, and had 3 or more comorbidities, with the most common being hypertension followed by chronic pulmonary disease and obesity. There were differences in rates of comorbidities across racial groups in every comorbidity analyzed, except rheumatoid arthritis and collagen vascular disease, coagulopathy, peptic ulcer disease, and blood loss anemia (Table 1).

Although most prescriptions were provided to White patients, Black and Hispanic patients had a higher mean number of prescriptions (White 2.92; 95% CI, 2.85-3.00, Black 4.36; 95% CI, 4.08-4.63, Hispanic 3.21; 95% CI, 2.72-3.70). MME was

Table 1. Sample Demographics for Individuals with Medicare Coverage Stratified by Race and Ethnicity

Demographics	Total (N = 17 105)	Non-Hispanic White (N = 14 016)	Non-Hispanic Black (N = 2374)	Hispanic (N = 477)	Non-Hispanic Other (N = 238)	*P* value
Age in years[a]	70.39 (11.99)	71.95 (10.85)	62.78 (14.21)	63.40 (13.98)	68.88 (13.09)	< 0.001
Sex						< 0.001
Female	59.2%	58.2%	65.1%	59.5%	54.6%	
Male	40.8%	41.8%	34.9%	40.5%	45.4%	
Readmission risk score[a]	3.21 (2.09)	3.03 (1.99)	4.20 (2.42)	3.35 (2.05)	3.53 (2.13)	< 0.001
Elixhauser comorbidity count[a]	3.20 (2.39)	3.09 (2.34)	3.89 (2.55)	3.03 (2.43)	2.98 (2.36)	< 0.001
Comorbidity count						< 0.001
0	13.0%	13.4%	9.7%	16.6%	15.1%	
1	14.1%	14.9%	9.0%	16.4%	15.1%	
2	16.5%	17.2%	13.1%	13.0%	17.6%	
3+	56.4%	54.5%	68.2%	54.1%	52.1%	
Elixhauser comorbidity list						
Hypertension uncomplicated	58.1%	56.8%	67.9%	49.9%	55.0%	< 0.001
Obesity	22.8%	21.7%	30.6%	22.9%	8.8%	< 0.001
Chronic pulmonary disease	22.1%	20.9%	30.6%	17.6%	18.1%	< 0.001
Depression	20.3%	19.6%	23.5%	23.7%	19.3%	< 0.001
Solid tumor, no metastasis	19.5%	20.6%	13.8%	15.7%	18.9%	< 0.001
Hypothyroidism	17.5%	19.1%	9.1%	14.9%	12.2%	< 0.001
Diabetes uncomplicated	17.3%	15.6%	25.9%	21.8%	23.5%	< 0.001
Cardiac arrhythmias	16.6%	18.1%	10.5%	8.4%	10.9%	< 0.001
Renal failure	16.0%	13.9%	27.3%	18.2%	18.1%	< 0.001
Diabetes complicated	12.1%	10.3%	21.7%	15.7%	15.5%	< 0.001
Congestive heart failure	11.2%	10.4%	16.6%	9.4%	8.0%	< 0.001
Peripheral vascular disorders	11.0%	11.1%	11.5%	6.5%	10.5%	0.014
Fluid and electrolyte disorders	8.4%	8.0%	10.2%	8.0%	12.2%	< 0.001
Rheumatoid arthritis and collagen vascular diseases	7.7%	7.6%	7.8%	9.9%	6.7%	0.309
Other neurological disorders	6.9%	6.7%	8.6%	6.1%	6.7%	< 0.01
Drug abuse	6.8%	5.4%	13.8%	10.9%	7.6%	< 0.001
Liver disease	5.8%	5.5%	7.0%	9.9%	6.7%	< 0.001
Deficiency anemia	5.7%	5.3%	8.2%	4.2%	5.9%	< 0.001
Pulmonary circulation disorders	5.7%	5.2%	9.5%	2.7%	3.4%	< 0.001
Valvular disease	5.0%	5.3%	4.0%	1.9%	3.4%	< 0.001
Coagulopathy	4.2%	4.4%	3.5%	4.0%	4.6%	0.222
Metastatic cancer	3.2%	3.4%	2.1%	2.9%	2.9%	0.008
Alcohol abuse	3.1%	2.9%	4.2%	4.4%	3.4%	0.002
Weight loss	2.5%	2.4%	3.7%	2.3%	1.7%	0.002
Lymphoma	2.1%	2.3%	1.4%	0.8%	0.4%	0.001
Hypertension, complicated	2.0%	1.7%	4.0%	2.1%	2.1%	< 0.001
Peptic ulcer disease (excluding bleeding)	2.0%	2.0%	1.7%	1.3%	2.9%	0.34
Blood loss anemia	1.1%	1.0%	1.5%	0.6%	1.7%	0.124
Paralysis	1.9%	1.5%	3.7%	3.1%	4.2%	< 0.001
Psychoses	1.1%	0.7%	3.3%	1.9%	1.7%	< 0.001
Sickle cell disease	0.7%	0.0%	4.8%	0.4%	0.0%	
HIV/AIDs	0.5%	0.2%	1.7%	1.0%	0.4%	< 0.001

[a]Data are reported as mean (SD).

Table 2. Mean Prescriptions for Individuals with Medicare Coverage Stratified by Race/Ethnicity

	Total (N = 17 105)	Non-Hispanic White (N = 14 016)	Non-Hispanic Black (N = 2374)	Hispanic (N = 477)	Non-Hispanic Other (N = 238)
Number of prescriptions[a]	3.13 (3.06 – 3.20)	2.92 (2.85 – 3.00)	4.36 (4.08 – 4.63)	3.21 (2.72 – 3.70)	2.49 (1.83 – 3.15)
Long-term percentage	11.4%	10.2%	18.2%	12.8%	8.4%
Short-term percentage	88.6%	89.8%	81.8%	87.2%	91.6%
MME[a]	40.30 (39.68 – 40.90)	39.65 (38.97 – 40.32)	44.67 (42.21 – 47.12)	38.99 (34.58 – 43.42)	37.57 (31.64 – 43.49)
Cumulative MME[a]	359.17 (347.06 – 371.85)	336.19 (322.51 – 349.87)	495.31 (445.72 – 544.91)	378.11 (288.90 – 467.33)	313.36 (193.74 – 432.99)

Abbreviation: MME, morhpine milligram equivalent.
[a]Mean, 95% CI.

highest for Black patients at 44.67 (95% CI, 42.21-47.12) (Table 2).

Model 1 - Unadjusted Linear Regression

In the unadjusted regression model, Black patients had significantly higher numbers of prescriptions (β 1.43; 95% CI, 1.23-1.62; $P<0.001$) (Table 3) and greater MME (β 5.02; 95 CI, 3.24-6.80; $P<0.001$) than White patients (Table 4). Hispanic and Other groups did not differ statistically from the White group for prescriptions or MME.

Model 2 – Controlling for Demographics and Total Comorbidity Count

After controlling for demographics and comorbidity count, Black patients continued to have significantly higher numbers of prescriptions than White patients (β 0.67; 95% CI, 0.47-0.88; $P<0.001$) (Table 3). Hispanic patients exhibited a statistically significant association with lower MME compared to White patients (β -4.32; 95% CI, -7.94 to -0.70; $P<0.05$). Male sex (β 4.39; 95% CI, 3.18-5.59; $P<0.001$) and age (β -0.44; 95% CI, -0.49 to -0.39; $P<0.001$) were also associated with MME (Table 4).

Model 3 – Controlling for Demographics and Individual Comorbidities

Finally, after controlling for demographics and individual comorbidities, race was no longer associated with number of prescriptions aside from patients of Other racial groups (β -0.65; 95% CI, -1.19 to -0.012; $P<0.05$). Individual comorbidities emerged as significant independent variables associated with greater numbers of prescriptions, with sickle cell disease (β 9.86; 95% CI, 9.08-10.64; $P<0.001$), drug abuse (β 5.22; 95% CI, 4.96-5.48; $P<0.001$), and paralysis (β 2.20; 95% CI, 1.73-2.67; $P<0.001$) being the comorbidities with the strongest association. A diagnosis of psychosis was associated with lower numbers of prescriptions (OR -1.27; 95% CI, -1.88 to -0.67; $P<0.001$) (Table 3).

Regarding MME, Hispanic patients continued to exhibit a statistically significant association with lower MME compared to White patients (β -4.41; 95% CI, -8.00 to -0,83; $P<0.05$).

Similar to number of prescriptions, sickle cell disease (β 52.36; 95% CI, 45.18-59.55; $P<0.001$), drug abuse (β 14.80; 95% CI, 12.42-17.18; $P<0.001$), lymphoma (β 8.54; 95% CI, 4.44-12.64; $P<0.001$), and metastatic cancer (β 7.69; 95% CI, 4.14-11.23; $P<0.001$) were associated with higher MME, among other individual diagnoses (Table 4).

Table 3. Relationship Between Number of Prescriptions and Race/Ethnicity for Individuals with Medicare Coverage

	Unadjusted Linear Regression	Linear Regression Adjusted for Demographics and Comorbidity Count	Linear Regression Adjusted for Demographics and Individual Comorbidities
Race (ref = non-Hispanic White)			
Non-Hispanic Black patients	1.43[a] (1.23 to 1.62)	0.67[a] (0.47 to 0.88)	0.08 (-0.12 to 0.28)
Hispanic patients	0.28 (-0.13 to 0.70)	-0.19 (-0.60 to 0.22)	-0.29 (-0.68 to 0.10)
Other non-Hispanic patients	-0.44 (-1.02 to 0.14)	-0.60[b] (-1.18 to -0.03)	-0.65[b] (-1.19 to -0.12)
Age	—	-0.06[a] (-0.06 to -0.05)	-0.03[a] (-0.04 to -0.03)
Sex, Male	—	-0.16[b] (-0.29 to -0.02)	-0.08 (-0.21 to 0.06)
Readmission risk score	—	0.10[a] (0.07 to 0.14)	0.07[a] (0.03 to 0.11)
Comorbidity count (ref = 0)			
1	—	0.66[a] (0.41 to 0.92)	--
2	—	1.03[a] (0.79 to 1.28)	--
3+	—	1.39[a] (1.17 to 1.61)	--
Elixhauser comorbidity list			
Alcohol abuse	—	—	-0.51[c] (-0.89 to -0.13)
Blood loss anemia	—	—	0.17 (-0.44 to 0.77)
Cardiac arrhythmias	—	—	-0.14 (-0.33 to 0.04)
Chronic pulmonary disease	—	—	0.51[a] (0.34 to 0.67)
Coagulopathy	—	—	-0.18 (-0.50 to 0.14)
Congestive heart failure	—	—	-0.02 (-0.24 to 0.21)
Deficiency anemia	—	—	0.27 (-0.01 to 0.55)
Depression	—	—	0.44[a] (0.27 to 0.61)
Diabetes, complicated	—	—	0.14 (-0.08 to 0.35)
Diabetes, uncomplicated	—	—	-0.12 (-0.30 to 0.06)
Drug abuse	—	—	5.22[a] (4.96 to 5.48)
Fluid and electrolyte disorders	—	—	0.19 (-0.05 to 0.42)
HIV/AIDS	—	—	-0.53 (-1.48 to 0.41)
Hypertension, complicated	—	—	-0.65[c] (-1.11 to -0.19)
Hypertension, uncomplicated	—	—	0.23[c] (0.08 to 0.37)
Hypothyroidism	—	—	0.08 (-0.09 to 0.26)
Liver disease	—	—	-0.02 (-0.30 to 0.26)
Lymphoma	—	—	0.96[a] (0.52 to 1.41)
Metastatic cancer	—	—	0.85[a] (0.47 to 1.24)
Obesity	—	—	0.08 (-0.08 to 0.24)
Other neurological disorders	—	—	-0.49[a] (-0.74 to -0.24)
Paralysis	—	—	2.20[a] (1.73 to 2.67)
Peptic ulcer disease (excluding bleeding)	—	—	0.94[a] (0.48 to 1.39)
Peripheral vascular disorders	—	—	0.10 (-0.11 to 0.31)
Psychoses	—	—	-1.27[a] (-1.88 to -0.67)
Pulmonary circulation disorders	—	—	0.31[b] (0.03 to 0.59)
Renal failure	—	—	-0.14 (-0.33 to 0.05)
Rheumatoid arthritis and collagen vascular diseases	—	—	0.13 (-0.11 to 0.37)
Sickle cell disease			9.86[a] (9.08 to 10.64)
Solid tumor, no metastasis	—	—	0.04 (-0.12 to 0.21)
Valvular disease	—	—	0.19 (-0.11 to 0.49)
Weight loss	—	—	0.04 (-0.37 to 0.45)

[a]$P>0.001$, [b]$P>0.05$, [c]$P>0.01$.

DISCUSSION

This review of opioid prescriptions found that at F&MCW,

Black patients received higher numbers of opioid prescriptions, and the MME prescribed was higher. However, as the data were adjusted for demographics and comorbidities, the relationship between opioid prescriptions and race and ethnicity lost significance. Multiple individual comorbidities were associated with both number of opioids and MME and, therefore, likely contribute to the differences in observed prescribing practices. Notably, the diseases associated with the highest number of prescriptions and MME were sickle cell disease, cancers, and substance use disorder.

This confirmed what was reported by Morden et al.[14] For Medicare-insured patients in this specific system, more opioids are prescribed to Black patients than White patients. This contrasts with national trends of lower opioid prescribing for patients of racial and ethnic minority groups.[7,8] Similar to the results of Peppard et al's review of opioid prescribing for all F&MCW patients,[15] individual comorbidities were important factors associated with opioid prescribing. Like Morden et al,[14] Meints et al recognized these trends in prescribing differences and discussed socioecological factors that may influence reasons for these disparities, including patient, clinician, and system factors.[8] They called clinicians to action to review their practices and to determine ways to address these issues.

Although this analysis was unable to determine precisely why we see these differences in opioid prescribing practices, we found that particular comorbidities seemed to be the driving factor for opioid prescriptions. Therefore, the prevalence and presentation of individual disease processes and their relation to racial and ethnic groups could explain the patterns observed. Moreover, F&MCW serves as the only tertiary referral center in Milwaukee and is 1 of 2 level I trauma centers in the state. Due to this, our system cares for a higher proportion of complex patient cases and has robust programs for the management of complex disease processes, such as cancer, sickle cell disease, and traumatic injury. Clinical interventions have been in place to address disparities in opioid prescribing by standardizing prescribing practice, which also may have influenced the findings seen at our health system.

For sickle cell disease and cancer in particular, opioid therapy is an important component of pain treatment.[27,28] In this analysis, sickle cell disease was identified as the comorbidity most strongly associated with number of prescriptions and MME. Sickle cell disease affected nearly 5% of Black patients with an ambulatory opioid prescription but had disproportionately large MMEs pre-

Table 4. Relationship Between Morphine Milligram Equivalent (MME) and Patient Race/Ethnicity for Individuals with Medicare Coverage

	Unadjusted Linear Regression	Linear Regression Adjusted for Demographics and Comorbidity Count	Linear Regression Adjusted for Demographics and Individual Comorbidities
Race (ref = non-Hispanic White)			
Non-Hispanic Black patients	5.02[a] (3.24 to 6.80)	1.25 (-0.56 to 3.07)	-0.85 (-2.72 to 1.02)
Hispanic patients	-0.65 (-4.39 to 3.10)	-4.32[b] (-7.94 to -0.70)	-4.41[b] (-8.00 to -0.83)
Other non-Hispanic patients	-2.08 (-7.32 to 3.17)	-4.01 (-9.05 to 1.04)	-3.93 (-8.92 to 1.06)
Age	—	-0.44[a] (-0.49 to -0.39)	-0.38[a] (-0.43 to -0.32)
Sex, male		4.39[a] (3.18 to 5.59)	4.37[a] (3.12 to 5.62)
EPIC risk score	—	0.30 (-0.01 to 0.62)	0.46[b] (0.11 to 0.82)
Comorbidity count (ref = 0)			
1	—	-0.37 (-2.63 to 1.89)	—
2	—	-0.05 (-2.25 to 2.14)	—
3+	—	-1.28 (-3.20 to 0.63)	—
Elixhauser comorbidity list			
Alcohol abuse	—	—	-3.60[b] (-7.11 to -0.09)
Blood loss anemia	—	—	-1.21 (-6.82 to 4.40)
Cardiac arrhythmias	—	—	0.37 (-1.35 to 2.09)
Chronic pulmonary disease	—	—	-0.16 (-1.65 to 1.33)
Coagulopathy	—	—	0.74 (-2.22 to 3.71)
Congestive heart failure	—	—	-2.11 (-4.23 to 0.01)
Deficiency anemia	—	—	1.04 (-1.54 to 3.62)
Depression	—	—	0.48 (-1.09 to 2.06)
Diabetes, complicated	—	—	-1.97 (-3.94 to 0.005)
Diabetes, uncomplicated	—	—	-0.16 (-1.81 to 1.50)
Drug abuse	—	—	14.80[a] (12.42 to 17.18)
Fluid and electrolyte disorders	—	—	-0.28 (-2.49 to 1.92)
HIV/AIDS	—	—	-6.48 (-15.17 to 2.21)
Hypertension, complicated	—	—	-2.88 (-7.12 to 1.36)
Hypertension, uncomplicated	—	—	-1.51[b] (-2.83 to -0.19)
Hypothyroidism	—	—	-1.00 (-2.60 to 0.59)
Liver disease	—	—	-1.10 (-3.71 to 1.51)
Lymphoma	—	—	8.54[a] (4.44 to 12.64)
Metastatic cancer	—	—	7.69[a] (4.14 to 11.23)
Obesity	—	—	-0.50 (-1.97 to 0.98)
Other neurological disorders	—	--	-4.07[a] (-6.42 to -1.73)
Paralysis	—	—	-1.96 (-6.29 to 2.37)
Peptic ulcer disease (excluding bleeding)	—	—	-1.50 (-5.69 to 2.69)
Peripheral vascular disorders	—	—	-2.13[b] (-4.10 to -0.16)
Psychoses	—	—	-8.17[c] (-13.79 to -2.56)
Pulmonary circulation disorders	—	—	-1.02 (-3.64 to 1.59)
Renal failure	—	—	0.69 (-1.05 to 2.44)
Rheumatoid arthritis and collagen vascular diseases	—	—	-2.29[b] (-4.50 to -0.08)
Sickle cell disease	—	—	52.36[a] (45.18 to 59.55)
Solid tumor, no metastasis	—	—	3.02[a] (1.46 to 4.58)
Valvular disease	—	—	-0.93 (-3.69 to 1.84)
Weight loss	—	—	-2.73 (-6.52 to 1.07)

[a]$P>0.001$, [b]$P>0.05$, [c]$P>0.01$.

scribed. Extensive guidelines are available for the management of both acute and chronic pain for sickle cell disease.[29] At F&MCW, prompt consultation with the specialized sickle cell disease team is recommended for the inpatient management of acute vaso-occlusive crisis. Clinicians caring for patients with sickle cell disease have utilized prescribing data to identify high-risk ambulatory patients and to perform risk-mitigation strategies, such as tapering doses in stable patients or in those who have undergone bone marrow transplant.[30]

In surgical patients, standardized prescribing strategies have been utilized to decrease variation in individualized prescribing practice.[5,31] At our institution specifically, standardized prescribing guidelines frequently are used across different specialties. The trauma and acute care surgery department, a department that cares for a high proportion of patients belonging to racial and ethnic minority groups, found that discharge prescribing guidelines for trauma patients reduced MMEs prescribed at discharge. Prior to implementation, Black patients were more likely to be prescribed ≥50 MMEs, a marker of increased risk for overdose death.[32] After guideline implementation, there were no racial differences in prescribing.[5] The acute care surgery team also has implemented a guideline that reduced the amount and length of opioid prescriptions postoperatively.[33] While these guidelines focus on standard regimens based on certain injury patterns or surgical procedures,[34] others prioritize tiered prescribing derived from inpatient individuals' opioid medication use.[35,36] Implementation of an electronic health record alert[37] can be utilized to identify patients who did not receive an opioid medication in the 24 hours prior to discharge to decrease discharge opioid prescribing.

Some comorbidities and disease presentations are influenced by socioeconomic factors. Regarding cancer, pain is highly prevalent—especially in patients with advanced disease.[38,39] Moreover, certain types of cancer are known to be especially painful, such as bone cancers, bony metastases,[40,41] and pancreatic cancer.[42] Patients belonging to racial and ethnic minority groups are more likely to be diagnosed with late-stage cancer and have decreased survival[43] resulting from complex socioeconomic factors that are strongly related to race and ethnicity, including neighborhood disadvantage, access to care, and education.[44-47] As it was out of the scope of the objective, the analysis was not stratified by cancer type, nor was there a higher number of cancer diagnosis in Black patients who received an opioid prescription. Therefore, these observations do not necessarily explain why there was a higher mean number of prescriptions and MMEs for Black patients, but it likely explains why there were strong prescribing associations in patients diagnosed with cancer.

The recognition that individual comorbidity factors play a large role in driving opioid prescriptions allows for opportunity to continue to address these disparities. The prior analysis, performed by Peppard et al, details pharmacy-led interventions, including the development of an enterprise-level pain stewardship pharmacist position to coordinate care across the ambulatory and inpatient environments and across all specialties.[15] This position was created in response to the prescribing data seen within our health system and may serve as model for other institutions reviewing prescribing practices and targeting interventions.

Substance use disorder also was associated with opioid prescriptions. It is well known that there is an association between chronic pain and opioid use disorder. There are complex physical, social, and psychological components to the disease that require multidisciplinary, holistic approaches to treatment.[48] The pharmacist-led pain stewardship team[15] has identified patients with substance use disorder across the health system and has developed strategies to increase access to medication-based treatment for opioid use disorder. This has included partnership with the psychiatry team to develop a guideline for medication-based treatment induction therapy[49] in both the emergency and inpatient settings and has successfully increased utilization of medications for opioid use disorder.

Ultimately, the optimal rate and MME of opioid prescribing is yet to be elucidated and likely varies based on myriad factors.[3] For patients who do benefit from opioid prescription, such as those with acute surgical pain,[3] co-prescription of naloxone is encouraged for all ambulatory opioid prescriptions. Naloxone co-prescription has reduced opioid-related overdose deaths in states where it is mandated.[50] At our institution, a best practice advisory alert is integrated into the electronic health record to identify patients at high risk of opioid-related adverse events who would benefit from naloxone co-prescription.[51]

Limitations

Some limitations of this analysis are worth noting. First, generalizability of the results may be limited given data were obtained from a single health system that belongs to a small group of systems that prescribe more opioids to patients of racial and ethnic minority groups.[14] While the ability to perform a multivariable regression analysis to account for covariates that influence opioid prescribing is applicable to any institution, these results and interventions may not be generalizable to other health systems that have a different pattern of prescribing disparities or that serve a less racially diverse patient population. Second, results are based on cross-sectional data; therefore, causality cannot be inferred from findings. Careful consideration of patient disease processes, risk for opioid use disorder, and quality of life is necessary in making decisions regarding opioid prescribing. While standardized prescribing guidelines are improving this body of evidence, further work is necessary to determine how guidelines affect racially unequal opioid receipt. In addition, future work is needed to objectively focus on groups that traditionally face disparities in opioid prescribing, such as patients with cancer.

This will allow continued practice evaluation and will promote multidisciplinary partnerships to further our ability to provide high quality and equitable care.

CONCLUSIONS

Utilizing multivariable regression analysis to evaluate opioid prescribing practices in Medicare patients, individual comorbidities were strongly associated with prescribing–particularly for sickle cell disease, cancer diagnoses, and substance use disorder. This is a complex finding that may be related to the prevalence and presentation of disease processes across racial and ethnic minority groups. Interventions to address differences in opioid prescribing at F&MCW have required multidisciplinary collaboration and commitment on the individual, divisional, and enterprise levels. Other health systems should consider similar evaluation of health disparities in opioid prescribing practices and interventions to reduce disparities.

Financial Disclosure: None declared.

Funding/Support: None declared.

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Epidemiological Analysis of Chlamydia and Gonorrhea Cases in La Crosse County, Wisconsin, 2001-2020

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ABSTRACT

Introduction: *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are the two most reported bacterial infections in the United States, with over 1.5 million and 500 000 cases reported in 2019, respectively. The number of infections continues to rise, with significant disparities at the national level in the rate of infection between age, race, and sex demographic classifications. Although the disparities in chlamydia and gonorrhea infections have been well described in the US, little research has been done on a smaller community scale, such as La Crosse County, Wisconsin.

Methods: We accessed data from La Crosse County, Wisconsin; the State of Wisconsin; and the United States for gonorrhea and chlamydia cases from 2001 through 2020 and completed both descriptive analysis and inferential statistical analysis.

Results: Gonorrhea and chlamydia rates have risen at the local, state, and national levels. Demographic analysis of the cases in La Crosse County conveyed that females and Black populations having higher rates of infection. Additionally, the 25- to 39-year age group had a marked increase in gonorrhea rates at the county and state levels.

Conclusions: We were able to show demographic differences in chlamydia and gonorrhea incidence rates. The authors recommend that the 25- to 39-year-old group should undergo more regular comprehensive screening for all sexually transmitted infections.

INTRODUCTION

In the United States (US), an estimated 20 million people are newly diagnosed with a sexually transmitted infection (STI) each year.[1] Data in the US from 2019 showed *Chlamydia trachomatis* infection topping 1.5 million and over 500 000 cases of gonorrhea caused by *Neisseria gonorrhoeae*.[2,3] Both *C trachomatis* and *N gonorrhoeae* are transmitted by direct sexual contact.[4,5] However, 77% of individuals infected with *C trachomatis* and approximately half of the *N gonorrhoeae* infections will display no symptoms, so often these infections go undiagnosed.[5]

Approximately 50% of all new STIs diagnosed each year in the US are in those aged 15 to 24.[1,4] Twice as many young women within the 15- to 24-year age bracket will have a chlamydia diagnosis compared to young men in the same age bracket.[1] Because women have more complications arising from chlamydia and gonorrhea infection than men, the Centers for Disease Control and Prevention (CDC) recommends women be screened more regularly than men for both infections.[6]

Disparities in STI rates do exist among different racial groups, but this is largely due to variations in access to health care, segregated housing, and the number of sexual partners.[7,8] However, in a California study, Black Americans were shown to have 6 times higher STI rates than White Americans, even when income was taken into consideration. Of note, Black Americans within the highest poverty group had the most cases of gonorrhea in this study, demonstrating that socioeconomic status has a significant bearing on STI rates.[9] Although race itself does not indicate a

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Table 1. Total Number of Annual Reported Cases and Incidence Rates, When Available, of *Chlamydia trachomatis* in La Crosse County, Wisconsin, and the US, 2001–2020

Year	La Crosse County		Wisconsin		United States	
	Cases	Rate[a]	Cases	Rate[a]	Cases	Rate[a]
2001	266	247	16 284	321	783 242	278
2002	281	259	17 000	312	834 555	297
2003	314	288	17 942	327	877 478	305
2004	396	362	19 217	349	929 462	320
2005	355	323	20 461	369	976 445	333
2006	353	319	20 190	362	1 030 911	348
2007	335	300	19 555	349	1 108 374	370
2008	369	327	20 996	372	1 210 523	401
2009	362	317	20 906	369	1 244 180	409
2010	364	317	23 236	408	1 307 893	426
2011	460	378	24 619	429	1 412 791	457
2012	389	337	23 726	414	1 422 976	457
2013	412	352	23 572	412	1 401 906	447
2014	486	416	23 154	406	1 441 789	456
2015	520	423	24 381	425	1 526 658	475
2016	524	469	26 894	470	1 598 354	495
2017	489	440	27 740	485	1 708 569	525
2018	539	476	26 797	490	1 595 559	538
2019	612	543	29 772	529	1 808 703	551
2020	598	495	22 277	378	1 335 916	403

[a]Incidence rate per 100 000 population.

Table 2. Total Number of Annual Reported Cases and Incidence Rates, When Available, of *Neisseria gonorrhoeae* in La Crosse County, Wisconsin, and the US, 2001–2020

Year	La Crosse County		Wisconsin		United States	
	Cases	Rate[a]	Cases	Rate[a]	Cases	Rate[a]
2001	55	51	6 011	111	361 705	129
2002	39	36	6 341	116	224 918	125
2003	19	17	5 663	103	335 104	116
2004	63	58	5 053	92	330 132	114
2005	46	42	5 869	106	339 593	116
2006	27	24	6 927	124	358 366	121
2007	62	55	6 752	120	355 991	119
2008	43	38	6 087	108	336 742	112
2009	61	53	5 201	92	301 174	99
2010	34	30	5 091	89	309 341	101
2011	54	45	4 789	84	321 849	104
2012	51	42	4 704	83	334 826	107
2013	25	22	4 599	81	333 004	106
2014	43	37	4 078	72	350 062	111
2015	54	43	5 260	93	395 216	123
2016	35	30	6 498	115	468 514	145
2017	48	44	7 661	135	555 608	171
2018	145	125	7 619	139	528 013	178
2019	87	77	9 054	161	616 392	188
2020	163	135	8 315	143	564 110	171

[a]Incidence rate per 100 000 population.

genetic predisposition to certain STIs like gonorrhea, lifestyle differences among certain races provide for a greater risk of STIs among those groups.[7-9]

In this study, chlamydia and gonorrhea rates were assessed in a smaller community and then compared to the State of Wisconsin and the US from 2001 through 2020. The relationship between age, sex, and race was assessed in relation to positive chlamydia or gonorrhea infection in La Crosse County compared to the State of Wisconsin and the US from 2001through 2020.

METHODS

Data Collection

All laboratory detected incident cases of *C trachomatis* and *N gonorrhoeae* in La Crosse County per year during 2001-2020 were collected from the La Crosse County Health Department. The total number of incident laboratory detected positive cases and cases per 100 000 for *C trachomatis* and *N gonorrhoeae* in Wisconsin and the US that represented the years 2001-2020 were collected from the CDC Nationally Notifiable Infectious Diseases and Conditions, United States: Weekly Tables.[10] This study was approved by the Institutional Research Board committee at the University of Wisconsin–La Crosse.

Because of a software change in the State of Wisconsin in 2012, demographic numbers for chlamydia and gonorrhea incidence rates in La Crosse County and Wisconsin before 2012 were unretrievable. All positive cases from 2012 through 2019 were reported by age, sex, and race for La Crosse County and the State of Wisconsin by using data collected from the Wisconsin Department of Health Services Sexually Transmitted Disease Surveillance Annual Reports.[11] The total number of chlamydia and gonorrhea cases, as well as rates per 100 000, were differentiated by sex and race for the US using data accessed from the CDC and the State of Wisconsin.[10,11] Cases with missing characterization of age, sex, and race were excluded from analysis. Age statistics for the US were not computed because of age breakdown data discrepancies with La Crosse County and the State of Wisconsin. For gonorrhea and chlamydia cases in La Crosse County and Wisconsin, the following age groups were used: 0 to 14, 15 to 24, 25 to 39, and ≥40.[11]

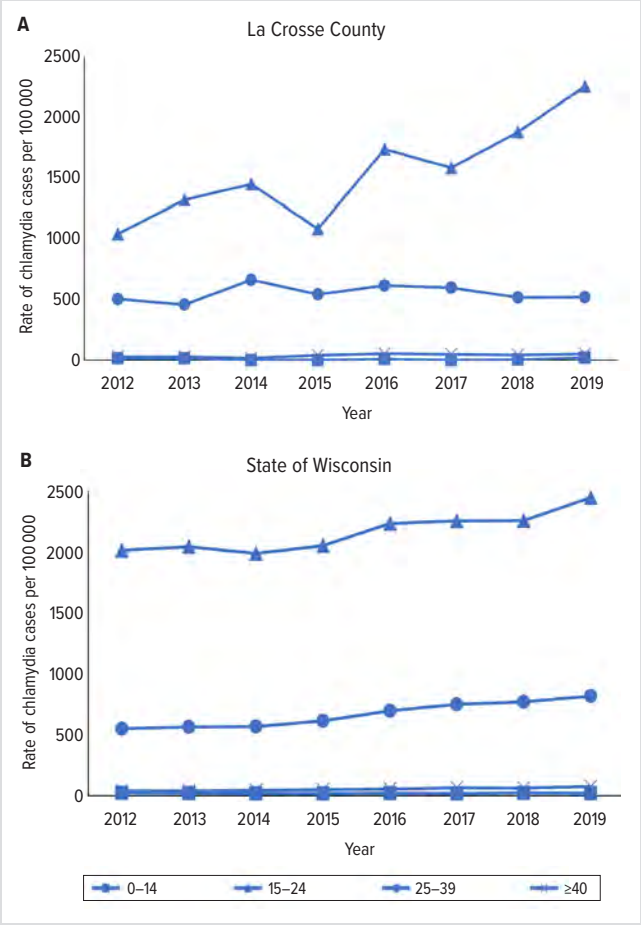
Descriptive Analysis

The total annual number of reported incident chlamydia and gonorrhea infections for La Crosse County, the State of Wisconsin, and the US, as well as the rates per 100 000 population, when available, were organized into tables. The annual rate of incident chlamydia and gonorrhea infections per 100 000 population in La Crosse County, the State of Wisconsin, and the US were graphed from 2011 through 2019.

Inferential Statistical Analysis

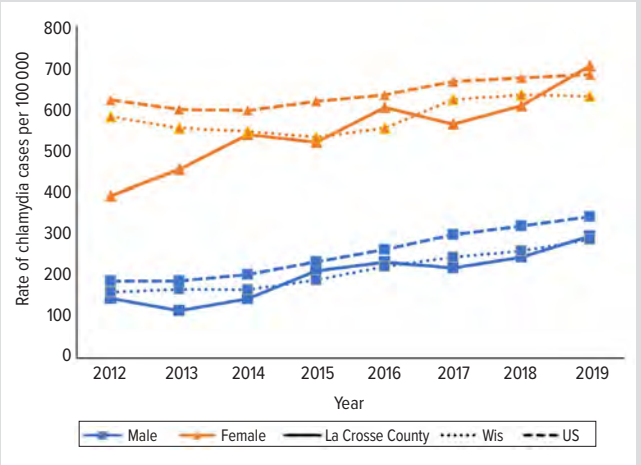
An analysis of variance with 2 categorical independent variables (2-way ANOVA) was performed for each demographic category (age, sex, and race) and location for both chlamydia and gonorrhea, followed by a Bonferroni post-hoc test when needed

Figure 1. Annual Incidence Rates of Chlamydia Infections per 100 000 Population for Those Aged 0–14, 15–24, 25–39, and ≥40 Years Old in (A) La Crosse County and (B) the State of Wisconsin, 2012–2019



Data were collected from the Centers for Disease Control and Prevention Annual Morbidity and Mortality Reports and the Wisconsin Department of Health Services Sexually Transmitted Diseases Surveillance Reports.

Figure 2. Annual Incidence Rates of Chlamydia Infections per 100 000 Population for Males and Females in La Crosse County, the State of Wisconsin, and the United States, 2012–2019



Data were collected from the Centers for Disease Control and Prevention Annual Morbidity and Mortality Reports and the Wisconsin Department of Health Services Sexually Transmitted Diseases Surveillance Reports.

to reduce false-positive results[12] using SPSS Statistics version 28.0.0.0 (IBM Corp). A *P* value of ≤0.05 was deemed significant.

RESULTS

We sought to analyze the relationship between age, sex, and race and positive *C trachomatis* and *N gonorrhoeae* infection in La Crosse County compared to the State of Wisconsin and the US during 2001-2020, and we found that the total number of annual incident cases of chlamydia and gonorrhea in La Crosse County, Wisconsin, and the US steadily rose during this time period (Tables 1 and 2), with an approximate doubling of chlamydia cases per 100 000.

Chlamydia Rates

Incidence by Age Group

Age-related data regarding the rate of chlamydia infection per 100 000 population were collected for individuals in 4 different age groups (0-14, 15-24, 25-39, and ≥40 years old) in La Crosse County and the State of Wisconsin. Chlamydia infections were highest in the 15- to 24-year-old age group in both the county (Figure 1A) and state (Figure 1B) and increased over the study period. Age-related data for the US from 2012 through 2019 were not included due to differences in age groupings at the national level versus the county and the state.

To further analyze the relationship between the rate of chlamydia infection and age group, a 2-way ANOVA F test showed a significant difference ($P<0.001$) in the average incidence rates within the 4 age groups in both the county and state. A Bonferroni post-hoc test analysis showed the average incidence rate of chlamydia infection during 2012-2019 among those aged 0 to 14 in La Crosse County was significantly lower ($P<0.001$) than those aged 15 to 24, with no significant differences among those aged 0 to 14 ($P=0.874$), 25 to 39 ($P=0.160$), and ≥40 years old ($P=0.847$). Similar findings also were observed when comparing the age groups within the state.

Next, average incidence rates of chlamydia infection by age group within each location were reviewed. The average incidence rate of chlamydia infection during 2012-2019 in both La Crosse County and the State of Wisconsin in those aged 0 to 14 and ≥40 years old were not significantly different ($P=1.000$). However, those aged 15 to 24 ($P<0.001$) and 25 to 39 years old ($P<0.001$) had significantly higher rates both in the county and the state compared to other age groups.

Incidence by Sex

The rates of chlamydia infection per 100 000 population in La Crosse County, the State of Wisconsin, and the US were analyzed for 2012-2019 to compare male and female rates. Infection rates were significantly higher in females versus males at all levels ($P=0.009$, Figure 2). Male and female chlamydia incidence rates rose steadily at the county, state, and national levels from

2012 through 2019, but no significant difference was observed ($P < 0.643$) when reviewing the relationship between location and sex.

Incidence by Race

Next, rates of chlamydia infection per 100 000 population were collected for White, Black, Native American/Alaskan Native, and Asian/Pacific Islander individuals in La Crosse County, the State of Wisconsin, and the US from 2012 through 2019. Black and Native American/Alaskan Native individuals demonstrated significantly higher chlamydia infection rates ($P < 0.001$) than the other races (Figure 3). La Crosse County and State of Wisconsin data showed Black individuals had a higher infection rate at the national level. Native American/Alaskan Native individuals in La Crosse County displayed higher chlamydia infection rates in 2012 and 2014-2016 compared to the rates in Wisconsin and the US.

No significant differences for White or Asian/Pacific Islander individuals at the county ($P = 1.000$), state ($P = 0.8660$, and national levels ($P = 0.400$) were detected. However, the chlamydia infection rate in the Black population was significantly higher in both La Crosse County ($P < 0.001$) and the State of Wisconsin ($P < 0.001$) versus the US, but no significant difference in chlamydia rates was noted for Black individuals between the county and the state ($P = 0.202$). Chlamydia rates were significantly higher in La Crosse County than the State of Wisconsin ($P = 0.037$) or the US ($P < 0.001$) for Native American/Alaskan Native individuals, but there was no significant difference between the State of Wisconsin and the US ($P = 0.433$) among this population.

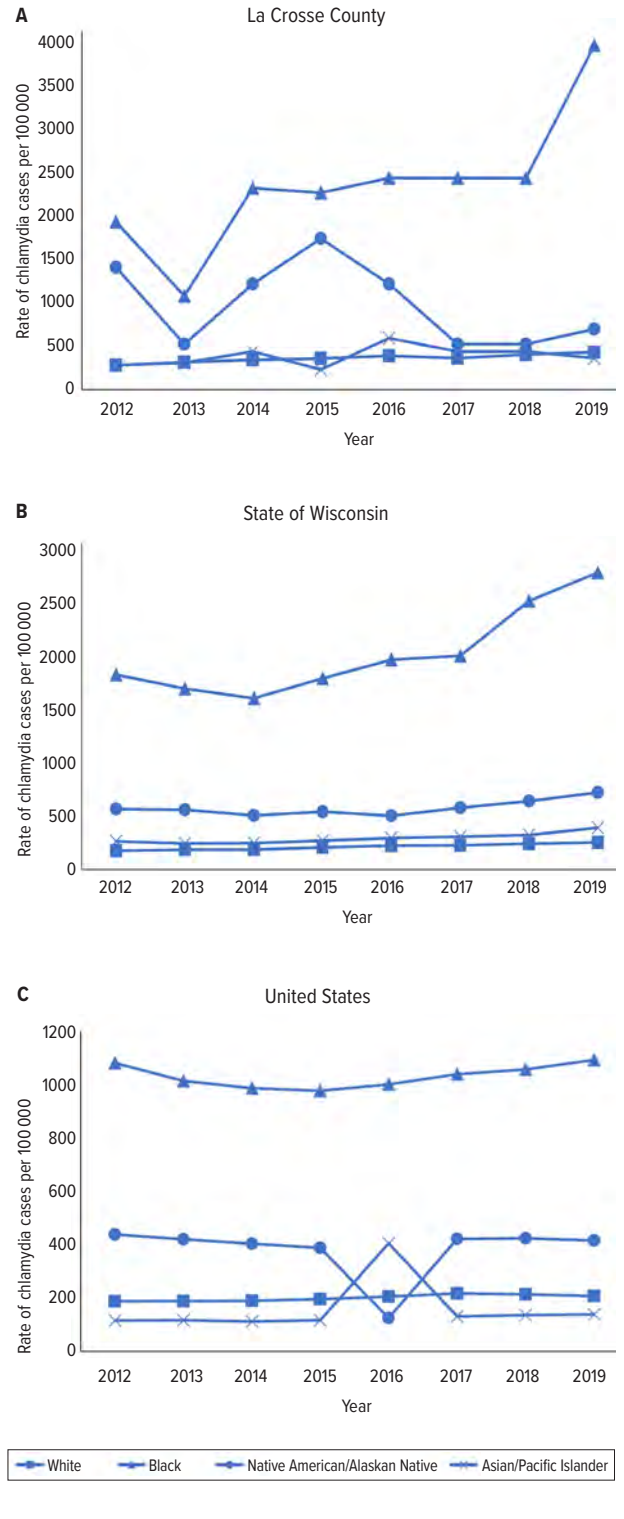
Next, Bonferroni post-hoc analysis of the 2012-2019 data in La Crosse County indicated significantly fewer chlamydia cases ($P < 0.001$) in White or Asian/Pacific Islander populations than Black or Native American/Alaskan Native populations, but no significant difference was observed for White versus Asian/Pacific Islander ($P = 1.000$) populations. However, the chlamydia rate was significantly higher ($P < 0.001$) in the Black population versus the Native American/Alaskan Native population in La Crosse County. Similarly, the State of Wisconsin and the US had significantly higher ($P < 0.001$) average chlamydia rates among Black individuals compared to all other groups. Both Wisconsin and the US had chlamydia infection rates ($P = 0.087$ to $P = 1.000$) that were not significant when Native American/Alaskan Native, Asian/Pacific Islander, and White populations were compared.

Gonorrhea Rates

Incidence by Age Group

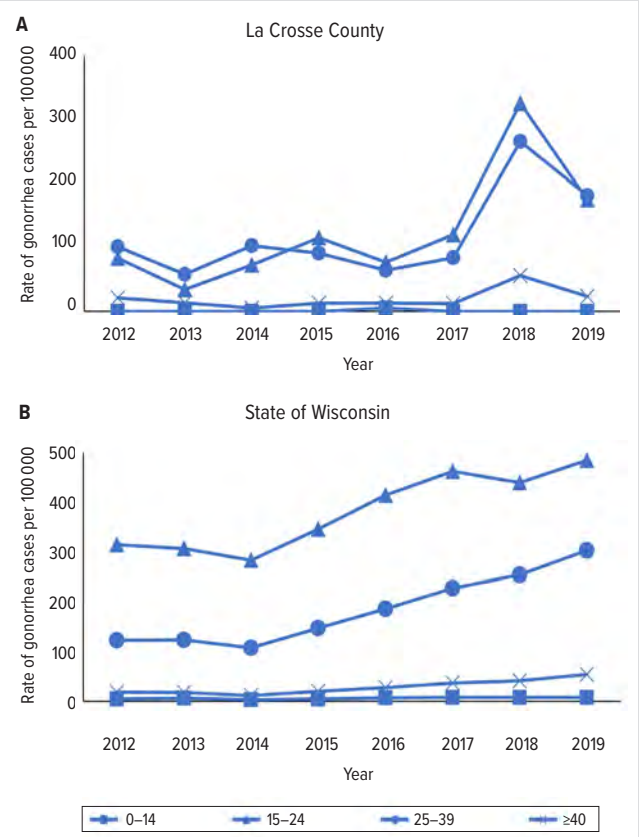
Using the incidence rate of gonorrhea infection per 100 000 at the county, state, and national levels, the total number of gonorrhea cases also rose over this time period (Table 2). To assess how age affects gonorrhea rates, the incidence rates of gonorrhea during 2012-2019 were collected only for La Crosse County

Figure 3. Annual Incidence Rates of Chlamydia Infections per 100 000 Population Identifying as White, Black, Native American/Alaskan Native, and Asian/Pacific Islander in (A) La Crosse County, (B) the State of Wisconsin, and (C) the United States, 2012–2019



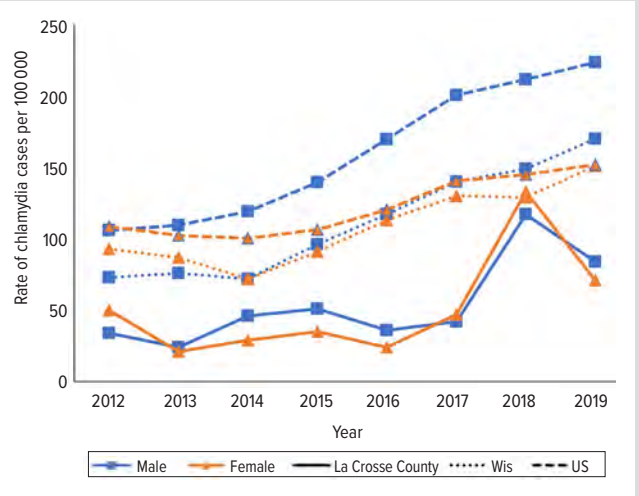
Data were collected from the Centers for Disease Control and Prevention Annual Morbidity and Mortality Reports and the Wisconsin Department of Health Services Sexually Transmitted Diseases Surveillance Reports.

Figure 4. Annual Incidence Rates of Gonorrhea Infections per 100 000 Population for Those Aged 0–14, 15–24, 25–39, and ≥40 Years Old in (A) La Crosse County and (B) the State of Wisconsin, 2012–2019



Data were collected from the Centers for Disease Control and Prevention Annual Morbidity and Mortality Reports and the Wisconsin Department of Health Services Sexually Transmitted Diseases Surveillance Reports.

Figure 5. Annual Incidence Rates of Gonorrhea Infections per 100 000 Population for Males and Females in La Crosse County, the State of Wisconsin, and the United States, 2012–2019



Data were collected from the Centers for Disease Control and Prevention Annual Morbidity and Mortality Reports and the Wisconsin Department of Health Services Sexually Transmitted Diseases Surveillance Reports.

and the State of Wisconsin. Gonorrhea infections rose significantly ($P < 0.001$) in La Crosse County (Figure 4A) and were even higher in the 15- to 24-year-old age group in the State of Wisconsin (Figure 4B). Within Wisconsin, the rate of gonorrhea infections in the 25- to 29-year-old age group was higher than rates in either the 0- to 14-year-old or ≥40-year-old age group. La Crosse County had gonorrhea rates that were similar for those aged 15 to 24 and 25 to 39 years old. Moreover, the F test showed there was a significant difference ($P < 0.001$) in the average higher incidence rate of gonorrhea infection between location and age group classification.

A Bonferroni analysis demonstrated that the average incidence of gonorrhea infection during 2012-2019 was not significantly different among the 0 to 14 age group ($P = 0.835$) and the ≥40 age group ($P = 0.689$) between La Crosse County and the State of Wisconsin. However, the gonorrhea rates among those 15 to 24 ($P < 0.001$) and 25 to 39 years old ($P = 0.006$) were significantly higher in the state versus the county.

A Bonferroni analysis demonstrated significantly lower gonorrhea incidence rates in those 0 to 14 years of age ($P < 0.001$) and ≥40 years of age ($P = 0.008$ to $P < 0.001$) compared to those 15 to 24 and 25 to 39 years old in La Crosse County and the State of Wisconsin. There was no significant difference between those aged 0 to 14 or ≥40 years old ($P = 1.000$) in average gonorrhea rates in the county or the state. However, the average incidence rate of gonorrhea infection among those 15 to 24 years of age was significantly higher ($P < 0.001$) than the rate among those 25 to 39 years old in the state, while there was no significant difference among those 15 to 24 or 25 to 39 years of age in the county.

Incidence by Sex

Although sex played a role in chlamydia cases, it did not appear to affect gonorrhea infection rates. Overall, the gonorrhea incidence rate rose significantly at the county, state, and national levels for both sexes during 2012-2019 ($P < 0.001$, Figure 5). The US had the highest overall rate and La Crosse County had the lowest. However, there was no significant difference in the average gonorrhea incidence rate in females versus males ($P = 0.144$) or between location and sex ($P = 0.266$).

Incidence by Race

People identifying as Black had the highest incidence rate of gonorrhea infection per 100 000 population compared to any other racial group at all levels (Figure 6). Within La Crosse County and the State of Wisconsin, the rate of infection in the Black and Native American/Alaskan Native populations versus other races was higher than the US.

An F test confirmed a significant difference ($P = 0.003$) in gonorrhea infection rates in La Crosse County, the State of Wisconsin, and the US when race was aligned with location. Significant differences ($P < 0.001$) were noted among the average incidence rate

of gonorrhea infections between the different racial groups as well as between location and racial classification. Using the Bonferroni post-hoc test, the average incidence of gonorrhea infection during 2012-2019 among those identifying as White ($P = 1.000$), Native American/Alaskan Native ($P = 0.231$ to 1.000) or Asian/Pacific islander ($P = 1.000$) was not significantly different when comparing all 3 levels. However, the Black population had significantly higher gonorrhea rates in the county and state ($P < 0.0001$) when compared to the rate in the US, but no significant difference was observed between the rates La Crosse County and the State of Wisconsin ($P = 0.362$).

Next, the 2-way ANOVA plus Bonferroni post-hoc test demonstrated that the average gonorrhea incidence rate during 2012-2019 was significantly higher in the Black population at the county, state, and national levels ($P < 0.0001$). There was no significant difference in the average gonorrhea incidence rate ($P = 0.076$ to 1.000) between those identifying as White, Native American/Alaskan Native, or Asian/Pacific Islander at the county, state, or national levels.

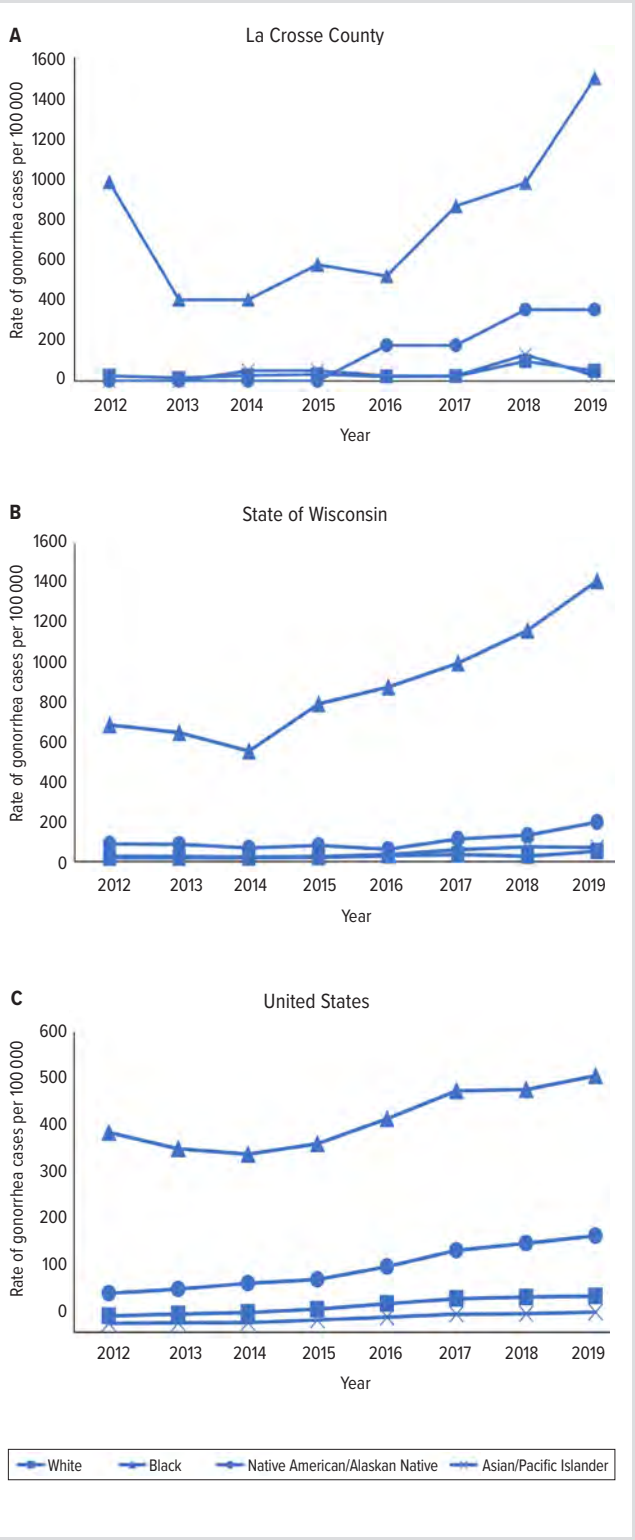
DISCUSSION

Chlamydia and gonorrhea rates have risen steadily over the last 2 decades despite better detection methods and screening for STIs.[1-4] Our study found an increase in the annual rate of chlamydia cases from 2001 through 2020 in the US (783 242 to 1 335 916), the State of Wisconsin (16 284 to 22 277), and La Crosse County (266 to 598). Cases of gonorrhea also rose nationally (361 705 to 564 110), in Wisconsin (6011 to 8315), and in La Crosse County (55 to 163) during this time period.

Past studies have shown that over 50% of newly diagnosed STIs in the US are in those aged 15 to 24.[1,4] Further, both diseases may be rising in those 25 to 39 years of age.[12,13] The highest infection rates in La Crosse County and the State of Wisconsin during 2012-2019 were in those aged 15 to 24, matching previous studies.[1,4] Additionally, the rates of chlamydia and gonorrhea infection in those aged 25 to 39 were lower than the rates in the 15 to 24 age group, but were significantly higher in La Crosse County and the State of Wisconsin than other age groups. The increase in cases in the older age groups in Wisconsin is a concern, because the CDC does not recommend screening for asymptomatic chlamydia and gonorrhea infections in this group of patients.[14-16]

Besides the higher number of STIs in certain age groups, females had higher chlamydia and gonorrhea rates than males, a disparity this study reaffirms for chlamydia cases.[1] However, the average rates of gonorrhea infection did not differ significantly when comparing males to females at the county, state, or national levels. The disparity in infection rates could be due to the asymptomatic nature of chlamydia infections and less screening for men who have sex with women.[1,4,5]

Figure 6. Annual Incidence Rates of Gonorrhea Infections per 100 000 Population Identifying as White, Black, Native American/Alaskan Native, and Asian/Pacific Islander in (A) La Crosse County, (B) the State of Wisconsin, and (C) the United States, 2012–2019



Data were collected from the Centers for Disease Control and Prevention Annual Morbidity and Mortality Reports and the Wisconsin Department of Health Services Sexually Transmitted Diseases Surveillance Reports.

CONCLUSIONS

We were able to show demographic differences in the incidence rates of both chlamydia and gonorrhea for the study period. Based on these findings, it is recommended that the 25- to 39-year-old group undergo more regular comprehensive screening for all sexually transmitted infections.

Financial Disclosures: None declared.

Funding/Support: None declared.

Acknowledgements: The authors wish to thank the La Crosse County Public Health Office, Jackie Grayson, and the Wisconsin Department of Health Services for their essential assistance with data access.

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Incidence of Lymph Node Metastasis in Patients With a Preoperative Diagnosis of Endometrial Intraepithelial Neoplasia

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ABSTRACT

Introduction: Endometrial cancer is the most common gynecologic cancer in the United States, and endometrial cancer staging historically has included lymph node assessment to inform prognosis and guide recommendations for adjuvant treatment. This study sought to determine the incidence of lymph node involvement in patients undergoing hysterectomy with sentinel lymph node dissection for a preoperative diagnosis of endometrial intraepithelial neoplasia (EIN) to allow for risk stratification and management by general gynecology and gynecologic oncology.

Methods: We performed a retrospective chart review of patients diagnosed with EIN who underwent hysterectomy from January 2018 through July 2021. We collected and analyzed patient characteristics, perioperative metrics, and postoperative data. Incidence of lymph node positivity on final pathology was the primary outcome of interest. We analyzed clinical and histologic risk factors for correlation with a final diagnosis of endometrial carcinoma. Chi-square, Fisher exact, and *t* tests were used for comparisons.

Results: One hundred patients met inclusion criteria, 40 of whom had an underlying endometrial cancer. The majority were stage IA grade 1 endometrioid carcinomas (95%). Per institutional protocol, all patients were recommended sentinel lymph node dissection, of which 84 (84%) patients ultimately underwent lymph node dissection. One patient was found to have a positive sentinel lymph node on final pathology (1.2%). Increasing endometrial stripe thickness was positively associated with risk of endometrial carcinoma on final pathology (22.39 mm ± 31.87 vs 11.78 mm ± 5.17, $P = 0.023$).

Conclusions: The incidence of lymph node involvement in patients with a preoperative diagnosis of EIN is low. Sentinel lymph node dissection is unlikely to affect adjuvant treatment recommendations following surgical staging. Standardized risk assessment methods are warranted for patients with a preoperative diagnosis of EIN to delineate the utility of lymph node assessment in this population.

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INTRODUCTION

Endometrial cancer is the most common gynecologic cancer in the United States, with an estimated 66 570 people diagnosed in 2021.[1] Endometrioid carcinoma, the most common histologic subtype, accounts for 75% to 80% of all cases.[2] Endometrial intraepithelial neoplasia (EIN), formerly referred to as complex atypical hyperplasia (CAH), represents a precursor lesion to endometrioid adenocarcinoma of the endometrium. The underlying risk of occult endometrial cancer with a diagnosis of EIN is estimated to be as high as 43%.[3,4] However, given EIN and well-differentiated endometroid carcinoma exist on a histologic spectrum, it is challenging to distinguish these lesions, leading to poor pathologic diagnostic reproducibility.[5-7] Definitive management with total hysterectomy is recommended when a diagnosis of EIN is made given the risk of concurrent cancer.[4]

Endometrial cancer staging historically has included lymph node assessment to inform prognosis and guide recommendations for adjuvant treatment.[8] Various methods of lymph node assessment have been described given the underlying risk of carcinoma with EIN, though there is a lack of consensus regarding the role of lymphadenectomy.[9-11] Intraoperative endometrial assessment is commonly performed following hysterectomy, along with lymphadenectomy, in patients with

high-risk features and cancer identified on frozen pathology for comprehensive staging.[12,13] The imprecision of intraoperative frozen section and the potential for unnecessary surgical staging for patients with benign final pathology pose limitations to this method. Sentinel lymph node dissection is used as an alternative to lymphadenectomy to stage endometrial cancer with comparable diagnostic outcomes while minimizing postoperative morbidity associated with complete lymphadenectomy.[14-18] Sentinel lymph node dissection (SLND) is increasing in the setting of EIN, despite evidence from 2 randomized studies demonstrating no survival benefit for lymphadenectomy in early-stage endometrial cancer.[12,19,20] However, it is unknown if sentinel lymph node dissection affects adjuvant treatment or survival outcomes for patients ultimately diagnosed with endometrial cancer following hysterectomy.

Several studies have examined the role of lymph node dissection in EIN amid lack of consensus regarding surgical management,[9,10] though there are limited data establishing the absolute risk of lymph node involvement in patients presenting with EIN.[10] The objective of this study was to quantify the incidence of lymph node metastasis in a consecutive cohort of women presenting for surgical management, including SLND, with a preoperative diagnosis of EIN.

Table 1. Patient Characteristics, N = 100

	n (%)[a]
Age, years; mean	56.8 (±10.8)
Body mass index, mean	40.4 (±11.4)
Race/ethnicity	
Non-Hispanic White	94 (94%)
Non-HispanicBlack	3 (3%)
Hispanic	2 (2%)
Asian	1 (1%)
Menopausal status	
Premenopause	38 (38%)
Postmenopause	62 (62%)
Medical history	
Hypertension	62 (62%)
Diabetes	24 (24%)
Polycystic ovary syndrome	7 (7%)
Surgical history	
Cesarean delivery	17 (17%)
Appendectomy	11 (11%)
Laparotomy	5 (5%)
Laparoscopy	23 (23%)
Personal cancer history	11 (11%)
Breast	7 (64%)
Thyroid	1 (9%)
Pancreas	1 (9%)
Granulosa cell tumor (concurrent)	2 (18%)

[a]Percentage unless otherwise noted.

METHODS

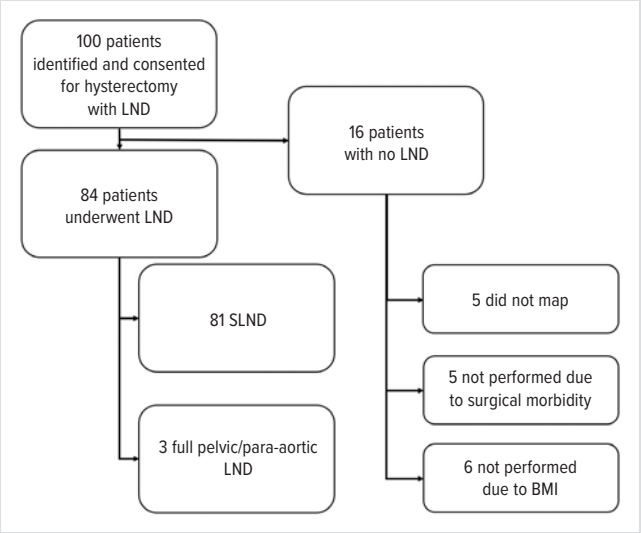
Following Institutional Review Board approval (IRB#2020-1404), we performed a retrospective cohort study of all patients with a preoperative diagnosis of EIN or CAH. We used *International Classification of Diseases*, *Ninth Revision (*ICD-9) or *Tenth Revision* (ICD-10) codes to identify all patients who underwent definitive surgical management for EIN/CAH with total hysterectomy from January 1, 2018, through July 31, 2021. All preoperative pathology specimens were reviewed and confirmed by institutional pathologists per division policy. We excluded patients who did not receive surgical management or whose surgery was not performed by a gynecologic oncologist.

In 2018, a uniform protocol for lymph node assessment at the time of hysterectomy for EIN was instituted at our institution. All patients undergoing hysterectomy for a preoperative diagnosis of EIN were managed surgically by a gynecologic oncologist, and lymph node sampling via sentinel lymph node dissection was recommended if no contraindications were present. If sentinel lymph node dissection could not be performed, a complete pelvic lymphadenectomy was recommended unless contraindications existed.

We manually reviewed the electronic medical record to collect baseline demographic and patient characteristic data. Race and ethnicity were self-reported by patients. Clinical characteristics including age, body mass index (BMI) (kg/m^2), menopausal status, and medical, surgical, and personal cancer history were collected. Perioperative outcomes, including method of endometrial biopsy acquisition (dilation and curettage [D&C], endometrial aspiration, hysteroscopy with D&C), operative time, estimated blood loss, perioperative blood transfusions, length of stay, and emergency department visit or readmission within 30 days also were recorded to secondarily identify risk factors for underlying carcinoma on final pathology. We abstracted pathologic data, including histology, grade, final cancer stage, mismatch repair status, tumor size (cm), depth of invasion, presence of lymphovascular space invasion, and pelvic washings status from the preoperative biopsy and final pathologic specimens. The number of patients with a preoperative diagnosis of "endometrial intraepithelial neoplasia – cannot rule out carcinoma" was recorded for analysis. Using established pathology diagnostic criteria from the Mayo Clinic, we dichotomized patients with a final diagnosis of cancer into high-risk and low-risk groups to examine associations between clinical data and final pathology results.[17] Lymph nodal tissue was analyzed by institutional gynecologic pathologists. Ultrastaging was used to assess sentinel lymph nodes on permanent specimens.[14]

The primary outcome – incidence of lymph node involvement at the time of hysterectomy – was defined by the presence of micrometastasis, or macrometastasis found within a lymph node specimen on final pathology. Secondary outcomes – risk factors for endometrial cancer and lymph node involvement on final pathology – were determined using statistical analysis. Descriptive statis-

Figure. Patients Undergoing or Omitted from Lymph Node Assessment at Time of Hysterectomy for Endometrial Intraepithelial Neoplasia



Abbreviations: LND, lymph node dissection; SLND, sentinel lymph node dissection; BMI, body mass index.

Table 2. Surgical Characteristics, N = 100

	n (%)[a]
Means of diagnosis	
Endometrial pipelle	60 (60%)
Dilation & curettage	4 (4%)
Hysteroscopy	36 (36%)
Surgical approach	
Robotic	58 (58%)
Laparoscopic	26 (26%)
Single-incision laparoscopy	9 (9%)
Abdominal	6 (6%)
Vaginal	1 (1%)
Lymph node assessment	
Full	3 (3%)
Sentinel	81 (81%)
None	16 (16%)
Lymph nodes positive (yes/no)	1 (1.2%)
Number of lymph nodes biopsied, mean	3.4 (± 2.8)
Final pathology	
Cancer	40 (40%)
Benign	60 (60%)

[a]Percentage unless otherwise noted.

tics were used to summarize demographic and clinic-pathologic data. Chi-square, Fisher exact, and *t* tests were performed using STATA version 16.1 (Stata Corp, College Station, Texas). A *P* value of < 0.05 was deemed statistically significant.

RESULTS

One hundred patients with a preoperative diagnosis of EIN met inclusion criteria. The mean age of the entire cohort was 56.8 years (±10.8), and mean BMI was 40.4 kg/m^2 (±11.4). The majority of patients were postmenopausal (62%) and self-identified as non-Hispanic White (94%). All patients underwent total hysterectomy and bilateral salpingo-oophorectomy. Complete patient characteristics are listed in Table 1. Eighty-one of the 100 patients who consented for lymph node assessment had bilateral sentinel lymph node dissection performed.

Three patients underwent complete bilateral pelvic lymphadenectomy at surgeon discretion following failed sentinel mapping. The Figure depicts surgical decision-making regarding completion of lymph node assessment. The large majority (93%) of procedures were completed laparoscopically, 6% via laparotomy, and 1% via a vaginal approach. Surgical characteristics of the entire cohort are listed in Table 2.

Forty patients were diagnosed with International Federation of Gynecology and Obstetrics (FIGO) grade 1 endometrioid adenocarcinoma on final pathology. Thirty-eight patients were diagnosed FIGO stage IA, 1 patient was diagnosed with Stage IIIC1 disease with metastatic involvement to 1 lymph node, and 1 patient with occult serosal involvement was diagnosed with Stage IIIA disease. None of the patients demonstrated >50% myometrial invasion or lymphovascular space invasion. The

Table 3. Characteristics of Patients Diagnosed with Endometrial Cancer on Final Pathology, N = 40

	n (%)[a]
Lymph mode assessment	
Full	2 (5%)
Sentinel	30 (75%)
None	8 (20%)
Histology	
Endometrioid	40 (100%)
Grade	40 (100%)
Stage	
IA	38 (95%)
IIIA	1 (2.5%)
IIIC1	1 (2.5%)
Microsatellite status	
MSS	38 (95%)
MSI	2 (5%)
Endometrial stripe thickness (mm), mean	15.6 (± 20)
Lymphovascular space invasion (yes/no)	0

[a]Percentage unless otherwise noted.

mean number of lymph nodes evaluated and removed per patient was 3.4 (±2.8). Only 1 of the 84 patients (1.2%) who underwent lymph node assessment was found to have lymph node involvement on final pathology. Of the patients diagnosed with Stage III disease, 1 patient received adjuvant treatment based on uterine factors, and 1 received adjuvant treatment based on lymph node assessment. Complete histopathologic characteristics are listed in Table 3.

Age, BMI, race and ethnicity, menopausal status, and mechanism of diagnosis were not significant predictors of cancer in univariate analysis. Increasing endometrial stripe thickness on preoperative ultrasound was associated with a statistically sig-

Table 4. Characteristics of Patients Based on Final Pathology (N = 100)

	Cancer (n = 40)	Benign (n = 60)	*P* value
Age, years; mean	55.7 (± 10.5)	57.5 (± 11)	0.421
Body mass index (kg/m^2), mean	41.6 (± 11.6)	39.6 (± 11.2)	0.389
Race			0.738
Non-Hispanic White	37 (92.5%)	57 (95%)	
Non-Hispanic Black	1 (2.5%)	2 (3.3%)	
Hispanic	2 (5%)	0	
Asian	0	1 (1.6%)	
Menopausal status			0.449
Premenopause	17 (42.5%)	21 (35%)	
Postmenopause	23 (57.5%)	39 (65%)	
Medical history			
Hypertension	25 (62.5%)	37 (61.7%)	0.933
Diabetes	10 (25%)	14 (23.3%)	0.848
Polycystic ovary syndrome	4 (10%)	3 (5%)	0.433
Surgical history			
Cesarean delivery	7 (17.5%)	10 (16.7%)	0.913
Appendectomy	5 (12.5%)	6 (10%)	0.695
Laparotomy	3 (7.5%)	2 (3.3%)	0.386
Laparoscopy	11 (27.5%)	12 (20%)	0.469
Personal cancer history			0.455
Breast	2 (5%)	5 (8.3%)	
Thyroid	0	1 (1.7%)	
Pancreas	0	1 (1.7%)	
Granulosa cell tumor (concurrent)	1 (2.5%)	1 (1.7%)	
Means of diagnosis			0.793
Endometrial pipelle	25 (62.5%)	35 (58.3%)	
Dilation & curettage	2 (5%)	2 (3.3%)	
Hysteroscopy	13 (32.5%)	23 (38.3%)	
Endometrial stripe thickness, mm (±)	22.39 (31.87)	11.78 (5.17)	0.023
Endometrial stripe ≥ 15 mm	18 (45%)	18 (30%)	0.016
Endometrial stripe ≥ 20 mm	8 (20%)	3 (5%)	0.006
Cannot rule out underlying carcinoma	14 (35%)	6 (10%)	0.003
Operating room time (minutes), mean	232 (± 60.4)	218 (± 40.7)	0.153
Estimated blood loss? (mL), mean	130.5 (± 217.8)	72 (± 52.9)	0.051
Perioperative blood transfusion (yes/no)	1 (2.5%)	1 (1.7%)	1
Lymph node assessment			0.396
Full	2 (5%)	1 (1.7%)	
Sentinel	30 (75%)	51 (85%)	
None	8 (20%)	8 (13.3%)	
Length of stay (days), mean	2.2 (± 0.66)	2 (± 0.95)	0.504
ED visit within 30 days (yes/no)	3 (7.5%)	3 (5%)	0.681
Readmission within 30 days (yes/no)	0	1 (1.7%)	1

Abbreviation: ED, emergency department.

Table 5. Characteristics of Patients Based on Mayo Criteria (N = 40)

	Meets Mayo (n = 12)	Does Not Meet Mayo (n = 28)	*P* value
Age (years), mean	55.58 (± 10.9)	55.7 (± 10.7)	0.092
Body mass index kg/m^2, mean	45.3 (± 12.4)	40.1 (± 11.2)	0.195
Race			1
Non-Hispanic White	11 (91.7%)	25 (89.3%)	
Non-Hispanic Black	0	1 (3.6%)	
Hispanic	1 (8.3%)	1 (3.6%)	
Asian	0	1 (3.6%)	
Menopausal status			0.589
Premenopause	4 (33.3%)	13 (46.4%)	
Postmenopause	8 (66.7%)	15 (53.6%)	
Medical history			
Hypertension	10 (83.3%)	15 (53.6%)	0.152
Diabetes	5 (41.7%)	5 (17.9%)	0.111
Polycystic ovary syndrome	1 (8.3%)	3 (10.7%)	0.818
Surgical history			
Cesarean delivery	2 (16.7%)	5 (17.9%)	1
Appendectomy	2 (16.7%)	3 (10.7%)	0.627
Laparotomy	0	3 (10.7%)	0.541
Laparoscopy	2 (16.7%)	9 (32.1%)	0.451
Personal cancer history			0.541
Breast	0	2 (7.1%)	
Granulosa cell tumor (concurrent)	0	1 (3.6%)	
Means of diagnosis			0.51
Endometrial pipelle	7 (58.3%)	18 (64.3%)	
Dilation & curettage	0	2 (7.1%)	
Hysteroscopy	5 (41.7%)	8 (28.6%)	
Stage			0.308
IA	10 (83.3%)	27 (96.4%)	
IIIA	1 (8.3%)	0	
IIIC1	1 (8.3%)	0	
Microsatellite status (MS)			0.515
MSS	11 (91.7%)	27 (96.4%)	
MSI	1 (8.3%)	1 (3.6%)	
Endometrial stripe thickness, (mm) mean	20.28 (± 56.73)	15.25 (± 8.35)	0.058

Abbreviations: MSS, microsatellite stable; MSI, microsatellite instability.

nificant increased risk of endometrial cancer on final pathology (22.39 mm ± 31.87 vs 11.78 ± 5.17, $P = 0.023$). This effect increased when endometrial stripe thickness was dichotomized at 20 mm (8 [20%] vs 3 [5%], $P = 0.003$), respectively. Additionally, a preoperative biopsy demonstrating "endometrial intraepithelial neoplasia – cannot rule out carcinoma" was significantly predictive of carcinoma on final pathology (14 [35%] vs 6 [10%], $P = 0.003$). Of the 16 patients who did not undergo lymph node assessment, 8 patients ultimately were diagnosed with endometrioid adenocarcinoma. Table 4 displays analyzed risk factors for carcinoma on final pathology.

Finally, we investigated factors correlating with high-risk and low-risk criteria for cancer on postoperative pathologic specimens based on validated guidelines from the Mayo Clinic (Table 5). In patients with a diagnosis of endometrioid carcinoma on final pathology, 12 patients (30%) met high-risk criteria based on tumor size ≥ 2cm. Other high-risk features considered included grade 3 histology or ≥50% of myometrial invasion; however, no patients in our cohort met these criteria. Age, BMI, menopausal status, mechanism of diagnosis, and preoperative endometrial thickness were not predictive of meeting high-risk criteria. Two of the 8 patients in whom lymph node assessment was not performed yet had a final diagnosis of

endometrioid adenocarcinoma met high-risk criteria based on tumor size alone.

DISCUSSION

The incidence of lymph node metastasis in patients with a preoperative diagnosis of EIN is low. Only 1 (1.2%) patient was identified to have lymph node involvement following surgical staging. Forty percent of patients in our cohort ultimately were diagnosed with endometrial cancer on final pathology, similar to rates reported elsewhere.[10,21] Patients with an increasing preoperative endometrial stripe thickness correlated with an increased risk of endometrial cancer ($P = 0.023$). Similarly, a preoperative diagnosis of "EIN – cannot rule out carcinoma" was significantly associated with endometrial cancer on final pathology ($P = 0.003$). The majority of patients (70%) diagnosed with endometrial cancer in our study notably were deemed low risk for lymph node metastasis by Mayo Clinic criteria, and nodal assessment guided adjuvant therapy recommendations in only 1 patient. When examining preoperative risk factors for a final pathologic diagnosis of endometrioid adenocarcinoma, our data confirm characteristics previously reported in other literature.[10,22]

It is important to differentiate a diagnosis of cancer from EIN insofar as it necessitates a different course of management upon diagnosis. Patients with EIN are recommended to have an extrafascial hysterectomy. In patients with low-risk endometrial cancer on hysterectomy pathology, adjuvant treatment is not recommended.[23] Prior literature has focused on predicting the individuals who will have a final post-hysterectomy diagnosis of cancer for those with a pre-hysterectomy finding of EIN. Our data support established data that a cohort of patients with increasing endometrial stripe thickness and histopathologic concerns for underlying carcinoma may benefit from surgical staging. Additionally, this information can be utilized for counseling regarding rates of nodal involvement in patients with preoperative diagnosis of EIN.

Our results are consistent with rates of lymph node involvement in the setting of EIN reported elsewhere. Touhami et al evaluated the risk of lymph node involvement in patients with a preoperative diagnosis of "EIN – cannot rule out carcinoma" compared to EIN, reporting a rate of lymph node involvement of 3.3% in a cohort of 120 patients undergoing hysterectomy with SLND.[10] Of these patients, 41.6% carried a preoperative diagnosis of "EIN – cannot rule out carcinoma," suggesting this cohort as higher risk for endometrial carcinoma on final pathology. Notably, rates of adjuvant treatment following surgical staging were not reported in this study.[10] Mueller et al found similar rates of lymph node involvement to our current study when evaluating operative outcomes for patients undergoing hysterectomy and SLND for a preoperative diagnosis of EIN. In 161 patients undergoing hysterectomy with SLND, 1 patient (0.6%) was found to have a positive sentinel lymph node.[21] Of the 98 patients diagnosed with endometrioid endometrial cancer, 10 received adjuvant treatment, with the majority receiving recommendations for adjuvant treatment based on high intermediate risk criteria[23] and not lymph node factors. Our study finds similar consistency, with 1 patient receiving adjuvant treatment based on lymph node metastatic disease, and 1 patient receiving adjuvant treatment based on serosal involvement. The demonstrated rate of lymph node involvement in patients with EIN has been repeatedly low; therefore, universal staging in this population likely subjects a low-risk group of these patients to unnecessary intervention.

Recent research has sought to determine risk factors and reliable methods for identifying patients with EIN who would benefit from staging surgery with a gynecologic oncologist. Intraoperative surgeon assessment of the specimen, as well as frozen-section pathologic analysis to assess for myometrial invasion and tumor size have been utilized. These methods have limitations and are associated with poor concordance with final pathology due to poor reproducibility across various institutions and surgeons.[24-26] These methods also require removal of the uterine specimen to determine the need for lymph node assessment, which precludes the use of SLND in this setting given disruption of lymphatic channels inherent to hysterectomy. Focus has thus shifted towards identifying risk factors suggestive of underlying endometrial cancer in the setting of EIN. Furthermore, Touhami et al reported a significantly increased risk of endometrial carcinoma in patients with a preoperative diagnosis of "EIN – cannot rule out carcinoma" compared to EIN alone, similar to our findings here.[10] Abt et al evaluated 378 patients with EIN undergoing hysterectomy to identify risk factors for endometrial carcinoma on final pathology.[22] Similar to our findings, they report a relative risk (RR) of 1.8 (95% CI, 1.2-2.5) for endometrial cancer on final pathology in EIN patients with a preoperative endometrial stripe thickness ≥ 15 mm. This effect was even more pronounced with an endometrial stripe thickness ≥ 20 mm (RR 2.0; 95% CI, 1.3-2.9), suggesting that increasing endometrial stripe thickness may be utilized preoperatively to risk stratify patients who may benefit from lymph node assessment and surgical staging with a gynecologic oncologist.

Current recommendations from the American College of Obstetricians and Gynecologists and the Society of Gynecologic Oncology suggest that premalignant endometrial lesions may be managed by a benign gynecologist or gynecologic oncologist. Given multiple reasonable options for treatment, this can lead to a management dilemma for patients with EIN.[4] Universal referral of patients with EIN to gynecologic oncology will result in unnecessary utilization of specialty services. This may have detrimental unintended consequences on certain populations or low resource areas where access to subspecialists is limited. However, it is also imperative to identify patients preoperatively who will benefit from referral to gynecologic oncology for surgi-

cal staging, so that the correct patients receive adjuvant therapy. Additionally, the benefits of multidisciplinary care, including a gynecologic oncologist, may be more readily extended to patients in the form of survivorship resources, sexual wellness following treatment, and clinical trial enrollment for patients with preinvasive disease.

Our study is strengthened by a consecutive cohort of patients recommended for and undergoing lymph node assessment, reducing selection bias for our patient population. Similarly, the majority of patients included completed lymph node assessment, whereas other series have relied on intraoperative decision-making to delineate need for lymph node evaluation—potentially skewing results towards a more high-risk patient population.[9,22] Given the relatively small sample size, we were unable to perform multivariate analysis related to our primary outcome.

Additional limitations of our study include those inherent to a single institutional retrospective review, and, as such, our results may not be applicable to patient populations largely different than our own. The majority of our patients diagnosed with endometrial cancer on final pathology were diagnosed with low-risk, stage IA disease. All patients identified in our cohort were diagnosed with endometrioid histology, thus our results have limited applicability to patients with high-grade or nonendometrioid histologies. Similarly, we did not incorporate comprehensive molecular characteristics of this low-grade group of carcinomas as this was not routinely performed at our institution during the specified time period. Given that the present study was conducted at a single academic institution with a predominantly non-Hispanic White population, our findings may not be generalizable to a population different than our own. We did not consider the cost-effectiveness of universal SLND, as this has been explored elsewhere, with findings suggesting that this practice is not universally cost effective due to the small proportion of patients who benefit from SLND.[26,27] Future research will seek to identify additional factors associated with elevated risk of high-risk endometrial cancer in patients with EIN, as well as incorporating molecular subtyping into risk stratification for patients with premalignant endometrial lesions.

CONCLUSIONS

This study reports a low incidence of lymph node involvement with a pre-hysterectomy diagnosis of EIN. The rate at which surgical lymph node assessment influences adjuvant treatment decisions is low in this patient population. With proper risk stratification, a low-risk group of patients with preoperative diagnosis of EIN may be spared surgical lymph node assessment.

Financial Disclosures: None declared.

Funding/Support: None declared.

Acknowledgements: These findings were presented at the Society of Academic Specialists in General Obstetrics and Gynecology Annual Meeting on May 5, 2022, San Diego, California, and virtually at the Mid-Atlantic Gynecologic Oncology Society Annual Meeting on October 22, 2021.

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Characteristics of Patients Disengaged From Pharmacist-Led Hypertension Management in Primary Care: An Observational Study

Isabel Wedig, PharmD; Anupama Joseph, MD; Tyler Ho, PharmD

ABSTRACT

Introduction: Hypertension is a leading cause of morbidity and mortality worldwide. Although it is often asymptomatic, adequate blood pressure control can help decrease the risk of cardiovascular, renal, and neurologic diseases. Clinical pharmacists can play a critical role in blood pressure management and have been shown to help patients meet their goals. Despite this, patients often disengage from pharmacy services, and reasons for this are not well understood. This study sought to evaluate characteristics of patients who are referred but not engaged in a primary care pharmacy antihypertensive service and explore potential reasons for disengagement.

Methods: Data from the 2023 fiscal year (July 1, 2022 – June 30, 2023) were collected from UW Health's electronic health record. Inclusion criteria were prespecified to include adults referred by their primary care provider to pharmacy services but who did not engage in care. Retrospective chart reviews were performed to gather demographic information on this population, and descriptive statistics were used for data analysis.

Results: Of the 168 individuals who met the inclusion criteria, 66.1% of participants were not currently at their blood pressure goal. The majority of patients did not engage in pharmacist services due to lack of patient interest (n = 114, 67.9%) or being managed by another health care member team (n = 36, 21.4%).

Conclusions: The majority of patients who did not engage with a pharmacist for hypertension medication management despite referral from their primary care provider are not achieving their blood pressure goal.

INTRODUCTION

Hypertension is a significant cause of morbidity and mortality worldwide.[1] It is estimated that hypertension is accountable for about 54% of stroke and 47% of ischemic heart disease cases – 2 of the top 5 leading causes of death in the United States.[2,3] Hypertension is frequently asymptomatic, but it is the most prevalent modifiable risk factor for cardiovascular disease. Adequate blood pressure control can help reduce risks of other diseases, including coronary heart disease, chronic kidney disease, stroke, heart failure, and arrhythmias.[4] There is a lack of consensus on the preferred hypertension goal for patients.[5,6] According to the American College of Cardiology/American Heart Association (ACC/AHA), all patients should have a goal blood pressure of less than 130/80 mmHg.[7] A less restrictive goal of less than 140/90 mmHg, recommended by the American Academy of Family Physicians, is also seen commonly in practice. Similarly, several factors contribute to uncontrolled blood pressure, including competing comorbidities, lack of understanding of hypertension, stress, food/housing insecurity, financial or transportation barriers, poor diet, and sedentary lifestyle.[8] A multifaceted approach addressing both pharmacologic and nonpharmacologic factors have the opportunity to improve hypertension control rates.

Incorporating pharmacists into the interdisciplinary workflow can help ease the burden on primary care providers while increasing patient health care access.[1] Additionally, a survey of 114 primary care providers found that they see a positive clini-

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cal impact and found no increase in workload when working with clinical pharmacists.[9] Pharmacists also can serve a critical role helping patients reach their specific blood pressure goals.[10-12] Matsumoto et al reported that in patients who had scheduled follow-up with a pharmacist, significant reductions in systolic blood pressure were seen compared to those with as-needed pharmacist follow-up (mean differences in systolic blood pressure: -8.89 mmHg in the scheduled group vs -3.23 mmHg in the as-needed group).[10] Similar outcomes were seen in patients who were managed by community pharmacists who provided medication education, medication management, and regular manual blood pressure measurements and who contacted primary care physicians through the electronic health record about blood pressure readings above goal. In patients who initially had uncontrolled or borderline blood pressure (blood pressure goal < 140/90 mmHg) reductions of 10.40 and 4.17 mmHg, respectively, were seen, and these reductions were continued or stabilized after the first year following enrollment.[11] According to Hartkopf et al, primary care pharmacists helped 74.2% of patients reach their blood pressure goal (< 140/90 mmHg) versus 41.5% of patients who were not managed by a pharmacist.[12]

At our study site, which is a large academic medical center in the upper Midwest, primary care pharmacists serve a variety of disease states, such as hypertension, diabetes, and hyperlipidemia. Working under detailed and specific delegation protocols for each disease state, pharmacists are independently responsible for medication titration and prescribing, vital sign monitoring, laboratory test ordering and assessment, and medication and lifestyle education. At the study site primary care clinics, patients can be referred to pharmacists for follow-up as deemed appropriate by the clinician. Once referred, patients will have an individual appointment with a pharmacist either in person, by telephone, or via a video visit. Appointments are scheduled as 30- or 60-minute blocks as selected by the pharmacist team. Each visit includes obtaining an accurate medication list, reviewing pertinent laboratory tests and vital signs, providing lifestyle recommendations, and adjusting medications as needed. Patients are then followed by the pharmacist team until either the patient meets their personal health goal(s) and/or specific clinical outcomes are met for each comorbidity/disease state. Despite the positive disease- and patient-oriented outcomes seen with pharmacist interventions, patients do not always accept referral to a pharmacist for medication management services. Therefore, this study sought to evaluate the demographics of those patients who were referred but did not engage in primary care pharmacy antihypertensive services and to explore reasons for disengagement.

METHODS

Setting and Study Design

This retrospective study was performed at the University of Wisconsin Hospital and Clinics (UW Health). UW Health is a

Figure 1. Inclusion and Exclusion Criteria Flow Chart

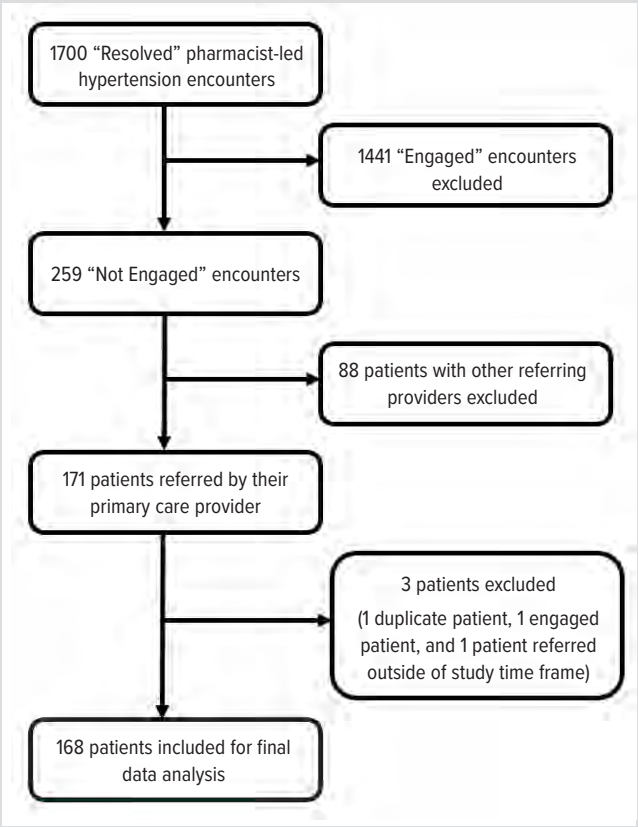
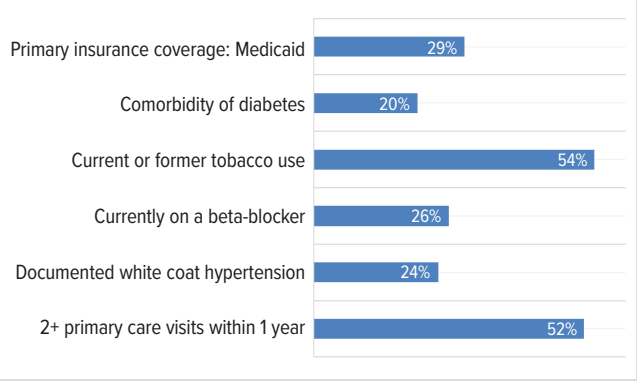


Table 1. Patient Characteristics

Age (average)	56 years (range 25 – 93 years); 56 ± 14 years
Sex	
Male	92 (54.8%)
Female	76 (45.2%)
Race	
White	126 (75%)
Black	27 (16.1%)
Asian	10 (6%)
American Indian or Alaska Native	1 (0.6%)
Native Hawaiian/Other Pacific Islander	1 (0.6%)
Other	1 (0.6%)
No response	2 (1.2%)
Ethnicity	
Non-Hispanic	152 (90.5%)
Hispanic	14 (8.3%)
No response	2 (1.2%)
Body mass index (average)	32.72 kg/m^2 (range 17.56 – 76.82 kg/m^2; 32.7 ± 9 kg/m^2)
Primary insurance	
Medicare	49 (29.2%)
Medicaid	49 (29.2%)
Commercial	53 (31.5%)
No insurance	17 (10.1%)
Documented "white coat hypertension"	40 (23.8%)
No. of primary care visits within 1 year from referral date	Average 2 visits per year (range 0 – 7 visits per year; 2.3 ± 3.5 visits)
Average no. of blood pressure medications per patient	1.8 (range 0 – 5; 1.8 ± 1.1)

Figure 2. Patient Characteristics – Unique Characteristics



Data help illustrate that patients referred to pharmacists also may benefit from services such as diabetes management, tobacco cessation, and more.

large, academic medical center located in Madison, Wisconsin, serving more than 800 000 patients each year across its 6 hospitals and more than 90 outpatient sites. This study was classified as exempt by the University of Wisconsin-Madison Institutional Review Board.

The patient population was identified through the Pharmacists in Primary Care program monitoring electronic database of hypertension patients from fiscal year (FY) 2023 (July 1, 2022 – June 30, 2023). The population was generated from the 11 primary care clinics where pharmacists are embedded into the workflow at the study site. Patients were included if referred by their primary care provider for pharmacist-led hypertension management. The pharmacy encounter needed to be marked as "resolved" to be included, meaning that the patient was no longer being contacted for engagement. Inclusion criteria were met if patients did not engage with this pharmacy service for reasons such as patient declined offer, lack of patient-perceived benefit, or lack of response to attempted contact. Per workflow, patients were contacted 3 times by phone with voicemail and sent a letter with no response before resolving.

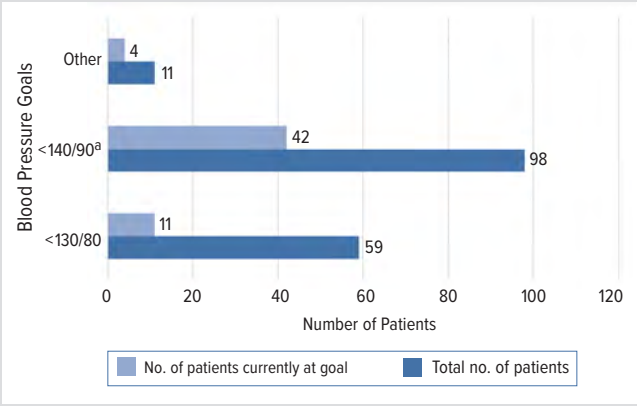
Data Sources and Statistical Analysis

An internal analytics platform was utilized to generate a report of patients. Additionally, the electronic health record was used to gather pre-specified, deidentified information: patient demographics (eg, sex, age, self-identified race, self-identified ethnicity, body mass index), comorbidities (diabetes, coronary artery disease, history of myocardial infarction, chronic kidney disease), patient health concerns (tobacco and contraceptive use), clinical details, and medication information via chart review. Patient-specific blood pressure goals were set by the patient's referring clinician. Clinic blood pressure readings were utilized to determine if a patient was or was not meeting their blood pressure goal. Chart reviews were completed by the primary author to gather data and assess trends. Descriptive statistics were used to analyze the data. An exploratory analysis was performed after initial data collection to further explore themes of the patient population.

Table 2. Blood Pressure Characteristics

Blood pressure goal, n (%)	
<130/80 mmHg	59 (35.1%)
<140/90 mmHg	98 (58.3%)
Other goal	11 (6.5%)
Average initial systolic blood pressure	154 ± 18 mmHg
Average initial diastolic blood pressure	92 ± 13 mmHg
Average systolic blood pressure when episode of care resolved	147 ± 19 mmHg
Average diastolic blood pressure when episode of care resolved	88 ± 12 mmHg
Average current systolic blood pressure	143 ± 21 mmHg
Average current diastolic blood pressure	86 ± 14 mmHg

Figure 3. Blood Pressure Goal Breakdown



[a]Goal set by the American Academy of Family Physicians.

RESULTS

A total of 168 patients referred by their primary care provider had resolved pharmacist encounters during FY 2023 (Figure 1). Table 1 summarizes the included patients' demographic information. Participants' average age was 56 years old; the majority identified as male (n = 92, 54.8%); 126 (75%) self-identified as White, 27 (16%) self-identified as Black; and 15 (8.3%) self-identified as Hispanic ethnicity. Forty-nine patients (29.2%) were insured by Medicaid and 17 (10.1%) had no insurance (Figure 2). Patient-specific blood pressure goals varied between those included. The blood pressure goal of less than 140/90 mmHg was most common for patients (n = 98, 58.3%) (Table 2). However, despite this less stringent blood pressure goal, 42 patients (42.9%) patients who have a blood pressure goal of less than 140/90 mmHg were not at their goal (Figure 3). This is similar to the findings of the entire patient population, as 111 (66.1%) participants were not currently at their blood pressure goal, despite being seen an average of 2 times by their primary care provider within 1 year of the referral date. Barriers to patient engagement included lack of patient interest (n = 114, 67.9%) or another health care member managing the patient's hypertension (n = 36, 21.4%) (Table 3).

Table 3. Pharmacy Referral Clinical Details

	n (%)
Reasons for referral decline[a]	
Clinic goals met	8 (4.8)
Patient-stated goals met	3 (1.8)
Provider-stated goals met	3 (1.8)
Change in patient medical status	2 (1.2)
Lack of patient interest	114 (67.9)
Patient barriers	1 (0.6)
Another health care member now managing patient	36 (21.4)
Medication discontinued	0 (0)
Patient expired	0 (0)
Other	2 (1.2)
No. of patients who reported vitals[b]	
Within 1 month of referral date	10 (6)
Within 6 months of referral date	10 (6)
UW Health outpatient pharmacy patients	9 (5.4)
Adherence packaging	1 (0.6)

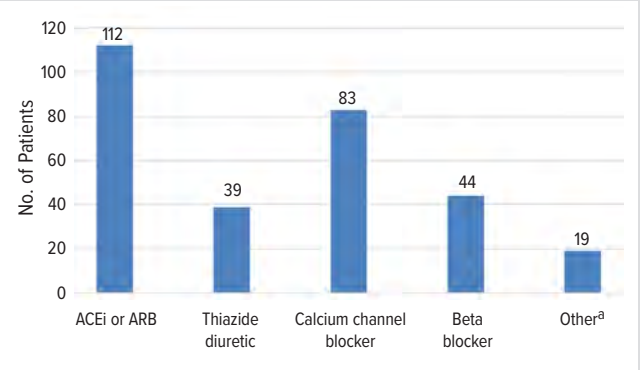
[a]One patient provided 2 reasons: clinical goals met and patient-stated goals met.
[b]Patients who recorded their blood pressure within 1 month differed from those who recorded at-home blood pressures within 6 months.

Patients were taking an average of 2 blood pressure medications (range 0-5). Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB) were prescribed most often, with 112 (66.7%) patients being on one of these two medications. Other frequently prescribed medications included calcium channel blockers (n = 83, 49.4%), beta-blockers (n = 44, 26.2%,), and thiazide diuretics (n = 39, 23.3%), as shown in Figure 4. Nineteen patients (11.3%) patients were on "other" medications for blood pressure control, including furosemide and spironolactone.

Exploratory Analysis

An exploratory analysis was conducted to evaluate how frequently patients with selected comorbidities were prescribed guideline-based medications (Table 4). This was done specifically to evaluate how frequently patients with type 2 diabetes and chronic kidney disease were prescribed ACEi or ARB therapy and how often patients with a history of myocardial infarction were on a beta blocker. The analysis found 33 patients (19.6%) had comorbid type 2 diabetes. Of those patients, 23 (69.7%) were not at their blood pressure goal. Furthermore, 4 (12.1%) patients with diabetes were not on an ACEi or ARB. The analysis also found that 50% (n = 10) of patients with chronic kidney disease were not on an ACEi or ARB. The study population included 9 (5.4%) patients who had a history of prior myocardial infarction, and 4 (44.4%) of these patients were not on a beta-blocker. Forty (23.8%) patients had documented white coat hypertension and 29 (70%) were not at their blood pressure goal. Eleven (6.5%) patients were not on any medications for blood pressure management, including 8 patients (72.7%) who were not at their blood pressure goal.

Figure 4. Blood Pressure Medicine Breakdown



Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.
[a]The most commonly prescribed "other" medications included furosemide or spironolactone; however, the specific indication of each medication on a patient's list was not assessed.

Table 4. Patient Comorbidities and Health Concerns

	n (%)
Diabetes	33 (19.6)
Coronary artery disease	13 (7.7)
History of myocardial infarction	9 (5.4)
Chronic kidney disease	20 (11.9)
Tobacco use	
Never used	77 (45.8)
Former use	62 (36.9)
Current use	29 (17.3)
Contraceptives	11 (6.5)

DISCUSSION

As inadequate blood pressure control can lead to cardiovascular, renal, and neurologic diseases, it is vitally important to achieve blood pressure goals in hypertension, the most prevalent modifiable risk factor. Pharmacists can play a key role in providing medication management to help patients achieve their clinical goal. The present study showed that the majority of this patient population had blood pressure goals that align with recommendations from the American Academy of Family Physicians (<140/90 mmHg). There were instances when "other goal" was selected by clinicians; this often included less than 135/85 mmHg (the middle of the 2 major blood pressure goals) or less than 150/90 mmHg, which was typically reserved for elderly patients. Despite less stringent blood pressure goals than recommended by the ACC/AHA guidelines, patients were still not meeting their blood pressure goals. The group of patients referred for pharmacist intervention (management) but who declined were seen, on average, twice a year by their primary care provider.

This study found that the major reason for disengagement from clinical pharmacy hypertension services was lack of patient interest, seen in over half of the patient population. One proposed reason for this is the misconception of the role of phar-

macists. Additionally, patients may or may not understand the training required to become a pharmacist or know the level of knowledge, skill, and expertise that pharmacists have regarding hypertension management. Furthermore, it is unknown to the authors if/how the referral to a pharmacist was brought up by health care providers. By ensuring the referring clinician optimally set expectations and defined pharmacist roles, patient understanding and participation may be improved. However, other barriers, such as lack of patient time, could also be confounding the results. To improve participation, aligning pharmacy visits on the same day as other appointments and/or having telehealth options could influence more patients to engage in pharmacy services. Evaluating the impact of patient perception of pharmacist roles and responsibilities via qualitative interviews, surveys, and focus group discussions will be a next step in addressing this further.

The Centers for Disease Control and Prevention and the Centers for Medicare and Medicaid Services have created a national initiative known as the Million Hearts Initiative to prevent 1 million heart attacks and strokes within 5 years.[13] This aims for 80% of US adults with hypertension to achieve blood pressure control with a blood pressure less than 140/90 mmHg. Yet, the rates of blood pressure control in this study were low, with only 33.9% (n = 57) patients at their blood pressure goal. This study noted that most patients are on blood pressure medications, and of those patients, the majority are prescribed first-line therapy options, such as ACEi/ARB, calcium channel blockers, and thiazide diuretics.[6,7] Per the 2017 ACC/AHA Hypertension Guidelines, secondary agents for hypertension management include loop diuretics, potassium-sparing diuretics, aldosterone antagonist diuretics, beta-blockers, direct renin inhibitors, alpha-1 blockers, central alpha-2 agonists, and direct vasodilators.[7] There were more patients on beta-blockers (n = 44, 26.2%) than expected in this patient population, as these are not first-line therapy recommendations. Beta-blockers have other indications for patients with comorbidities including history of myocardial infarction, atrial fibrillation, or history of hyperkalemia. Beta-blockers require less laboratory monitoring compared to ACEi/ARB or thiazides. This could influence practice patterns for patients with poor adherence to obtaining follow-up labs. The exploratory analysis showed that for patients with type 2 diabetes and/or chronic kidney disease, many currently are not on recommended therapy of an ACEi or ARB.

Limitations

In evaluating the demographics of disengaged patients, 27 (16%) self-identified as Black, 49 (29.2%) were insured by Medicaid, and 17 (10.1%) had no insurance. Although this study evaluated the demographic and insurance status of disengaged patients, these percentages are higher than seen in our site's city population (6.7% Black, 11.4% Medicaid insurance, 5.5% uninsured). An important future direction in this research is to compare demographic and comorbidity data from patients who engage with pharmacy services versus those who do not, to identify and target hypertension management in potentially vulnerable patient populations.

Clinic-reported blood pressure measurements were used to determine if a patient was or was not meeting their blood pressure goal. These measurements typically are performed using an automatic blood pressure cuff versus a manual reading for standardization. However, improper blood pressure measurement technique could confound results. One potential next step is to complete a qualitative study in which medical assistants, licensed practical nurses, and registered nurses who may by checking blood pressures are interviewed about technique and protocols they follow for elevated readings or other scenarios in order to improve standardization.

Another limitation of this study is that patient medication adherence was not assessed. Lack of adherence to medications would be a large contributing factor to inadequate blood pressure control. One future direction would be to evaluate medication adherence as a contributing factor to blood pressure not at goal and to assess if referrals to internal pharmacies or for pill packaging services improves adherence. Additionally, indications for each antihypertensive medication were not evaluated. Further analysis is needed to evaluate indication-based prescribing frequency in patients with hypertension in our study to better target blood pressure control to help achieve the Million Hearts Initiative.

CONCLUSIONS

The purpose of this initial retrospective study was to determine the primary reason for disengagement or declined referral from a primary care pharmacy antihypertensive service to guide future interventions. The results show the majority of patients who were referred but not engaged in pharmacy services are not meeting their blood pressure goal. The primary reason identified for disengagement was lack of patient interest. Targeting this patient population would allow for overall better blood pressure control for patients within the health system. Qualitative methods or differential recruiting strategies could help explore patients' perceptions of the pharmacy role and understand why pharmacy services were declined. Further study of this patient group is needed to allow them the same potential for improved outcomes seen with pharmacist interventions.

Funding/Support: None declared.

Financial Disclosures: None declared.

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The Empty SmartLink Solution: A Quality Improvement Initiative to Improve History and Physical Notes Documentation Using Clinical Decision Support

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ABSTRACT

Introduction: The use of structured documentation via auto-populated discrete fields is important to facilitate medical decision-making, research, and quality improvement. If these fields are not filed properly, they will appear "empty," leaving behind incomplete documentation. Examples include past medical history (PMH), past surgical history (PSH), family history (FH), and active hospital problems (AHP).

Objectives: Our SMART aim was to decrease the incidence of "no PMH/PSH/FH/AHP on file" in history and physical notes (H&Ps) at our single children's hospital from 7.9%, 18.7%, 8.3%, and 17.0%, respectively, to less than 5% over 4 months.

Methods: A multidisciplinary team utilized quality improvement methodology. The population included all encounters admitted to pediatric hospital medicine. The outcome measure was percentage of H&Ps with "no PMH/PSH/FH/AHP on file." The process measure was percentage of H&Ps using the proper template. Interventions included a clinical decision support tool in H&P templates to display a hard stop if "no PMH/SH/FH/AHP on file" appears and documentation education. Statistical process control charts were used to analyze measures.

Results: "No PMH/PSH/FH/AHP on file" decreased from baseline to 1.2%, 2.2%, 2.9%, and 4.2%, respectively, showing special cause variation. H&P template use remained high at 87.2%.

Conclusions: The creation of a simple clinical decision support tool was associated with a decreased incidence of "no PMH/PSH/FH/AHP on file," achieving our goal. Utilizing automatic clinical decision support reduced the need to rely on education to cause a change, an important element of our tool. Future steps include implementation of a hard stop in other required areas of discrete documentation and ongoing evaluation of sustained change.

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INTRODUCTION

Clinical documentation has changed significantly with the widespread implementation of the electronic health record (EHR) since the start of the 21st century, and it continues to remain an essential component of safe patient care.[1-4] The transition to EHRs has shown mixed results regarding documentation completeness, time spent, and note quality and length.[5-9] These differences are largely attributed to heterogeneity in the degree of standardized, structured documentation.[10]

Standardized, structured documentation can refer to standardized templated notes on a larger scale, as well as discrete fields that display information obtained via clinician entry to capture key data elements (eg, drop-down lists) or auto-population from elsewhere in a patient's chart. Discrete field structured documentation facilitates real-time clinical care decision-making and promotes future research and quality improvement (QI) initiatives.[8,10,11] On the other hand, unstructured documentation, such as free text, is difficult to extract without natural language processing or artificial intelligence, limiting its potential.

Many parts of the history and physical (H&P) notes can be auto-populated via these discrete fields. However, if a piece of information is not filed to the chart as discrete structured data, the SmartLink will appear as "empty." In the case of a patient's past medical history, when there is no information in the history section, the SmartLink populates "no past medical history on file" (Figure 1A). While the use of SmartLinks does reduce documenta-

tion burden by auto-populating standard parts of a note, if not used properly, documentation can be incomplete.

Clinical decision support (CDS) is one avenue that can support clinician efficiency, documentation, and standard of care, and it typically falls into 4 categories: data entry, data review, assessment and understanding, and triggered by user task.[7] There are 5 "rights" that need to be considered when implementing CDS: (1) the right information, (2) to the right person, (3) in the right intervention format, (4) through the right channel, (5) at the right time in workflow.[12,13]

Our aim was to decrease the percent of encounters with H&P notes at our institution that contained "no past medical history on file," "no past surgical history on file," "no family history on file," or "no active hospital problem on file" (PMH/PSH/FH/AHP) to less than 5% in 4 months. We followed the Standards for Quality Improvement Reporting Excellence (SQUIRE) 2.0 guidelines.[14]

METHODS

This QI study took place at 1 tertiary care pediatric hospital with approximately 5300 pediatric hospital medicine (PHM) admissions in 2021. The institution's EHR vendor, Epic (Epic Corp, Verona, Wisconsin), is used in all patient-facing clinical care settings. The PHM service at the time had 33 hospitalists, 4 hospital medicine fellows, about 95 residents (including categorical pediatrics, medicine-pediatrics, preliminary pediatrics, pediatrics-anesthesiology, and child neurology, as well as emergency medicine and family medicine residents completing a pediatric rotation), and 10 advanced practice providers (APPs). Each child admitted to the hospital has an H&P note for their encounter written by a resident or an APP. The PHM service has created multiple disease-specific H&P templates for common diagnoses such as asthma, bronchiolitis, croup, hyperbilirubinemia, febrile neonates, and teen H&Ps. These disease-based templates are kept updated with local clinical practice guidelines. The H&P note templates, including all disease-specific templates, contain SmartLinks to auto-populate the PMH/PSH/FH/AHP from other areas in the EHR. Residents are able to use and share individual SmartPhrases for disease-specific H&Ps instead of the PHM disease-specific H&P templates.

Inclusion criteria included H&P notes written by a resident for admissions to the PHM service during March through June 2021. The APP notes were excluded from this study as APPs use separate note templates and do not attend the same meetings used for interventions in this project.

We chose 5% as our goal as it was below the previous average of empty documentation, which ranged from 7.8% to 18.2% for each of the different documentation components. While we strive for complete documentation every time, we acknowledge that there will always be room for further improvement. We began data collection 4 months before the end of the academic year and did not want to include new residents in July in this study given the significant learning curve in the beginning of residency.

Figure 1. History and Physical Notes Template (A) Before and (B) After Intervention of the Clinical Decision Support (CDS) Hard-Stop Tool

A. Empty SmartLinks when the History section has incomplete documentation.
B. CDS hard-stop tool prompting providers to document patient history.

At the time of project conception, we chose to focus on decreasing the incidence of "empty" auto-populated SmartLinks because billing was focused on the presence or absence of PMH/PSH/FH discrete data elements. In this context, we considered any documentation other than an "empty" SmartLink to be successful.

Interventions

A multidisciplinary team consisting of 2 pediatric residents, 3 pediatric hospitalists, and 1 Epic analyst used quality improvement methodology,[15] and developed a key driver diagram to understand the factors that led to having "empty" SmartLinks in completed H&Ps (Figure 2). As the key driver diagram was created, the 5 "rights" ofider CDS were consed when designing the interventions: the right information, to the right person, in the right intervention format, through the right channel, at the right time in workflow.[12,13] Three interventions were evaluated using QI methodology of plan, do, study, act cycles.

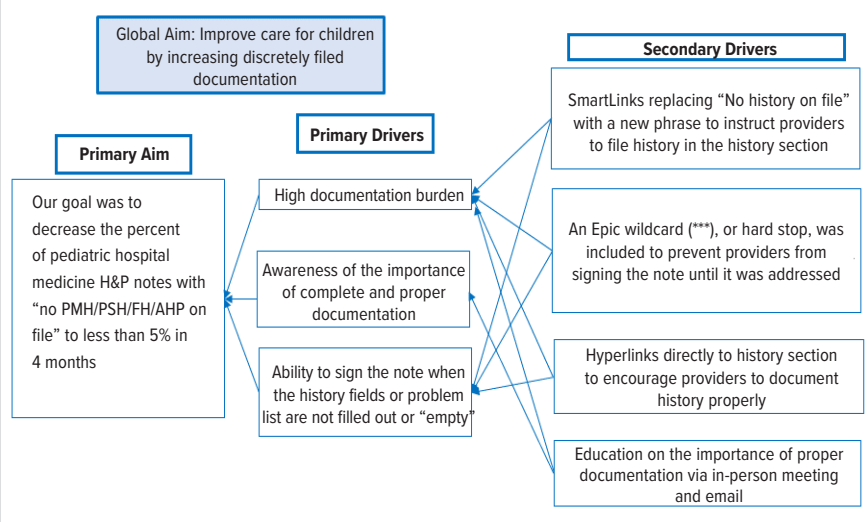
Intervention 1: We created a documentation-focused automatic hard-stop CDS tool that was built into all the PHM H&P templates to address empty SmartLinks for a patient's PMH/PSH/

FH/AHP. Using Epic's criteria-based rule function – referred to as CER – if there was no PMH/PSH/FH/AHP filed, then a new, separate SmartLink would appear prompting and instructing the user to use the appropriate history/problem section in Epic to enter the discrete information (Figure 3). This SmartLink included (1) an Epic wildcard (***) or hard stop that must be addressed before the note can be signed and (2) a link (like a hyperlink) to the appropriate history sections to encourage efficient documentation of history components. The clinician then refreshes the SmartLink in the note and the entered information appears within the H&P in the appropriate section (Figure 1B).

Intervention 2: Education on the new H&P note template with the hard-stop CDS tool was presented during a weekly resident meeting. This included education on pertinent components of an H&P, including information on the general templates, disease-specific templates, proper documentation phrasing, and impact on billing. Residents were then walked through the familiar components of the template followed by introduction of the new hard-stop CDS tool. We stressed the importance and requirement of using the PHM H&P note templates over individual SmartPhrases, as SmartPhrases would not contain the new hard-stop CDS tool or updated clinical practice guideline information.

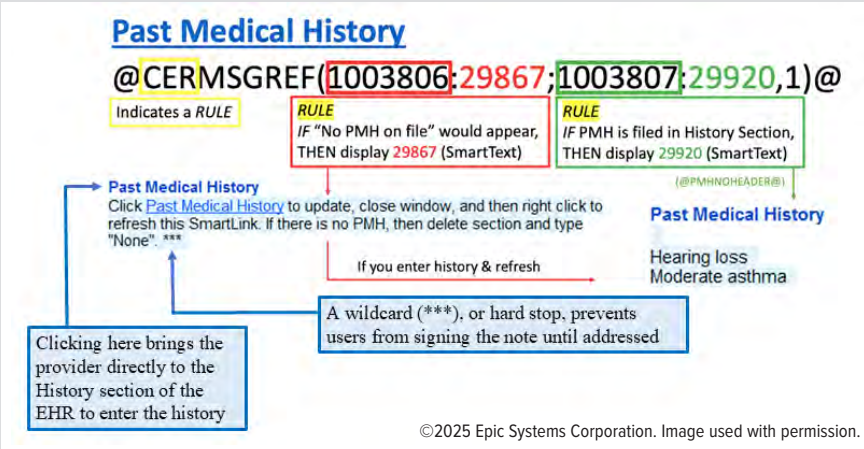
Intervention 3: An email was sent to the residents with a reminder to use the PHM H&P note templates, again stressing the importance of the note build for optimal documentation.

Figure 2. Key Driver Diagram



Abbreviations: H&P, history and physical notes; PMH, primary medical history; PSH, primary surgical history; FH, family history; AHP, active hospital problems.

Figure 3. EPIC Build Code of Clinical Decision Support Hard-Stop Tool



The rules indicate what would be shown to the user in the note documentation. The red arrow walks user through steps when the SmartLink is "empty" and how to address it to complete documentation.

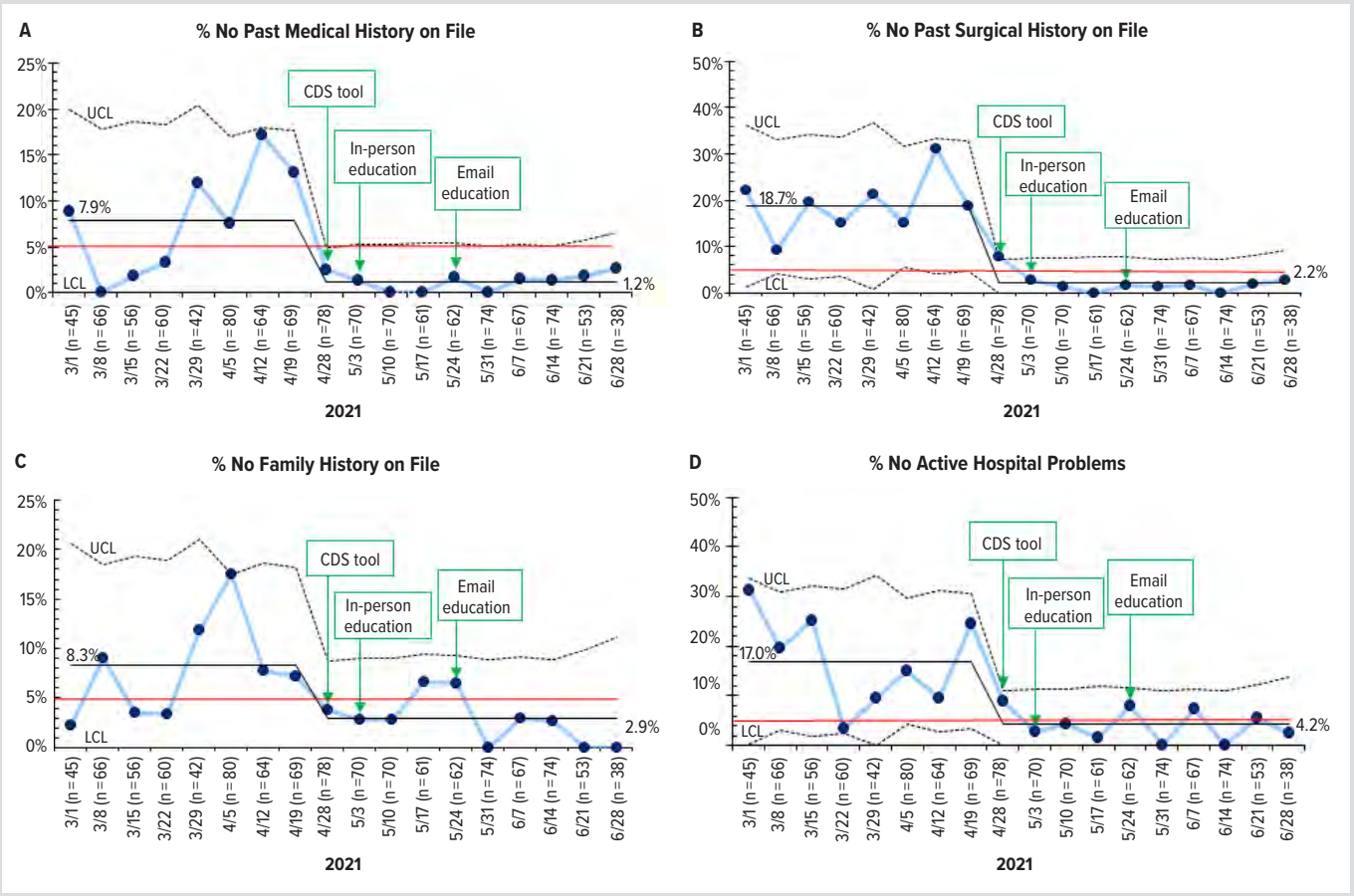
Study of the Interventions

Data collection occurred via Epic data reports on all H&Ps during the specified timeframe and data then were filtered by admission service and note writer. Each H&P was reviewed manually for the presence of auto-populated or free text PMH/PSH/FH/AHP, which is determined using a native Epic hover function. Manual chart review was performed by 2 members of the QI team (SC and SM). Each H&P was reviewed by 1 reviewer. If a note was missing any aspect of the patient's history or was left blank, it was considered "not on file." If the method of documentation (auto-populated vs free text) could not be identified with certainty by the first reviewer, the second reviewer would review the note. If there was still no conclusion, a third member (SB) of the study team would review to determine the documentation method. Template use was quantified by the same method as PMH/PSH/FH/AHP documentation. Data from March 2021 through April 2021 were used to establish a baseline. Data from May 2021 through June 2021 – 10 weeks after implementation of the hard-stop CDS tool – were used to assess the interventions. One-week intervals were used to analyze the data.

Quality Improvement Measures

The primary outcome measure was the percentage of PHM H&P notes written that included empty SmartLinks for PMH/PSH/

Figure 4. Outcomes Measures



Statistical process control charts by week showing the percent of history and personal notes with "no PMH/PSH/FH on file" and "no active hospital problems." Red line is the goal line.

Abbreviations: UCL, upper control limit; LCL, lower control limit; CDS, clinical decision support.

FH/AHP, stating these components were "not on file." The process measure was the percentage of PHM H&P notes written that used the PHM H&P template that contained the hard-stop CDS tool. The balancing measure was the percentage of PHM H&P notes written where "none" was free texted for family history instead of entering pertinent positive or negative medical history. Balancing measures can help quantify if the changes being made to one part of a system are resulting in new problems in other parts of the system.[16] This was chosen because all children should have medical family history, even if it is only pertinent negative history related to their admission problem. If the hard-stop CDS tool implementation led to note writers deleting the tool and typing "none" instead entering the data, it was expected that the number of charts with "none" typed for family history would increase. Although this was used for our balancing measure, we considered "none" as adequate documentation for family history for our outcome measure as it still aligned with the original aim of reducing "no history on file."

This project was deemed exempt from review by the Institutional Review Board.

Analysis

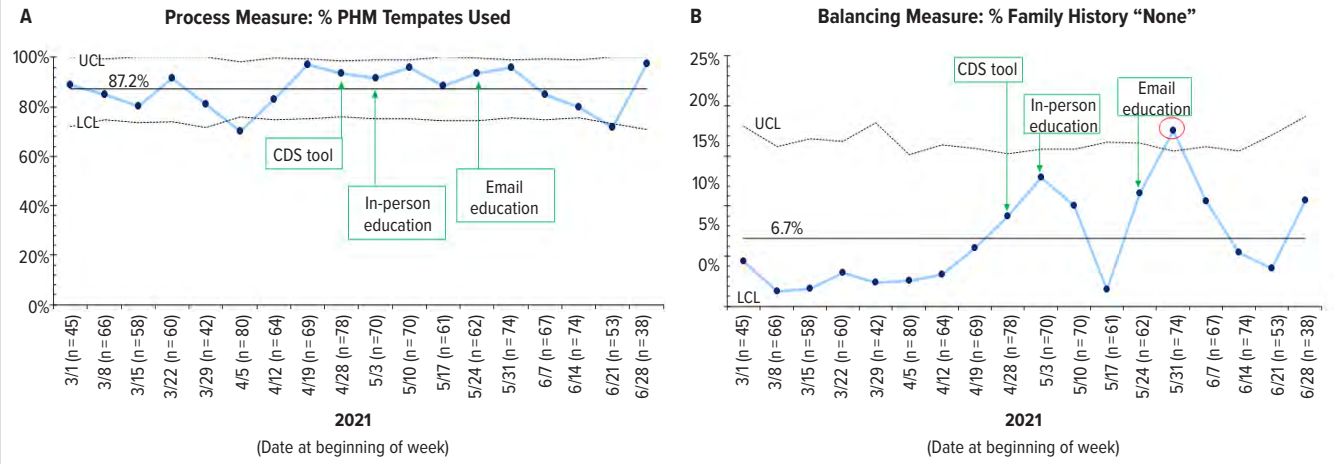
Statistical process control charts (P charts) were created using QI Charts for Microsoft Excel to assess for changes in measures. Standard tests were applied to distinguish special cause variation from common cause variation, including shifts when 8 or more consecutive points above or below the center line or points outside upper and lower control limits occurred?.[17] Control limits corresponding to ± 3 σ limits from the mean were included.

RESULTS

From March 2021 through June 2021, 1129 admission H&P notes were reviewed manually and met inclusion criteria. Each H&P note was assessed for the documentation of PMH, PSH, FH, and AHP.

For the primary outcome measure, the percentage of H&P's with past medical history "not on file" decreased from a baseline mean of 7.9% to 1.2% after interventions. Past surgical history "not on file" decreased from 18.7% to 2.2%. Family history "not on file" decreased from 8.3% to 2.9%. The percentage of H&P's with "no active medical problems" decreased from 17.0%

Figure 5. Process Measure (A) and Balancing Measure (B)



Process control charts by week.
Abbreviations: UCL, upper control limit; LCL, lower control limit; CDS, clinical decision support.

to 4.2% (Figure 4). There was special cause variation, based on standard QI methodology, for each of these outcomes given that each had at least 8 consecutive points below the respective baseline mean.[16]

Our process measure of the percentage of H&P notes written using the PHM H&P note template was consistent throughout the project at 82.7% with no special cause variation seen (Figure 5A). Lastly, our balancing measure, the percentage of family history listed as "none" remained unchanged at a mean of 6.7% throughout the project despite interventions. The week of May 31, 2021 does show special cause variation with 1 point above the upper control limit, but this was not sustained in subsequent weeks (Figure 5B).

DISCUSSION

After our interventions, the percent of PHM H&P notes with PMH/PSH/FH/AHP "not on file" decreased, achieving our goal of less than 5% for each piece of documentation. An important aspect of achieving our goal was the implementation of the hard-stop CDS tool, a high reliability intervention that we aligned as closely as possible with the 5 rights of CDS.

In the literature, there have been a variety of CDS tools that have shown improvement in documentation of discrete data across multiple settings.[10,18-21] The tool we created primarily addresses data entry as it prompts clinicians to complete important aspects of documentation that may affect patient care. By creating a hard-stop CDS tool for empty SmartLinks within the H&P note, it prompted the clinician to address data entry prior to signing the note, an example of a tool that applied the 5 CDS rights. The right person is given the right information through the right format at the right time to encourage the clinician to do the right thing: properly document a patient's history. Instructions were built into our tool that guided the clinician on the optimal use of the tool, encouraging use of structured fields in the EHR to file the information.

While the SmartLink hard-stop CDS tool intervention coincided with the initial decrease in "empty" documentation, educational interventions did not produce further change. A systematic review of interventions to improve inpatient EHR documentation found that user education was one of the most widely used interventions that demonstrated improvement;[21] however, educational interventions require individuals to remember changes and implement them in real time, ultimately relying on individuals to alter their workflow. We did not find that education interventions further improved documentation, which points toward an important aspect of the CDS tool: automaticity. Utilizing automatic or involuntary CDS reduces the need to rely on the individual to implement change—an important benefit of implementing the widespread tool.

Regarding the special cause variation seen in 1 week when evaluating family history, a possible explanation is that new rotating residents started that week and did not learn how to use the tool until later in the rotation. We have since edited the family history hard stop to state "document positive and/or negative family history" to discourage the use of "none."

We were fortunate that our H&P template use started high and remained high. Although H&P templates can improve documentation, the use of templates are sporadic and often are replaced by individual user SmartPhrases.[22-25] Illness-specific H&P templates are for common admission diagnoses, and their use can increase targeted documentation.[26] However, illness-specific templates are most successful at institutions whose documentation culture does not include many individual user

SmartPhrases. Influencer SmartPhrases, or an individual's commonly used SmartPhrases, can be edited to contain the desired documentation phrases. This then allows leverage to counteract low template use.[25]

Limitations

Our study did have a few limitations, including generalizability to other members of the health care team, measuring changes in documentation stored in the history tab, ability to measure time to complete, and accuracy of H&P documentation.

The exclusion of hospitalist APPs and subspecialty patients decreases the generalizability of our intervention. PHM APPs were excluded because they use a different PHM H&P template that they have adapted to their workflow, which is different from a resident learner. Subspecialty groups were excluded as they use their own separate H&P templates. However, similar principles can be applied in these other scenarios.

During the manual review process, we observed that some clinicians would insert the new PHM H&P template but replace sections with their own individually created phrases. This was evident from specific wording used that matched an outdated and retired template. Due to the method of chart review, we were unable to quantify the degree to which the templates were changed.

While we saw a decrease in the incidence of PMH/PSH/FH/AHP "not on file," it is important to acknowledge that we did not audit change in documentation in the History section, only the presence or absence of empty SmartLinks. In other words, free typed medical history was not considered "empty." If we wanted to investigate the use of the embedded hyperlink as a change documentation workflow, a more thorough audit of date and time each new piece of information was added to the history section would be needed. Lastly, we were not able to measure the accuracy of the information documented in patient's H&P as that would require follow-up confirmation from the family for each patient and is out of the scope of this QI study.

At the time of these interventions, billing was focused on the presence or absence of PMH/PSH/FH discrete data elements. Since completion of this project, billing regulations have changed such that the presence of a patient's history in the H&P note is not a required billing element. However, this work is still important as complete documentation is an important component for patient care.

CONCLUSIONS

Using a simple SmartLink, hard-stop CDS tool within the PHM H&P note templates, the percent of charts with PMH/PSH/FH/AHP "not on file" decreased, achieving our goal of less than 5%. Our interventions were simple and resulted in significant change to our documentation without negative consequences, such a maintained increase in "none" documented for family history. Our PHM H&P template use was high prior to our interventions, and we saw no change in template use after our interventions. This simple CDS tool can be implemented easily into many EHRs and demonstrates that you do not have to rely on individual education to achieve improved documentation. Future directions would include measurement of exclusively auto-populated fields and incorporating this hard-stop CDS tool into templates outside of PHM.

Financial Disclosure: None declared.

Funding/Support: None declared.

Acknowledgements: The authors would like to acknowledge the analyst, Jason Seidl, who helped build the clinical decision support tool.

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Comparing Magnetic Resonance Imaging and Computed Tomography Machine Accessibility Among Urban and Rural County Hospitals in Wisconsin

Benjamin Burdorf, MD; William MacDonald, MD; Pravallika Kesarla, BS; Samantha Burdorf, MBA

ABSTRACT

Introduction: There is higher disease incidence and worse outcomes in rural America when compared to urban America. In states like Wisconsin, where 32.9% of the population resides in rural areas, this is particularly worrisome. The Center for Healthcare Quality and Payment Reform found that 30% of rural hospitals in the US are at risk of closing due to financial instability. A substantial cost to rural hospitals is the provision of radiologic services. Thus, the study investigated if a disparity exists in availability of magnetic resonance imaging (MRI) and computed tomography (CT) machines among Wisconsin's urban and rural county hospitals.

Methods: Wisconsin hospitals were asked how many MRI and CT machines were carried at their facility. This information was compiled in a spreadsheet and cross-referenced with the county in which it resided, along with the county's population, urban-rural classification, and land area in square miles.

Results: We found that the state of Wisconsin compared favorably with the national average in terms of the number of persons and square miles per MRI and CT machine. When comparing Wisconsin counties based on their urban-rural classification, a disparity exists in rural counties regarding square mileage per CT and MRI machine.

Conclusions: With distance for service creating a barrier to accessibility, rural county residents would benefit from more in-hospital MRI and CT machines. Based on these findings, further research is warranted to investigate the potential vulnerability of other rural populations regarding accessibility to radiologic resources.

INTRODUCTION

The US Food and Drug Administration and the Centers for Disease Control and Prevention report that rural America faces higher disease incidence in conjunction with worse outcomes than urban areas and note that difficulty accessing health care resources was a major contributing factor.[1,2] This disparity is concerning, particularly because the US Census Bureau reports that 20% of the country's population resides in a rural area.[3] In Wisconsin, 32.9% of the population is rural,[4] and the state has 58 Critical Access Hospitals (CAHs) – the sixth highest total in the country.[5] Further, despite government assistance, in 2024, the Center for Healthcare Quality and Payment Reform found that 30% of rural hospitals in the US are not financially sustainable and risk closing.[6] Although there are many financial hurdles facing rural hospitals, one that is particularly substantial is affording the installation, maintenance, and operation of computed tomography (CT) and magnetic resonance imaging (MRI) machines.[7]

In light of the serious pressures on rural hospitals, this report aims to assess whether a discrepancy exists in the accessibility of MRI and CT machines between Wisconsin's urban and rural county hospitals. Of note, a literature review did not identify research investigating this question for the state of Wisconsin; however, this report closely mirrors prior work completed by the corresponding author for the state of Minnesota.[8]

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Table. In-hospital Magnetic Resonance Imaging and Computed Tomography Machine Data by Wisconsin County and Rural-Urban Classification Using Their Respective Populations and Land Areas

Locale	County	Population	Land (Mi^2)	MRIs	CTs	Person/MRI	Mi^2/MRI	Person/CT	Mi^2/CT
Rural	Adams	21226	646	0	1	N/A	N/A	21226	646
Rural	Ashland	16039	1045	1	3	16039	1045	5346	348
Rural	Barron	46843	863	4	5	11711	216	9369	173
Rural	Burnett	17036	822	0	1	N/A	N/A	17036	822
Rural	Clark	34691	1210	0	2	N/A	N/A	17346	605
Rural	Crawford	16007	571	1	1	16007	571	16007	571
Rural	Dodge	88282	876	3	4	29427	292	22071	219
Rural	Door	30526	482	1	1	30526	482	30526	482
Rural	Dunn	45651	850	1	1	45651	850	45651	850
Rural	Grant	51276	1147	2	3	25638	573	17092	382
Rural	Green Lake	19220	349	1	1	19220	349	19220	349
Rural	Jackson	20836	988	1	1	20836	988	20836	988
Rural	Jefferson	85784	556	1	2	85784	556	42892	278
Rural	Juneau	26866	767	1	1	26866	767	26866	767
Rural	Lafayette	16877	634	0	1	N/A	N/A	16877	634
Rural	Langlade	19559	871	1	1	19559	871	19559	871
Rural	Lincoln	28376	879	0	2	N/A	N/A	14188	439
Rural	Manitowoc	81172	589	2	2	40586	295	40586	295
Rural	Marinette	41988	1399	1	2	41988	1399	20994	700
Rural	Monroe	46109	901	2	4	23055	450	11527	225
Rural	Oneida	38212	1113	2	5	19106	556	7642	223
Rural	Pepin	7410	232	0	1	N/A	N/A	7410	232
Rural	Polk	45709	914	3	3	15236	305	15236	305
Rural	Portage	70718	801	1	3	70718	801	23573	267
Rural	Price	14179	1254	0	1	N/A	N/A	14179	1254
Rural	Richland	17090	586	1	1	17090	586	17090	586
Rural	Rusk	14186	914	1	1	14186	914	14186	914
Rural	Sauk	65777	831	3	4	21926	277	16444	208
Rural	Sawyer	18559	1257	1	1	18559	1257	18559	1257
Rural	Shawano	40886	893	1	1	40886	893	40886	893
Rural	Taylor	19975	975	1	1	19975	975	19975	975
Rural	Trempealeau	30899	733	0	2	N/A	N/A	15450	366
Rural	Vernon	31060	792	0	2	N/A	N/A	15530	396
Rural	Vilas	23763	857	0	1	N/A	N/A	23763	857
Rural	Walworth	105380	555	2	2	52690	278	52690	278
Rural	Washburn	16911	797	0	2	N/A	N/A	8456	399
Rural	Waupaca	51488	748	1	1	51488	748	51488	748
Rural	Waushara	24999	626	0	1	N/A	N/A	24999	626
Rural	Wood	73993	793	5	7	14799	159	10570	113
Urban	Brown	270036	530	10	8	27004	53	33755	66
Urban	Calumet	52718	318	0	1	N/A	N/A	52718	318
Urban	Chippewa	66807	1008	0	1	N/A	N/A	66807	1008
Urban	Columbia	58193	766	1	2	58193	766	29097	383
Urban	Dane	568203	1197	14	15	40586	86	37880	80
Urban	Douglas	44144	1304	0	1	N/A	N/A	44144	1304
Urban	Eau Claire	106837	638	4	5	26709	159	21367	128
Urban	Fond du Lac	103836	720	3	2	34612	240	51918	360
Urban	Green	36816	584	1	2	36816	584	18408	292
Urban	Iowa	23865	763	1	1	23865	763	23865	763
Urban	Kenosha	167817	272	2	2	83909	136	83909	136
Urban	La Crosse	120294	452	3	4	40098	151	30074	113
Urban	Marathon	137958	1545	3	6	45986	515	22993	257
Urban	Milwaukee	918661	241	25	37	39942	10	29634	8
Urban	Oconto	39633	998	1	2	39633	998	19817	499
Urban	Outagamie	192127	638	4	5	48032	159	38425	128
Urban	Ozaukee	93009	233	3	4	31003	78	23252	58
Urban	Racine	195846	333	4	7	48962	83	27978	48
Urban	Rock	164060	718	7	7	23437	103	23437	103
Urban	Sheboygan	117841	511	2	3	58921	256	39280	170
Urban	St. Croix	96017	722	4	4	24004	181	24004	181
Urban	Washington	137688	431	2	3	68844	215	45896	144
Urban	Waukesha	410434	550	11	18	37312	50	22802	31
Urban	Winnebago	170718	434	4	8	42680	109	21340	54

Abbreviations: Mi^2, square miles; MRI, magnetic resonance imaging; CT computed tomography.

METHODS

All Wisconsin hospitals listed in the Wisconsin Hospital Association directory were contacted via their general phone line.[9] Hospitals that provided services to an exclusive subset of the population, such as veterans or Native Americans, were excluded. Researchers explained the study's objective to either a Radiology Department technician or the hospital's director of Radiology, then asked how many MRI and CT machines they carried at their facility and whether each unit was permanent or part of a mobile service. After this information was obtained for each hospital, it was cross-referenced with the county in which it resided, along with the county's population, land area in square miles,[10] and urban-rural classification (Figure 1).[11] The number of persons and square mileage per MRI and CT machine for each county was generated (Table). Mobile units were excluded (Figure 2). Microsoft Office was used to map densities and determine percentile rankings (Figures 3 and 4). The data were further analyzed in Excel by grouping counties into their respective urban-rural classifications (Figure 1) to determine how they compared collectively (Figure 5). Data for the state of Wisconsin as a whole were compared to US data from the Organisation for Economic Co-operation and Development (OECD).[12]

RESULTS

CT Machine Accessibility

Of Wisconsin's 72 counties, 9 counties did not have an in-hospital CT machine. Based on urban-rural classification (Figure 1), 7 counties without an in-hospital CT machine were rural and 2 were urban (Figure 3). Wisconsin averaged fewer people per CT machine (n = 26039) than the national average (n = 37024). Wisconsin's urban counties averaged 29011 per CT machine, while rural counties averaged 18551 (Figure 5). In terms of square miles per county per CT machine, the state of Wisconsin averaged 239 versus the national average of 395. Wisconsin's

Figure 1. Wisconsin County Map with Urban-Rural Classifications According to the Wisconsin Hospital Association

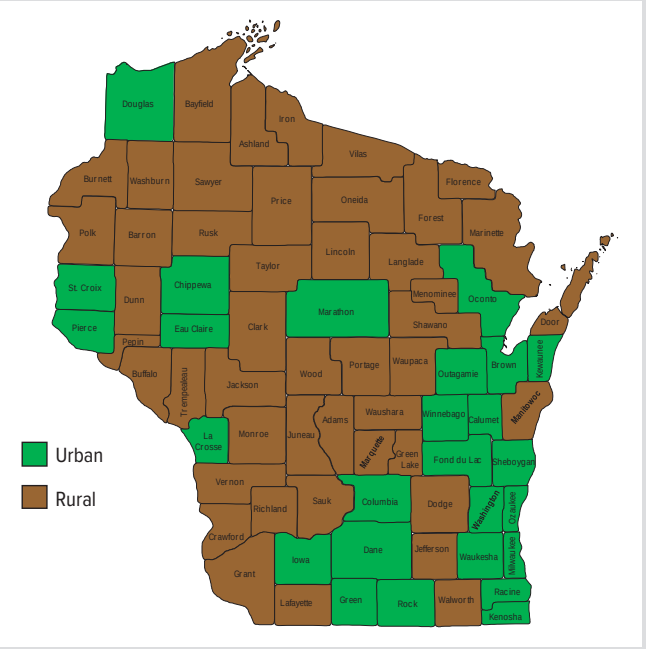


Figure 2. Wisconsin County Map and Table Highlighting Usage of Mobile Magnetic Resonance Imaging Services

County	Hospitals with Mobile MRI	County	Hospitals with Mobile MRI
Adams	1	Oconto	1
Barron	1	Oneida	1
Brown	1	Ozaukee	1
Burnett	1	Pepin	1
Chippewa	1	Portage	2
Clark	2	Price	1
Columbia	1	Trempealeau	2
Douglas	1	Vernon	2
Eau Claire	1	Vilas	1
Grant	1	Washburn	2
Lafayette	1	Waushara	1
Lincoln	1	Winnebago	1
Milwaukee	2		

urban counties averaged 216 square miles per CT machine and rural counties averaged 407 (Figure 5). Data by county for persons per CT machine and square miles per CT machine are shown in Figure 3 and the Table.

MRI Machine Accessibility

Twenty-four of Wisconsin's 72 counties did not have an in-hospital MRI machine. Based on urban-rural classification (Figure 1), 19 counties without an in-hospital MRI machine were rural and 5 were urban (Figure 4). Fourteen of the 24 utilized a mobile MRI service (Figure 2). The state of Wisconsin averaged fewer people per MRI machine (n=38 382) than the national average (n = 55 773). Wisconsin's urban counties averaged 39 390 people per MRI machine, while rural counties averaged 32 568 (Figure 5). In terms of square miles per county per MRI machine, the state of Wisconsin averaged 352 versus the national average of 595. Wisconsin's urban counties averaged 294 square miles per MRI machine, while rural counties averaged 714 (Figure 5). Data by county for persons per MRI machine and square miles per MRI machine are shown in Figure 4 and the Table.

DISCUSSION AND CONCLUSIONS

There are no established guidelines regarding the recommended number of MRI or CT machines based on population or square miles. This raises the question of how to determine an appropriate value for adequate representation in a given population. For guidance, we used data from the OECD to generate national averages to compare with state-level statistics. Overall, Wisconsin performed better than the nation in terms of MRI and CT machines per person and square miles (Figure 5).

When examining the urban-rural classifications for persons per MRI and CT machine, the data showed that rural populations were better represented than urban populations (Figure 5). Although rural populations have fewer people per MRI and CT machine, the distance to these resources is what serves as the barrier. This is illustrated by examining square mileage per MRI and CT machines by urban-rural classification. For square mileage per CT machine, Wisconsin's rural counties averaged 407 – higher than the national average of 395 and almost double the 216 seen in Wisconsin's urban counties. Because CT machines play a vital role in acute care, the value of their accessibility cannot be understated.

However, the greatest disparity shown by this research involves MRI machines. The average square mileage per MRI machine in Wisconsin's rural counties is 714, which is greater than the national average of 595 and more than double the 294 seen in the state's urban counties. Granted, mobile MRI services

Figure 3. Wisconsin County Maps with Color Spectrums Illustrating the Percentile Performance Among Counties with (A) In-hospital Computed Tomography (CT) Machines by Persons per CT Machine and (B) Square Mileage per CT Machine

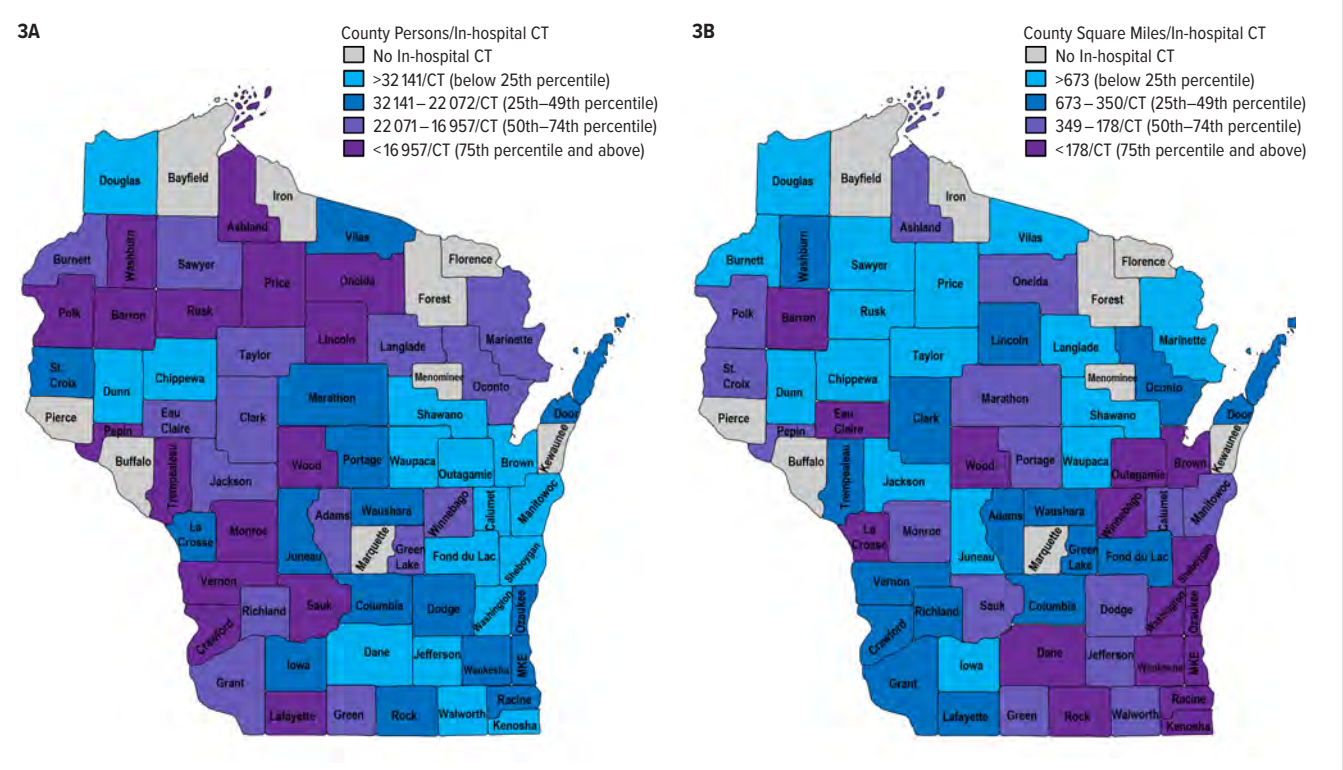


Figure 4. Wisconsin County Maps with Color Spectrums Illustrating the Percentile Performance Among Counties with (A) In-hospital Magnetic Resonance Imaging (MRI) Machine by Persons per MRI Machine and (B) Square Mileage per MRI Machine

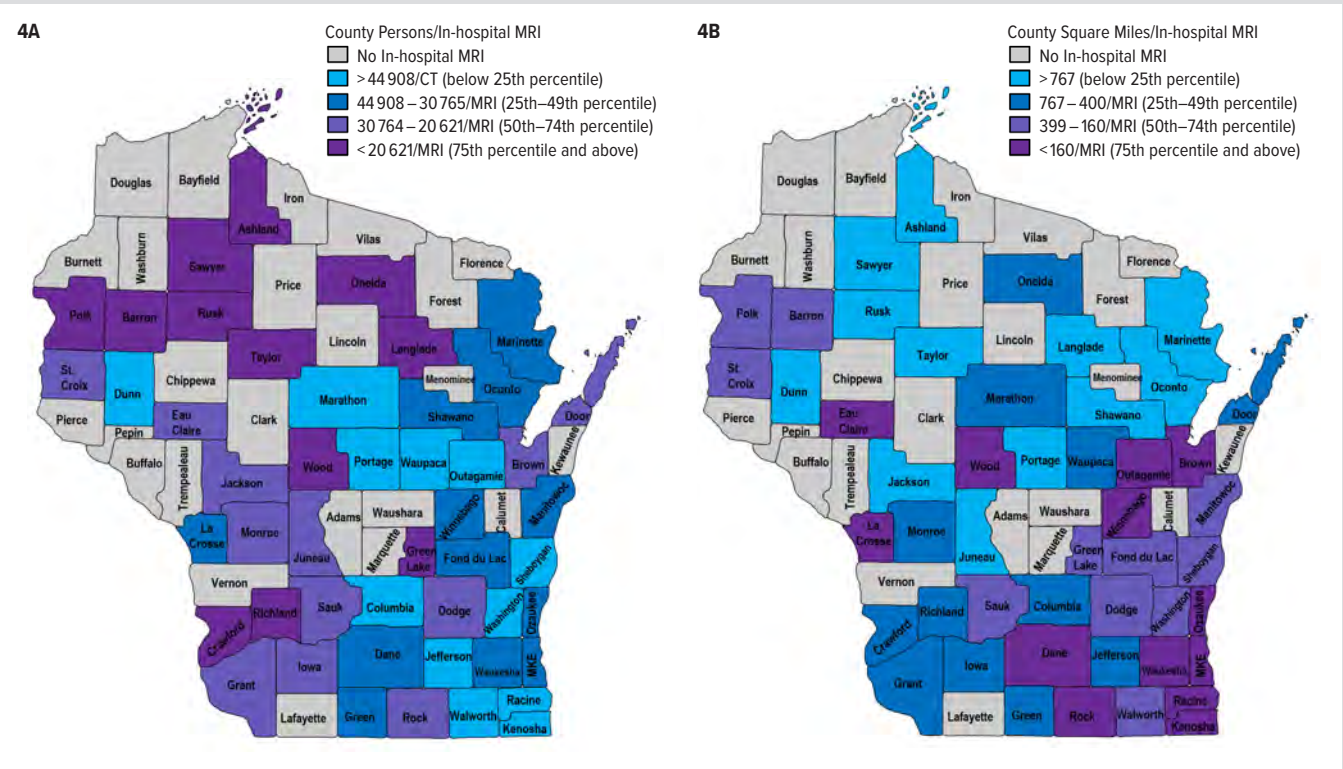
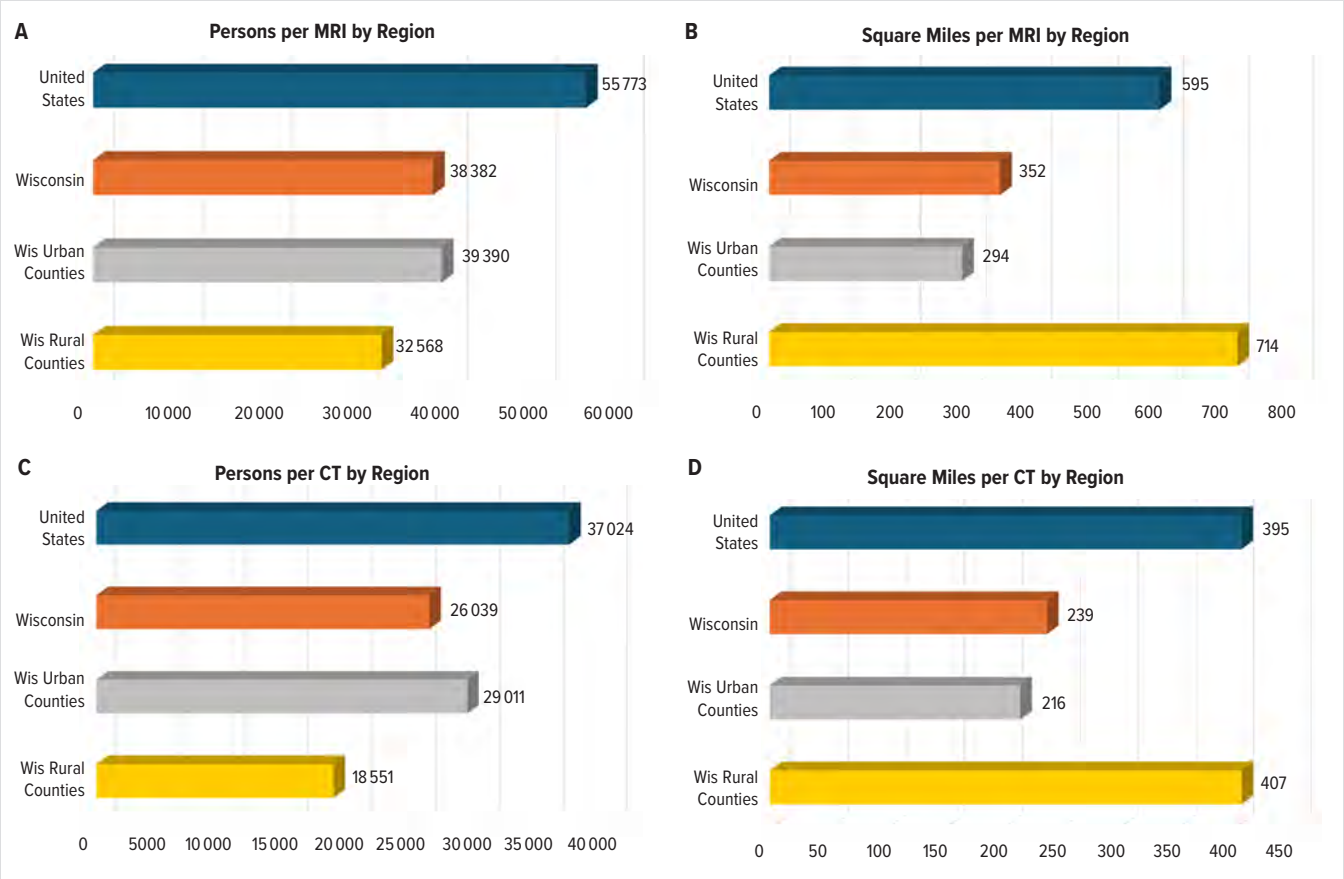


Figure 5. Bar Graphs Portraying National, State and Urban-Rural Classification Performance by (A) Persons per Magnetic Resonance Imaging (MRI) Machine, (B) Square Miles per MRI Machine, (C) Persons per Computed Tomography (CT) Machine, and (D) Square Miles per CT Machine



partially address this misrepresentation. Hospitals that utilize mobile MRI services indicated that MRI availability ranged anywhere from 2 days a week to once every 2 weeks. This means that the majority of rural patients must arrange an additional visit or, with more time-sensitive health concerns, travel to a different health facility, thereby creating inadvertent barriers for people in rural communities.

As reported by the Association of American Medical Colleges, the long distances and time required to receive health services often result in those who need care delaying or avoiding it altogether.[13] If a rural patient has to make another appointment or travel to another facility for radiologic services, they must again face any challenges they overcame for their initial visit. Thus, rural hospitals would benefit from the implementation of in-hospital CT and MRI machines.

Limitations

Potential sources of error in this research include inaccurate information relayed by contacted radiology technologists. There were a few instances where, when asked how many MRI and CT machines their facility had, technologists provided answers that also included the machines at hospital-affiliated outpatient service centers. In addition, it is possible that some newer hospitals were not contacted, as 2 hospitals listed on the Wisconsin Hospital Association's website had been closed for almost a year, highlighting the possibility that information had not been updated within that time.

Another limitation is the exclusion of outpatient radiology centers. It would be logical to investigate to what extent outpatient radiology centers fulfill the disparities revealed in the rural setting by this research. Unfortunately, this would be difficult to determine with no referenceable database tracking these facilities.

Future directions for research include better characterizing the effect of limited accessibility to MRI and CT machines on a community's health, determining the ideal square mileage per MRI and CT machine for a given population, and exploring ways to make these resources more affordable in rural settings. Although these questions are unanswered, we can draw a reasonable conclusion from the data presented here. When comparing Wisconsin counties by their urban-rural classification, disparity exists regarding the square mileage per CT and MRI machine in rural counties. Given the primary root of accessibility issues

residing in distance for service, patients would benefit from more rural county in-hospital MRI and CT machines. Based on these findings, it is pertinent to conduct further research to investigate the potential vulnerability of other rural populations and their access to radiologic resources.

Funding/Support: None declared.

Financial Disclosures: None declared.

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A Novel Coach-Approach to Clinical Faculty Mentoring and the UW Department of Medicine Clinical Faculty Development Program

James D. Alstott, MD; Chariti Gent, MA, MCC, CPCC; Christine Fabian Bell, MS; Daniel R. Marlin, MPA; Anthony Hernandez, PhD; Esther Schulman, BS; Sharon Gehl, MBA; Lynn M. Schnapp, MD; James H. Stein, MD

ABSTRACT

Introduction: Clinical faculty at academic health centers may benefit from specific mentorship and proficiencies that are distinct from those on research tracks. We describe the creation, activities, and 1-year impact of a faculty development program that included novel professional coaching training (the Clinical Faculty Mentoring Program), which was supplemented by skills- and knowledge-building activities (the Clinical Faculty Development Series).

Methods: The goals and components of the Clinical Faculty Mentoring Program and Clinical Faculty Development Series are described in detail. A mixed methods evaluation plan guided collection of confidential survey and interview data before and after the first year of these activities. We used paired *t* tests to identify statistically significant changes.

Results: The 43 clinical mentors reported significant gains in job satisfaction, teaching attitudes, knowledge of mentorship competencies, and confidence with coaching skills for mentorship (all $P < 0.05$). Of mentor respondents, 88% found the coach approach to mentoring program to be "very" or "somewhat" helpful. Coaching behavioral domains with the greatest evidence of improvement were supporting the mentee to integrate new awareness, insight, and learning into their worldview and behaviors ($P = 0.0503$) and managing time and focus of mentoring sessions ($P = 0.022$). All 37 mentees had at least 1 meeting with a mentor (100%). Over 9 months, 39 virtual Clinical Faculty Development Series sessions had an average participation of 38 participants (range 22-59). A majority of surveyed faculty (>55%) agreed or strongly agreed the sessions provided valuable opportunities for skills development with teaching, leadership, wellness, diversity, equity, inclusion, and promotion.

Conclusions: Among clinical mentors, our novel coach approach to clinical faculty mentoring and skill-building had favorable effects on job satisfaction, knowledge of mentorship competencies, and confidence in coaching skills. Outcomes from the Clinical Faculty Development series supported the mentoring program outcomes. Longitudinal follow-up is needed to determine how this program will impact mentees.

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INTRODUCTION

Engaged faculty with a strong sense of professional fulfillment and organizational value are vital to sustaining and growing academic health centers' tripartite mission of clinical service, education, and research. However, early career faculty may lack the understanding and skills to navigate successful careers at an academic health center, and their professional identity formation and fulfillment increasingly are threatened by greater clinical and administrative demands, burnout, and balancing work-life integration. These issues are amplified for women and persons underrepresented in medicine (URiM) minority groups, in part due to a perception of low institutional inclusion and promotion to leadership roles.[1,2]

Faculty development programs at academic health centers have assumed responsibility for advancing faculty towards promotion, supporting mentorship, creating collaborative networks, and fostering education, research, and additional professional skills.[3,4] However, most of the literature regarding the effectiveness of mentoring academic health centers has focused on scientific researchers, not clinicians. Some data suggest that faculty development programs may increase career satisfaction and engagement, utilization and satisfaction with mentorship opportunities, research productivity, and promotion rates.[5-10] Indeed,

faculty who participate in professional development are more fulfilled, productive, and are less likely to leave their institution.[5,11-15] Mentoring programs have been identified as particularly impactful at promoting faculty vitality; however, mid-career and senior clinical faculty may not have the knowledge base and mentoring skills to provide impactful guidance,[9,16] and the optimal approach to mentor training and its effects on the mentor's career development and professional vitality are not known.

To address the needs of clinicians in the University of Wisconsin (UW) Department of Medicine (DOM), we developed and implemented a Clinical Faculty Development Program that had 2 components: a Clinical Faculty Mentoring Program (CFMP), which used a novel coaching approach to train faculty mentors, and a Clinical Faculty Development Series (CFDS), with a unique focus on topics of specific interest to clinicians (Box 1). Traditional mentoring programs are mentor-driven, with the mentor functioning as a problem-solver who provides advice and guidance to mentees regarding career goals and challenges. The CFMP used coaching principles to teach clinician mentors how to focus on mentee behaviors and how to foster their mentee's self-awareness and growth using principles from positive psychology and motivational interviewing. The primary aim of this program was to provide clinicians with robust experiences that cultivate skill-building, mentorship, and opportunities to enhance professional satisfaction and engagement with the promotion process. The CFDS supported this training and was directed at all clinical faculty in the UW DOM. The long-term goals of these programs are to increase clinician vitality, attenuate burnout and physician distress, improve the DOM's climate, and increase faculty retention. In this paper, we describe the activities and impact of the first year of the CFMP and CFDS, with particular focus on the mentors who completed the novel coach approach to clinical mentoring.

Box 1. University of Wisconsin Department of Medicine Clinical Faculty Development Program – Structure and Activities

Goals of Clinical Faculty Development Program
- Skills building
- Mentorship
- Professional satisfaction
- Engage in promotion process
- Enhance faculty vitality

Component 1: Clinical Faculty Mentoring Program
- Mentor-mentee matching
- Mentor training (7 x 90' sessions)
- Content expertise (1 session)
- Coach approach (6 sessions)
- Protected time for training and meeting at least once annually

Component 2: Clinical Faculty Development Series
- Core content areas
- Clinical teaching
- Diversity, equity, and inclusion
- Professional and leadership skills
- Promotion
- Work-life balance
- Virtual format
- Blended learning

METHODS

The UW-Madison Health Sciences Human Subjects Committee (the institutional review board [IRB] for the UW School of Medicine and Public Health) determined that our evaluations did not meet the definition of human subjects research. The activities and analyses described in this report were deemed quality assurance and the committee declined to review them or request completion of IRB-approved consent forms. Participation in all surveys and interviews was fully confidential. Informed consent for participation in the interviews was provided orally to Wisconsin Center for Education Research staff. All data, including who chose to participate in these interviews, were analyzed anonymously. No minors or prisoners participated in this study.

Setting

The UW DOM comprises 446 faculty in 11 divisions. This mentoring program was designed for clinical faculty who spend most of their time in direct patient care; excellence in clinical practice is the primary goal for their academic promotion, with consideration of significant accomplishments in teaching and service. Most clinical track faculty in the UW DOM are at the rank of assistant clinical professor (56%), followed by associate clinical professor (30%), and clinical professor (14%). The mean (standard deviation) age for clinical faculty by rank are 42 (10.1, range 28-75) years for assistant clinical professors, 49 (8.3, range 36-74) years for associate clinical professors, and 55 (6.1, range 45-68) years for clinical professors. Females comprise 45% of clinical track faculty. The UW does not disclose the race/ethnicity distribution of faculty, though we allowed voluntary disclosure of race/ethnicity from program participants.

Clinical Faculty Mentoring Program

The mentorship component of the CFMP (Box 1) was created following the Science of Effective Mentorship by the National Academies of Sciences, Engineering, and Medicine: a professional, working alliance in which individuals work together over time to support the personal and professional growth, development, and success of the relational partners through the provision of career and psychosocial support.[17]

Assistant clinical professors who had joined the UW DOM after July 2020 were required by departmental promotion guidelines to participate in the CFMP. The first step was identifying mentors. Mentors were recruited by email to all associate or full clinical professors in the department. Division heads also encouraged their faculty participation at division meetings. Next, mentors and mentees completed surveys that indicated their professional interests and preferences for mentor-mentee matching (ie,

Figure 1. Timeline of Clinical Faculty Mentoring Program (CFMP) Activities and Evaluation Process

same/different academic division, gender identity, race/ethnicity, professional interests, nonprofessional interests; see Appendix: Supplement Text 1 and 2). After surveys were completed, a DOM staff member and the vice chair for faculty development matched mentees with mentors based on survey responses; requests regarding specialty, professional interests, and gender identity were prioritized and used for tentative matches. Then, mentors completed a structured training curriculum that consisted of seven, 90-minute virtual sessions from September 2022 through June 2023. The first session covered 3 components of the mentoring knowledge base: promotion standards and processes; faculty well-being and institutional resources; and diversity, equity, and inclusion (DEI) resources.

The next 6 sessions used a novel "Coach Approach to Clinical Faculty Mentoring" to deliver information about professional coaching competencies. Utilizing the International Coaching Federation's (ICF) core competency framework and drawing from the UW's ICF-accredited Certified Professional Coach program curriculum, each of the 6 sessions provided lessons in the foundational components of a coach approach to faculty mentoring.[18] Components included but were not limited to understanding the coaching mindset, designing the mentor-mentee relationship/alliance, and communicating effectively via powerful questioning and listening actively.[19] These sessions integrated hands-on and experiential exercises inside and outside of class for mentors to practice their newly acquired skills. Mentors were excused from clinical activities during their training sessions and to meet with their mentees. They were encouraged to meet with their mentees at least once in the first year of the program. Recommendations to start meeting were made after 4 of the 7 training sessions were completed.

Clinical Faculty Development Series

We simultaneously initiated a CFDS (Box 1) that provided weekly, 1-hour learning sessions that focused on a wide variety of topics related to clinical faculty, including promotion, teaching, professional and leadership skills, work-life balance, and DEI (Appendix: Supplemental Table–CFDS Session Titles and Categories). The CFDS was open to all clinical faculty in the UW DOM, not just participants in the CFMP. Each session provided a blended learning opportunity that usually included didactic and interactive components, such as small group breakout sessions, "open mic" large group discussions, and role-playing/simulation activities. Content for each of the 39 sessions was provided by UW experts in each field. CFDS sessions occurred every Tuesday over the noon hour from September 2022 through June 2023 and were held virtually to maximize attendance of faculty working across various geographic sites in the UW DOM. CFDS lectures were recorded and uploaded with the permission of the presenter to an internal video lecture archive for faculty who could not attend to view asynchronously. The CFDS was promoted via institutional email to all UW DOM faculty, internal video DOM, websites, and DOM newsletter. Weekly reminder emails were sent to faculty with the upcoming week's CFDS topic.

Program Evaluations

The timeline of the CFMP activities and evaluations are shown in Figure 1. Professional staff from the Wisconsin Evaluation Collaborative at the Wisconsin Center for Education Research led the CFMP evaluation. A mixed methods evaluation plan guided collection of confidential survey and interview data. Qualtrics surveys were used to collect mentor and mentee baseline data before the program began and for a post-survey that coincided with the end of the coach approach to mentoring sessions. Both pre- and post-surveys focused on understanding of promotion processes, satisfaction with workplace processes, and workplace climate. Mentor surveys included confidence in mentoring skills. After completion of the coaching training, mentors also were surveyed for impressions, utilization, and feedback.

Table 1. Clinical Faculty Mentoring Program Survey Response Rates

	Pre-Survey N (%)	Post-Survey N (%)	Both Pre- and Post-Survey N (%)
Mentors (N = 43)	34 (79.1)	37 (86.0)	29 (67.4)
Mentees (N = 37)	26 (70.3)	23 (62.2)	18 (48.6)

The data from the post-surveys are described below. Responses from mentors and mentees who completed both pre- and post-surveys were used to evaluate the effects of the CFMP on the outcomes. Additionally, 6 mentors and 5 mentees participated in confidential, semi-structured interviews over Zoom with experts from Wisconsin Center for Education Research about their experience with the CFMP. Interviews were audio recorded, transcribed, and thematically coded with NVivo software (Lumivero, Denver, Colorado).

Participant attendance data for the CFDS were obtained for each session. After the final session, Qualtrics surveys were used to elicit semi-quantitative feedback and qualitative responses from participating faculty. The question "Based on what you experienced as part of the CFDS, to what extent do you agree …" was used to assess whether the aims of the CFDS were successful. A 5-point Likert scale (1 = strongly disagree to 5 = strongly agree) was used for responses. Values are described as means and standard deviations. Paired *t* tests were used to compare pre- to post-survey values among participants who completed both surveys. A *P* value of <0.05 was considered statistically significant. P values were not adjusted for multiple comparisons given the sample size; they were interpreted conservatively and in context.

Table 2. Demographics of Clinical Faculty Mentoring Program Survey Respondents (Post-survey)

	Mentors	Mentees
Academic Rank (%)		
Assistant professor	8.8	100
Associate professor	64.7	—
Professor	26.5	—
Years of Employment (%)		
≤ 5 years	8.3	100
6 – 10 years	36.1	—
11 – 19 years	47.2	—
≥ 20 years	8.3	—
Gender identity (%)		
Female	48.6	36.8
Male	45.7	52.6
Another gender/prefer not to say	5.8	10.5
Race/ethnicity (%)		
Asian American or Asian	5.7	30
White	74.3	40
Another race/ethnicity	8.6	10
Prefer not to say	11.4	20
Division (n)		
Cardiovascular medicine	8	3
General internal medicine	7	—
Hospital medicine	6	10
Divisions with <3 mentors or mentees:	13	6
• Allergy, pulmonary and critical care		
• Gastroenterology and hepatology		
• Geriatrics and gerontology		
• Hematology, oncology, palliative care		
• Nephrology		
• Rheumatology		

RESULTS

CFMP Participants

Response rates for participating CFMP faculty are shown in Table 1. Demographic data from the post-survey are in Table 2. Most mentors were associate clinical professors and had been employed by the UW DOM for 6 to 19 years. A similar number of male and female mentors participated; among mentees there were more males and participants who preferred not to report their gender identity. Most mentors were White; mentees had more diverse URiM representation. Faculty from 9 clinical divisions within the DOM participated in the mentoring program. Of post-survey respondents, 67% of mentors and 100% of mentees reported having had at least 1 mentor/mentee meeting, and 28% of mentors reported meeting more frequently with their mentee, on either a monthly or quarterly basis. Of note, some mentors had more than 1 assigned mentee, and some mentors had not yet been assigned a mentee by the end of the first year.

CFMP Mentor Outcomes

Our primary findings describe changes in mentor job satisfaction, teaching attitudes, mentoring knowledge, and confidence in mentoring and coaching skills from before to after participating in the CFMP (Table 3). We identified statistically significant improvements in almost all domains, with the largest and most consistent improvements in knowledge of mentoring competencies and resources, particularly promotion guidelines and processes, promoting career development through education, promoting career development through opportunities for networking, aligning personal career goals with the UW DOM's overall goals, and managing imposter phenomenon. Absolute improvements in these areas ranged from 0.69-0.88 points (all $P < 0.001$). We also observed statistically significant improvements in confidence in coaching and mentoring skills in each of these areas, though the absolute magnitude of improvement was slightly lower (0.49-0.55 points, all $P \leq 0.02$).

Mentors' confidence in modeling most coaching behaviors did not change appreciably after participation in mentor training and meeting with their mentees (Figure 2). The 2 question responses with the strongest evidence for improvement were "supporting the mentee to integrate new awareness, insight, learning into their worldview and behaviors" ($P = 0.0503$) and "managing time and focus of mentoring session" ($P = 0.022$). For 9 of 10 questions, the modal response for the post-survey was

the same as in the pre-test. Results were similar by gender identity and by years of experience (≤10 vs >10 years). Means of mentors' perceptions of the UW DOM climate, their professional fit, equitable procedures, and support for professional development were high at baseline (3.90-4.31, on a scale of 1.0 ["not at all"] – 5.0 ["a great deal"]); post-survey mean values increased for these domains, but differences were not statistically significant (data not shown).

Overall, 44% of respondents found the strategies used in the coach approach to mentoring program "very helpful," another 44% found them "somewhat helpful," and 1 respondent selected "somewhat unhelpful." Similarly, 56% responded that they were "very likely" to use a coach approach to mentoring junior faculty, and 28% responded that they were "somewhat likely" to use this approach, with 8% responding that they were "somewhat unlikely" or "unlikely" to use it.

Representative narrative comments from mentors about the aspects of the CFMP are in Box 2. Mentors' comments highlighted the practical aspects of the program, sense of community, appreciation for the "formal structure and progressive nature of the training," and the overall effect participation in CFMP had on individual mentoring practices. Some mentors expressed differing views on the coach approach to mentorship. Comments also focused on the challenge of the time commitment necessary for mentor training and mentorship meetings.

Table 3. Changes in Mentor Job Satisfaction, Teaching Attitudes, Mentoring Knowledge, and Confidence after Completing the Clinical Faculty Mentoring Program

	Pre-Mean	SD	Post-Mean	SD	*P* value
Job Satisfaction and Attitudes					
I understand my current job in the DOM	4.55	0.69	4.72	0.53	0.202
I am satisfied with the amount of time I have to meet and fulfill the obligations of my job description	3.25	1.11	3.79	1.05	0.017
Overall, I am satisfied with my career	3.93	0.75	4.31	0.66	0.001
I am confident about my path to promotion	4.00	0.74	4.64	0.49	<0.001
My day-to-day activities give me a sense of accomplishment	3.90	0.90	4.38	0.73	0.041
The DOM supports work-life balance	3.28	1.10	3.72	0.96	0.017
I am satisfied with my own work-life balance	3.17	1.10	3.55	1.12	0.046
Teaching Attitudes					
I am satisfied with the influence I have over the focus of my teaching	4.28	0.75	4.59	0.64	0.148
I am satisfied with the extent that my teaching contributes to promotion	4.04	0.85	4.54	0.71	0.010
I am satisfied with the balance of clinical and teaching duties	3.76	1.09	4.25	0.80	0.020
Knowledge of Mentoring Competencies and Resources					
Promotion guidelines and process	2.62	0.82	3.50	1.04	<0.001
Promoting career development through education	2.38	0.73	3.25	0.97	<0.001
Promoting career development through opportunities for networking	2.38	0.73	3.11	0.83	<0.001
Aligning personal career goals with DOM's overall goals	2.55	0.87	3.25	0.93	<0.001
Burnout recognition and mitigation	2.79	0.82	3.32	0.94	0.005
Building resilience	2.66	0.72	3.25	0.93	0.001
Supporting diversity, equity, and inclusion in the workplace	2.83	0.89	3.39	1.03	0.007
Managing imposter phenomenon	2.52	1.06	3.21	0.83	<0.001
Confidence in Coaching/Mentoring Skills					
Promotion guidelines and process	2.72	0.80	3.21	0.83	0.002
Promoting career development through education	2.59	0.73	3.14	0.76	<0.001
Promoting career development through opportunities for networking	2.55	0.83	3.07	0.90	0.001
Aligning personal career goals with DOM's overall goals	2.76	0.95	3.25	0.84	0.020
Burnout recognition and mitigation	2.83	1.04	3.29	0.85	0.035
Building resilience	2.82	0.94	3.25	0.93	0.043
Supporting diversity, equity, and inclusion in the workplace	2.82	0.98	3.21	0.99	0.011
Managing imposter phenomenon	2.64	1.06	3.14	1.04	<0.001

Abbreviation: DOM, Department of Medicine.
Scale: 1.0 ("not at all")– 5.0 ("a great deal").

CFMP Mentee Outcomes

Surveyed mentees reported high baseline pre- and post-mean levels of agreement on items assessing understanding their current job description, job/career satisfaction, path to promotion, and work-life balance (data not shown). Mentees reported increased confidence in all 8 domains of emphasis from mentoring sessions, but differences in pre/post means did not reach statistical significance given the small sample size (Figure 3). Numerically, at least half of participants reported higher confidence on the post-survey than on the pre-survey for all but 1 measure (aligning personal career goals with DOM's overall goals; data not shown). Representative narrative comments from mentees regarding program highlights and areas for improvement are summarized in Box 2. Qualitative responses echoed a similar theme as that of mentors related to difficulty with finding time for preparing for and participating in mentoring meetings.

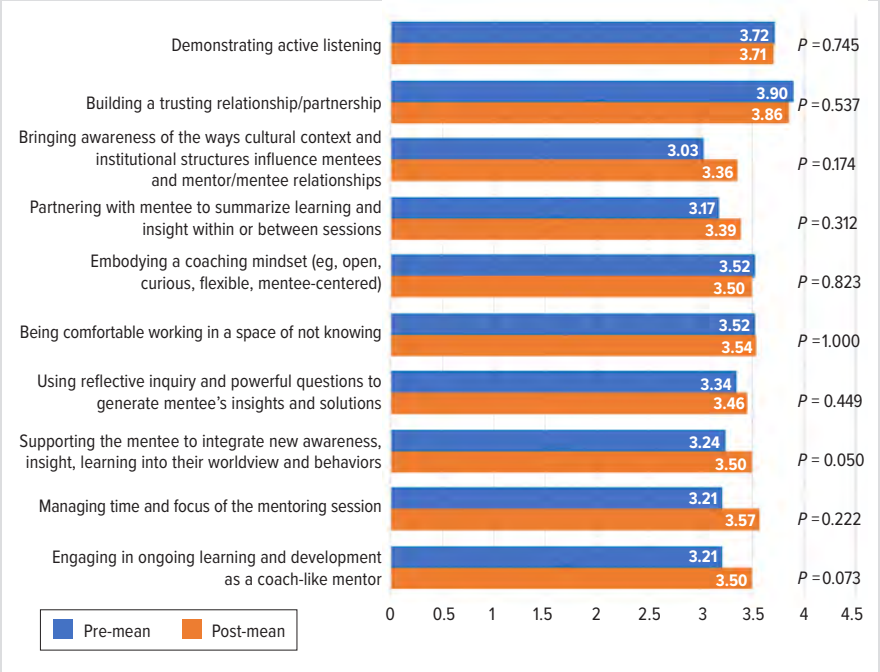
CFDS Outcomes

From September 2022 through June 2023, 39 sessions were attended by 239 unique faculty. On average, 38 individuals participated in each session (range 22-59); 44% were assistant professors, 34% were associate professors, and 22% were professors. The sessions with the highest attendance were on the topics of time management and organization skills (n = 50), promotion (n = 49), physician burnout (n = 47), being a woman in medicine (n = 47), building an anti-racist environment (n = 45), feeling fulfilled by your job (n = 43), learning climate (n = 43), promoting

clinical reasoning (n = 43), setting professional goals (n = 42), and public speaking (n = 42).

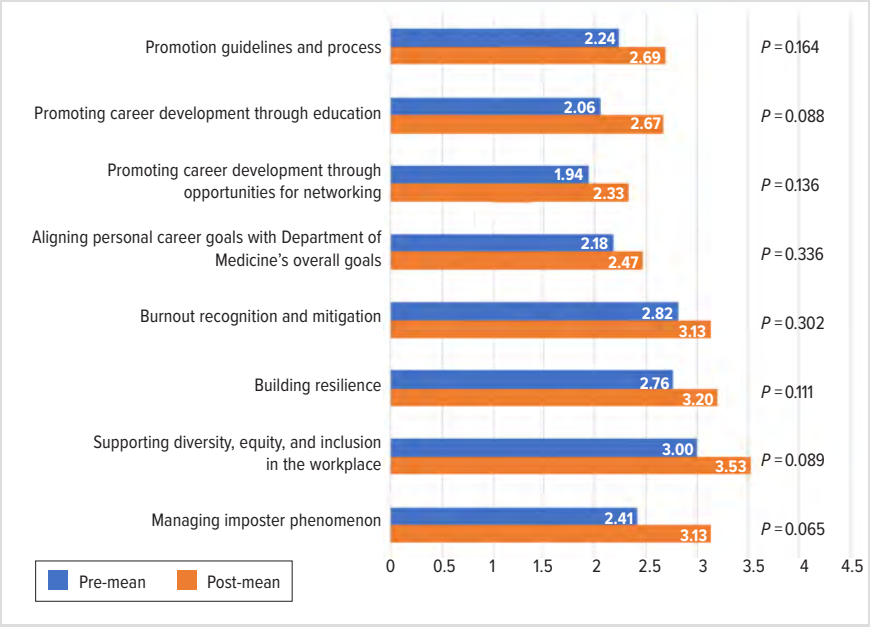
The post-CFDS survey was completed by 99 faculty. Respondents represented all 11 divisions in the UW DOM. Overall responses were favorable, with 70% of respondents agreeing or strongly agreeing that the skills they learned helped them professionally and 56% to 60% agreeing or strongly agreeing that they learned to be a better teacher in the clinical environment, learned how to recognize and address bias, and that the skills they learned are important for leadership. Positive themes that emerged from narrative comments were appreciation for the variety of topics, interactive format, and opportunity to gain perspectives from other faculty. The sessions on clinical teaching were particularly well-received. The most notable challenge was the timing of the sessions given the busy schedules of clinical faculty.

Figure 2. Mentor Changes in Confidence at Modeling Coaching Behaviors



Scale: 1.0 ("not at all")– 5.0 ("a great deal").

Figure 3. Mentee Changes in Skills and Knowledge



Scale: 1.0 ("not at all")– 5.0 ("a great deal").

DISCUSSION

The UW DOM Clinical Faculty Development Program combined a novel professional coach approach to formal mentoring (the CFMP) and a recurring series of interactive sessions aimed at building a diverse set of skills and boosting the vitality of its clinical faculty (the CFDS). Our primary finding was that mentors who participated in the CFMP reported statistically significant improvements in almost all domains queried, with notable self-reported improvements in knowledge of and confidence in using coaching skills to mentor junior faculty in the areas of promotion guidelines and processes, promoting career development through education, promoting career development through opportunities for networking, aligning personal career goals with the DOM's overall goals, and managing imposter phenomenon. The vast majority of mentor respondents (88%) found the strategies used in the Coach Approach to Mentoring Program to be "very" or "somewhat" helpful, 84% responded that they were "very" or "somewhat likely" to use a coach approach to mentoring junior faculty, and 28% responded that they were "somewhat" likely to use this approach when mentoring junior faculty. All mentees had at least 1 meeting with a mentor, and mentees reported increased confidence in each domain we focused on. The CFDS was well-attended and appeared to support the outcomes from the CFMP by fostering a culture of mentorship, facilitating professional skills-building, and providing opportunities for interpersonal interactions.

Mentoring programs at academic health centers often are proj-

Box 2. Representative Narrative Comments from Mentor and Mentee Participants in the Clinical Faculty Mentoring Program

MENTOR COMMENTS

Program Highlights

- "I have really enjoyed the series of coach approach to mentoring to help me be a better mentor; it has really changed my approach to mentoring and teaching residents and students."
- "The classes are great and what is learned is good for every aspect of life, not just the workplace. … I feel privileged to be a part of this."
- "Great to have time to connect with others who are acting as mentors."
- "Nice opportunity to learn new strategies for mentorship, great chance to connect with colleagues I might not have otherwise met."

Areas for Improvement/Challenges

- "As with many worthwhile endeavors, the challenge is balancing the time it takes to do this well with all the other competitors for that time."
- "Keeping up with sessions. Finding the time to attend the program."
- "During many sessions I would have preferred to listen more and do less group work."

Coach Approach: Positives

- "I feel more prepared for my next mentor meeting to be able to help them without me doing all the talking. I think that there is a lot of good information from those coach approach sessions about how to get a conversation going, create a comfortable environment, and then really let the person reflect themselves on what they want to do and you can be the sounding board, but you don't have to find all of the answers, which is wonderful."
- "Learning more about the role of listening. Allowing people to just talk and ask probing questions rather than redirecting can be so useful."
- "It's been really helpful as a new language that I think I've learned in how to talk to the mentee and help him come to realizations without me telling him how he should do things."

Coach Approach: Critiques

- "I am not sure that a mentor needs to be a strong coach. Career development is important, a mentor should refer to experts if coaching is required."
- "I like to help people solve problems directly, not just ask open-ended questions until they figure out a solution themselves."
- "The coaching categories/presentations were beyond the scope of my understanding of what a mentor should be."

MENTEE COMMENTS

Program Highlights

- "It is nice talking to someone and gathering and reviewing materials regularly to keep on track for promotion."
- "The options for choosing a mentor were helpful."
- "One thing my mentor did was provide me with some opportunities for getting involved in more teaching opportunities."
- "I felt like I have someone I can talk to. I think it's always nice to have some kind of support system – especially when I'm completely new to everything… It's been really helpful for my career, but also just knowing someone who can help me if I ever needed the guidance and support."

Areas for Improvement/Challenges

- "Give us time off to do this and continue to emphasize its importance."
- "Work with divisions to clear time for both the mentor and mentee."
- "Small group assignments might have improved participation as well. Would have liked to interact with faculty from other divisions in a similar career stage."
- "It probably would be more helpful to have [a mentor from my division] because our division is constantly changing, and there's different opportunities for leadership within the division. I'm not sure if [my mentor] is necessarily going to have a finger on the pulse of that kind of stuff."

ect-focused and outcome-driven.[5,7,12] Although we used a dyad mentorship model and adhered to best practices in the science of effective mentoring, our CFMP was novel by using coaching as the basis of mentor training, rather than the traditional "mentor as problem-solver and advisor" approach. Coaching aims to enhance mentee's self-awareness and growth and is based on principles from positive psychology and motivational interviewing.[20] Professional development coaching programs in health professions have beneficial effects, such as aiding faculty in achieving professional goals, decreasing reports of burnout, and increasing work engagement and satisfaction.[21,22] Coaching is a skill that clinical faculty can apply in leadership roles and when working with learners and advanced practice providers.[23,24] After coach training, mentors in the CFMP indicated that the coaching skills were effective and impactful for mentoring junior faculty.

To understand the extent to which mentors internalized and implemented behaviors taught in the coach approach training, we assessed their level of confidence to model specific coaching behavior. Most domains showed only small improvements when assessed in aggregate (ie, group means) or using individual change scores. However, the 2 domains showing greater evidence of change – (1) supporting the mentee to integrate new awareness, insight, learning into their worldview and behaviors and (2) managing time and focus of mentoring sessions – are two of the more critical aspects of what makes a coach approach such a powerful paradigm for mentors.

Coaching, at its root, is about creating deeper learning that promotes action to create behavioral change. Being able to coach a mentee to successfully integrate new awareness into their worldview and to act accordingly, coupled with the very practical skill of managing time and focus of a mentor coaching session, are keys to the overall success of any coaching or coach-approach engagement. Improving confidence in these coaching behaviors positions the mentor/mentee relationship for success. We also suspect that these trends reflected "response shift bias," whereby mentors "did not know what they did not know" in the presurvey; that is, as

they took part in mentoring throughout the year, they recalibrated their confidence based on what they learned. Indeed, several participants indicated this informally during the training sessions. Other faculty mentoring programs also have described differences between mentor confidence in mentoring competencies and adopting mentoring behaviors.[25] These findings highlight the need not only for effective mentor training but also for follow-up and continuous mentorship skills building.

The CFMP was initiated at the same time as the CFDS. The CFDS was open to all clinical faculty in the UW DOM, so these activities overlapped temporally and many CFMP participants attended CFDS sessions. Thus, observations about the impact of CFMP must be considered based on the background of this program and the individual effects of each cannot be ascertained. In addition to its unique focus on faculty development topics of specific interest to clinicians, the CFDS supported the outcomes of the CFMP due to overlapping topics and exposure of CFMP participants to presenters and participants from outside the program. Another unique aspect of both the CFMP and CFDS was that they were initiated and conducted virtually due to the COVID-19 pandemic. Virtual sessions permitted a wider audience to attend, including faculty working at distant clinical sites and those working from home, as observed in another study.[26] Furthermore, digital recordings allowed asynchronous viewing for faculty. The chat function and breakout rooms were options for greater audience participation, creating a more active learning environment. Virtual presentations were well received, though some faculty still expressed a desire for face-to-face experiences.

Finding time to participate in the CFMP and CFDS was the major challenge identified by respondents. Faculty in the CFMP agreed that the time reserved for mentor training and annual meetings was fair and sufficient; however, finding time in a busy clinician's day for ongoing mentor-mentee meetings and participation in the noon-hour CFDS sessions were challenged by competing clinical and administrative demands. Addressing time constraints would allow faculty to engage more consistently, further cultivating a vibrant culture of faculty development. Future directions to assure sustainability include increasing the pool of mentors and opportunities for mentor trainees, creating digital tools to facilitate implementation of mentoring strategies and other skills, and central administrative support for scheduling meetings.

Limitations

Since our program enrolled early career faculty who mostly were in their first year of employment and it initiated during a late stage of the pandemic, we do not know the impact of these programs on longer-term outcomes, such as promotion, teaching effectiveness, well-being, and faculty vitality. Success in promotion and scholarship from faculty participating in faculty development programs typically has been measured 3 to 10 years after program initiation.[5,6,12] However, there were signals in our data that faculty participation in these programs improved confidence, work satisfaction, and perceptions of the DOM's support of their professional development and mentorship – even in the first year, with most mentees having only 1 to 2 sessions with their mentors.

In addition to response shift bias, a major limitation of our data is response bias. The data presented reflect the responses of people who participated and responded to the pre- and post-surveys. We do not know the responses of those who chose not to respond. Because the survey responses were confidential, we were not able to identify and contact participants who did not respond and thus could not provide more detailed data analyses by race/ethnicity or academic division due to the small numbers of participants in those subgroups. Since the overlap of participation between the CFDS and CFMP was so marked and because of the confidential nature of the responses, we are not able to identify sizable enough subgroups to isolate the individual effects of each program.

CONCLUSIONS

The UW DOM Clinical Faculty Development Program created a novel coach approach to mentoring and a weekly faculty development series to provide clinicians with experiences that promoted skill-building, mentorship, and professional opportunities. Mentors who participated in the CFMP reported improved knowledge of and confidence in using coaching skills to mentor junior faculty in promotion guidelines and processes, career development through education and opportunities for networking, aligning personal career goals with our department's goals, and managing imposter phenomenon. Mentors overwhelmingly indicated that the program was helpful and will be useful. The CFDS was well-attended and supported the outcomes from the CFMP. Longitudinal follow-up is needed to determine how this program affects mentees and if it achieves its long-term goals.

Financial Disclosure: None declared.

Funding/Support: This project was funded by the University of Wisconsin Department of Medicine.

Availability for data and materials: The datasets generated and/or analyzed during the current study are not publicly available due to personally identifying information but are available from the corresponding author on reasonable request.

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Exploration of Factors That Positively Influence Medical Student Reception of Question-Based Teaching in Clinical Settings

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ABSTRACT

Introduction: Academic medicine literature has reported hesitation from clinical teaching physicians to use questions when teaching medical students due to its negative connotation of "pimping." However, newer literature suggests that most students prefer questions, while only a small minority are less welcoming. Some teaching physicians, however, have concerns about using questions due to the risk of humiliating or embarrassing medical students in clinical settings.

Methods: Medical students who completed core clerkship rotations at a public medical school in the Midwest were invited to participate in 1 of 4 virtual focus groups. Students were asked to reflect on 3 clinical teaching vignettes. Inductive thematic qualitative analysis was performed to create a codebook. The transcripts were coded by 2 independent coders for emerging themes.

Results: Twenty-six students participated across 4 groups. Four major themes were identified that demonstrate positive student reception of teaching physicians and their questions: teaching physicians (1) engaging students, (2) setting clear expectations, (3) empathizing with the medical student experience, and (4) asking questions to teach rather than evaluate. Thematic coding of the 3 vignettes resulted in initial intercoder reliabilities of 85.4%, 87%, and 79%, prior to achieving 100% consensus. Students described the ideal teaching physician to be patient, engaged, and respectful.

Conclusions: By engaging medical students, setting clear expectations early on, empathizing with the medical student experience, and asking questions with the purpose of teaching, teaching physicians can be less hesitant about upsetting medical students when utilizing questions as a teaching tool.

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INTRODUCTION

Questions have been a mainstay of teaching throughout recorded medical education. The Socratic method, named for the Greek philosopher Socrates, is a questioning technique used in academic medicine that allows students to apply their knowledge to clinical scenarios.[1] The goal of Socratic teaching is to build upon the student's level of understanding and encourage self-directed learning. However, the practice of teaching medical students by asking questions has taken on the negative connotation of "pimping" in recent years. "Pimping," first defined by Brancati in 1989, is a form of teaching where the teaching physician in a clinical learning environment poses a series of difficult questions to the learner.[2] Though not always used maliciously, this style of questioning has become associated with reaffirming the hierarchical nature of medicine and reported student embarrassment, humiliation, and belittlement in group settings.[3]

Recent literature highlights that teaching physicians may feel they are walking on eggshells when using questions to teach medical students due to fear of it being misconstrued as "pimping"—particularly at institutions that encourage students to report all forms of mistreatment, including public embarrassment, humiliation, and belittling, without fully considering teaching physician perspectives or actions.[4] However, newer literature suggests that the majority of students do, in fact, prefer to be asked questions on clinical rotations, while only a small minority are less welcoming of questions from teaching physi-

Table 1. Clinical Vignettes and Probing Questions for Focus Groups Regarding Student Reception of Faculty, University of Wisconsin School of Medicine and Public Health 2023

Vignette A

The attending physician, Dr. A, is rounding on the medical student's patient. After the student presents the daily updates in SOAP format (Subjective, Objective, Assessment, and Plan), the following dialogue takes place:

Dr. A: Thank you. Why do you think your patient has leg edema?

Student: I am not entirely sure. I just know that we diurese them because of fluid overload.

Dr. A: Correct and that's okay. Let's see if we can get through the mechanism together. What chronic disease does this patient have?

Student: Uncontrolled heart arrhythmia.

Dr. A: Yes. And you said uncontrolled which is important. Essentially the heart was overworked leading to dilated heart chambers. Can you take it from here?

Student: Okay so dilated chambers leads to the heart not pumping correctly. So blood isn't moving forward resulting in fluid buildup.

Dr. A: Perfect! There is also fluid in the lungs which is why they are hypoxic. So, we diurese to decrease fluid overload and also give oxygen to minimize hypoxia and decrease the stress on the heart. This is a nice example of how understanding the mechanism guides therapy. Good job working through that, [student name]! What questions do you have?

Probing Questions:

1. What are your thoughts on this teaching interaction?
2. Why would this be an attending you would or would not like to work with?
3. What did Dr. A say that you, as a learner, liked or didn't like?
4. What would you write on their rotation evaluation based on this interaction?

Vignette B

Dr. B, the attending physician, asks to meet with the medical students that just joined the service. After introductions, Dr. B explains the student expectations, provides a list of topics that the student is expected to read about for each week, and then gives a detailed explanation of what the student evaluation is based off of. Dr. B then says the following:

I like to teach medical students by asking questions. My objective is to identify gaps in your knowledge of medical facts and concepts, thereby guiding me on what to teach you about. The questions will correspond to your assigned reading topic each week. I care less about you getting the answer right and much more about you thinking through the questions and reasoning through an answer. When you get a question wrong, I don't want you to feel embarrassed. Instead, I want you to think of it as an opportunity to learn something new!

Probing Questions:

1. What are your thoughts on this interaction?
2. Why would this be an attending you would or would not like to work with?
3. What did Dr. B say that you, as a learner, liked or didn't like?
4. Why might this kind of orientation be valuable or invaluable?
5. What would you write on their rotation evaluation based on this interaction?

Vignette C

Dr. C, the attending physician, is operating with the medical student. The following interaction then takes place.

Dr. C: Okay, time for questions. What is this structure here?

Student: I think it's the inguinal canal.

Dr. C: What is this structure?

Student: The peritoneum.

Dr. C: Correct.

5 minutes later, the conversation continues.

Dr. C: What are the contraindications for this surgery?

Student: Metastatic spread.

Dr. C: Good.

3 minutes later, the conversation continues.

Dr. C: More questions. What is the cancer staging based off of?

Student: The Ann Arbor criteria.

Dr. C: That is incorrect. Is radiation indicated for this patient?

Student: No.

Dr. C: Explain.

Student: We can resect with good margins.

Dr. C: Good.

30 minutes later the case ends.

Probing Questions:

1. What are your thoughts on this teaching interaction?
2. Why would this be an attending you would or would not like to work with?
3. What did Dr. C say that you, as a learner, liked or didn't like?
4. What would you write on their rotation evaluation based on this interaction?

cians.[5] Furthermore, a study from the University of Washington School of Medicine found that the style of questioning used in medical teaching was not a risk factor for public humiliation as long as learners were appropriately conditioned to the teaching practice.[6] Student responses from this study identified that the perceived intent of the teaching physician was the most important factor for whether students experienced public humiliation from questioning.

One way to improve student perception of using questions as a teaching tool is to foster a healthy student-teaching physician relationship. Several studies highlight the importance of clear communication between the student and teaching physician to encourage positive and respectful interactions that build trusting relationships in the learning environment.[7,8] We hypothesized that when students have developed positive and trusting relationships with teaching physicians, they are more generous about accepting various teaching styles, including direct questioning in clinical settings. Existing literature, namely by Abou Hanna et al, used a survey approach to quantify student opinions regarding questioning.[5] By utilizing a qualitative study design, we hoped to delve deeper into specific student experiences and identify factors that make students more receptive and respond positively to questions from teaching physicians. The goal of this study was to determine how teaching physicians can use questions in a positive way that promotes learning.

METHODS

Study Design

A focus group approach was chosen to generate qualitative data to explore student perceptions of questions from teaching physicians.

The script for the focus groups was constructed using an iterative process by a resident and a senior faculty leader of health professions education (JJA and EMP). To guide the focus groups, the script contained 3 teaching vignettes with probing questions to

facilitate discussion (Table 1) and 4 general discussion questions. Teaching vignettes were based on common clinical scenarios that were reviewed by 5 additional teaching physicians selected based on teaching credentials. These 4 discussion questions were analyzed:

1) What piece of advice would you give every attending physician regarding teaching on the wards?
2) Think of your favorite attending physician you have worked with clinically. What was it that made them your favorite?
3) What 3 adjectives would you choose to describe the ideal attending physician in a clinical teaching role?
4) How do you think students' perception of teachers is affected by factors such as age, reputation, cultural background? Are there other factors that matter (political beliefs, gender, race)?

The University of Wisconsin Institutional Review Board deemed this study exempt (ID: 2022-0940, exempt on August 31, 2023).

Participants and Focus Groups

Eligible participants were third- and fourth-year medical students who completed their required core clerkships by March 2023 at the University of Wisconsin (UW) School of Medicine and Public Health. Core clerkships at this medical school are completed by second-year and third-year students through 4 integrated clinical content blocks over a 12-month period. These core clerkships took place at statewide teaching hospitals that have longstanding affiliations with the UW School of Medicine and Public Health.

Students were recruited in February 2023 via email and approved social media outlets. Those students who responded were invited to participate in one of four 90-minute virtual focus groups, with a participant cap of 8 students per focus group. All participants stayed for the entire duration of the focus group. Basic demographic information was collected using an anonymous survey prior to the focus groups.

All focus groups were conducted by 1 facilitator from the research team (JJA) and followed the same guide with questions and optional probes for consistency. The focus group facilitator (JJA) was guided in facilitation techniques by a senior faculty member (EMP) who has experience with peer-reviewed published qualitative research, as well as training and direct experience in focus group facilitation. Sessions were conducted and recorded via Zoom (Zoom Video Communications, San Jose, California). Sessions were auto-transcribed by Zoom and reviewed by the research team (ASJ). All identifying information was removed from the final transcripts. All video files and unedited transcripts were deleted once final deidentified transcripts were created and checked for accuracy.

Students were given a thank you gift for attending the focus group. Internal funding was provided by the UW Department of Ophthalmology and Visual Sciences Resident Research Fund.

Table 2. Demographics and Specialty Interests of Student Participants in Focus Groups Regarding Student Reception of Faculty

Age (mean, range)	26.2, 6
Gender (n, %)	
Male	7 (27%)
Female	19 (73%)
Training year (n, %)	
Third year	14 (54%)
Fourth year	12 (46%)
Race (n, %)	
White	23 (88%)
Black or African American	2 (8%)
Asian	1 (4%)
Surgical Interest (n, %)	
Surgical	8 (31%)
Nonsurgical	18 (69%)
Speciality of interest (n, %)[a]	
Anesthesiology	2 (8%)
Diagnostic radiology	1 (4%)
Emergency medicine	3 (12%)
Family medicine	4 (15%)
General surgery	3 (12%)
Internal medicine	3 (12%)
Neurosurgery	1 (4%)
Obstetrics/gynecology	1 (4%)
Orthopedic surgery	1 (4%)
Pediatrics	5 (19%)
Plastic surgery	1 (4%)
Psychiatry	2 (8%)
Vascular surgery	1 (4%)

[a]Two students selected more than one specialty of interest, resulting in n of 28.

Data Analysis

Inductive thematic qualitative analysis was performed to create a codebook to analyze the transcripts.[9,10] Transcripts were reviewed to identify codes from student responses to the vignettes. Codes were subsequently categorized into thematic areas. Themes were identified by vignettes that were either a positive or negative example of teaching physician behavior. The codebook was created by the research team (JJA, ASJ, EMP).

Transcripts were coded independently and reviewed for agreement by 2 coders (JJA and ASJ). The codebook was used to analyze the following student responses: vignette A, vignette B, vignette C, discussion question 1, discussion question 2. While the codebook was derived from the vignettes, we intentionally used the same codebook for deductive thematic analysis of the discussion questions to determine if similar themes emerged in open discussion. Positive and negative student responses were coded as the same code when comments on the underlying teaching physician behavior was consistent. This allowed identification of key themes. The intercoder reliability was calculated and discrepancies were addressed among coders by discussion to reach consensus to result in a final intercoder reliability of 100%.

The top 3 adjectives were identified from discussion question 3. Discussion question 4 was an open-ended question with a wide

variety of responses, and content analysis was used to identify common themes by frequency.

RESULTS

Thirty-two students accepted the initial invitation to participate, but only 26 students ultimately participated across the 4 focus groups. Resulting focus groups ranged in size from 5 to 8. Demographic information for student participants is shown in Table 2.

Coding

The final codebook consisted of 4 themes and 17 codes (Table 3). A total of 343 responses were tallied and agreed on by both coders. Responses were coded and categorized into thematic areas (Tables 4 and 5). The most common theme across the focus groups was using questions for teaching rather than evaluating (35%, n = 121), followed by being engaging and interactive with students (29%, n=98), setting expectations (20%, n = 68), and empathizing with the medical student experience (16%, n = 56). The 6 most common subthemes were setting explicit expectations at the beginning (12%, n = 40), creating a safe space (10%, n = 36), elaborating on a topic after asking questions (10%, n = 34), acknowledging student effort (9%, n = 30), using guiding questions to lead the student to the answer (7%, n = 25), and the teaching physician normalizing not knowing (7%, n = 23).

The intercoder reliability was calculated using the following formula:

$$2M/(N_1 + N_2)$$

M = total number of decisions agreed upon by coders, N_1 = number of decisions made by coder 1 (JJA), N_2 = number of decisions made by coder 2 (ASJ).

Thematic coding of the 3 vignettes resulted in intercoder reliabilities of 85.4%, 79%, and 87% for the themes. Intercoder reliabilities for discussion questions 1 and 2 were 79.4% and 78%, respectively. We met to discuss discrepancies to reach 100% consensus for analysis.

Table 3. Codebook for Coding Student Responses in Focus Groups Regarding Student Reception of Faculty

Code	Examples
THEME A: Being Engaging and Interactive	
1 Introductions	Taking time to introduce themselves at beginning of rotation
	Attending learning student name
	Being aware of student coming into rotation
2 Taking time to ask questions	Dedicating time to students
	"Taking time out of busy day"
3 Acknowledging student effort	Compliment their knowledge (good job)
	Acknowledging if they have been reading
	Using student name
	Giving positive reinforcement
4 Getting to know student	Asking about interests/hobbies, career goals
	Mentorship
	Rapport
5 Giving student role/responsibility	Using student note
	Autonomy
	Not ignoring student presentation
	Responsibility
	"Carrying their own patients"
	Participate in surgery
THEME B: Setting expectations	
1 Giving explicit expectations at the beginning	Be exact about how students are graded and what they are expected to do
	Set goals of learning for the rotation
	Providing "structure"
	Giving learning objectives
	"Goals of the rotation"
2 Specifying learning material/tools	Providing reading material
	Giving reading schedule
	Specifying content students responsible for knowing
3 Explicitly stating they will be teaching	Stating they want to teach
	Explaining why/how they ask questions to teach
THEME C: Empathizing with the medical student experience	
1 Transition statement that questioning session is about to begin	Giving students a heads up they are about to be "put on the spot"
2 Meeting student at their level of understanding	"Learning gaps"
	Tailoring teaching to student level of understanding
	Figuring out or asking how much they know about a topic before teaching/questioning
3 Time-realistic expectations	Give appropriate amount of reading material
	Give appropriate timeline
4 Faculty normalizing not knowing	Faculty says "that's okay"
	Negative: "how could you not know this?" or similar
	"This is a hard concept to get down"
THEME D: Using questions to teach rather than evaluate	
1 Elaborating on topic after questions asked/answered	If incorrect, explaining the correct answer vs saying "wrong"
	If correct, taking it a step further
	Providing feedback after a question
	Negative: not explaining the incorrect/correct answer
2 Body language/tone during teaching session	Negative: rolling eyes or equivalent
	Inviting body language, eye contact
	Negative: student feeling like they are talking to themselves
	Handing instrument gently vs aggressively in operating room
	Laughing "with" vs "at"
3 Guiding questions/building up questions	Asking small questions to get from A to B to C
	Having clear purpose to the question
	Not giving the answer right away. Letting the student try
	Helping student work their way through a complex mechanism
4 Opportunity for student to ask questions	Faculty asking if there are any questions
	Giving time for questions
5 Creating a safe space	Judgement free; not worrying about feeling stupid
	Welcoming, (non)intimidating, comfortable
	If student mentions faculty verbally normalizes not knowing, code under 12

Vignettes

In vignette A, the most common theme was using questions for teaching rather than evaluating (57%), followed by being engaging and interactive with students (27%). In vignette B, the most common theme was setting expectations (57%), followed by empathizing with the medical student experience (12%). In vignette C, the most common theme was using questions for teaching rather than evaluating (66%), followed by being engaging and interactive with students (19%). In total for all the vignettes, the most common theme was the focus of the teaching physician on using questions for teaching rather than evaluating.

Table 4. Themes of Student Responses in Focus Groups Regarding Student Reception of Faculty

Theme	Vignette A n (%)	Vignette B n (%)	Vignette C n (%)	DQ1 n (%)	DQ2 n (%)	Total n (%)
Intercoder reliability	(85.40)	(79)	87	79.4	78	
Being engaging and interactive	18 (27)	10 (11)	15 (19)	20 (47)	35 (59)	98 (29)
Setting expectations	0 (0)	54 (57)	2 (3)	7 (16)	5 (8)	68 (20)
Empathizing with the medical student experience	11 (16)	20 (21)	10 (13)	6 (14)	9 (15)	56 (16)
Using questions to teach rather than evaluate	38 (57)	11 (12)	52 (66)	10 (23)	10 (17)	121 (35)

Abbreviation: DQ, discussion question.

Notable student quotations from the vignette discussions that exemplified each theme were identified and include the following examples.

Being engaging and interactive with students

"I tend to acknowledge on my reviews when I can tell the attending [physician] is actually taking some time to walk through and teach something. I really appreciate that because I know they're busy." (vignette A)

"I think one positive thing, while it's a little more subtle, there still is a little bit of positive reinforcement. … Dr. C says, 'good that's correct'." (vignette C)

"At the bare minimum, I liked that this attending [physician] talked to the student in the OR (operating room)." (vignette C)

Setting expectations

"Hopefully the readings are a reasonable length. Because I have had it where you have 60 pages on a pdf … that would be kind of an unrealistic expectation." (vignette B)

"I really like that the expectations were really clear. I think that sometimes, as a medical student, it can feel really overwhelming to be asked a bunch of questions because you're not really sure like what the point is, or how that attending [physician] is trying to use that question-and-answer style. So I think that saying explicitly 'This is how I'm using it, and this is what I'm hoping you get out of it' really helps alleviate some of that anxiety that comes along with being quizzed and makes it a more useful experience." (vignette B)

"Sometimes there's almost this expectation that we find the gaps in our knowledge. But how are we supposed to know what those are from the beginning? So, having someone who is an expert in whatever field that you're working in that day or week, say, 'Here are the things that I really think are important for you to get out of this rotation, and this is what I want you to walk away from' … is super helpful." (vignette B)

Table 5. Codes of Student Responses in Focus Groups Regarding Student Reception of Faculty

	Top 3 Subthemes	n (%)
Vignette A	Creating a safe space	16 (24)
	Guiding questions	15 (22)
	Acknowledging student effort	10 (15)
Vignette B	Giving explicit expectations in beginning	28 (29)
	Specifying learning material/tools	14 (15)
	Faculty normalizing not knowing	12 (13)
Vignette C	Elaborating on topic after asking question	27 (34)
	Body language/tone	10 (13)
	Taking time to teach/ask questions	9 (11)
Discussion Q1	Acknowledging student effort	7 (16)
	Giving explicit expectations in beginning	7 (16)
	Getting to know student	6 (14)
Discussion Q2	Giving student role/responsibility	14 (24)
	Acknowledging student effort	8 (14)
	Getting to know student	8 (14)
Total	Setting explicit expectations at beginning	40 (12)
	Creating a safe space	36 (10)
	Elaborating on topic after asking question	34 (10)

Abbreviation: Q, question.

Empathizing with the medical student experience

"I really like that they started off by acknowledging that you did know something and then also normalize a little bit that it's okay not to know the answer or not to know everything." (vignette A)

"I think the use of the specific word 'when' in Dr. B's conversation … is really important, and it establishes you're going to get questions wrong, and that's okay. It's not an if, it's a when." (vignette B)

"I do appreciate that this person moved on after a wrong answer or asked a different question. They didn't say something like 'medical students at your level should know this,' or they didn't give those little extra flavorings that people who really want to make you feel bad give you. I appreciate that." (vignette A)

Using questions for teaching rather than evaluating

"I think a lot of the choices of the attending's language were just really intentionally positive. But I just liked that Dr. A. said,

'Let's see if we can get through the mechanism together,' and asking, 'Can you take it from here?' Just very intentional choices of words to make it a less stressful experience." (vignette A)

"When the student in this scenario gets a question wrong, there's no 'tell me why you thought,' or 'what kind of guided you to that answer' and then actually providing the correct answer. It was just move on to the next one. And so basically see how many questions you can get right." (vignette C)

"I also think some of the attending [physician] responses are really short, like 'what are the contraindications?' And the student mentions one thing, and then the attending just says good. They don't really go on to say any other contraindications or take a moment to teach." (vignette C)

Discussion Questions

Question 1

When asked what advice students would give teaching physicians before teaching on the wards, the most common themes were being engaging and interactive with students (47%) and using questions for teaching rather than evaluating (23%). The most common codes were acknowledging student effort (16%), giving explicit expectations in beginning (16%), and getting to know the student (14%).

Question 2

Student descriptions of their favorite attending physician elicited 2 major themes: being engaging and interactive with students (59%) followed by using questions for teaching rather than evaluating (17%). Most common codes were giving students a role and responsibility (24%), acknowledging student effort (14%), and getting to know the student (14%).

Question 3

When asked for 3 adjectives to describe the ideal attending physician in a clinical teaching role, the most common responses were being patient (16%), engaged (11%), and respectful (9%). We noticed that the first response per focus group set the tone for future responses from students (Appendix Table 1).

Question 4

When discussing factors that affect student perception of teaching physicians, the following major themes emerged:

- Attending physicians with similar demographics to the student can create a more comfortable learning environment and be a role model (37%, n = 7).
- Attending physicians who recently finished training can be more relatable, friendlier, and empathetic to the student experience (16%, n = 3).
- Student treatment norms vary by specialty and can affect student perception of an attending physician prior to starting the rotation (10%, n = 2).

DISCUSSION

Questions are one of the primary teaching tools used in clinical teaching. The Socratic method of questioning has been a mainstay in clinical teaching for over a century, but this process also has been referred to as "pimping," a term coined by Brancati in 1989 to describe a series of difficult questions to the trainee.[2,11] Pimping has been associated with student humiliation in group settings and shame for not knowing the answer. Furthermore, teaching physicians who pimp students have been criticized for teaching by intimidation, establishing the medical "pecking order," and creating a hostile atmosphere.[3] Although pimping has this negative connotation, students can view this experience as a learning tool given that incorrect answers are often more memorable than correct ones.[12]

The goal of our study was to identify factors that impact students' perceptions of teaching physicians, thereby giving them more grace in utilizing different teaching styles. In this report, we found that teaching physicians who are engaging with students, set expectations, are aware of the medical student experience, and utilize questions to teach versus evaluate are better received by students. These themes have been described previously in the literature as ways to improve mentor-mentee relationships.

Leary et al conducted an interview-based study of 44 pediatric hospitalists that showed setting specific expectations at the beginning of the mentoring relationship was necessary for its success.[13] Mentors and mentees can have different expectations, and establishing clear parameters in the beginning allows the relationship to be tailored to individual preferences. In addition, building rapport was described by Atkinson et al in the European *Journal of Pediatrics* to be an integral component of effective clinical mentoring.[14] Learners are more receptive to feedback and guidance when there is a respectful and trusting relationship with their mentor. Furthermore, having open dialogue with the student allows the mentor to gain a deeper understanding of the learner's individual goals, thus promoting a growth over assessment mentality.

Our findings add to the existing literature by providing concrete examples of characteristics students value in teaching physicians. For example, students suggested specific verbiage for how to normalize a student not knowing the answer by saying "when a question is answered incorrectly" as opposed to "if." Additionally, several students highlighted the importance of positive reinforcement, even in phrases as simple as "good" or "that is correct." Both are examples of simple and tangible ways teaching physicians can improve student reception of questions in real-world clinical environments.

There are limitations in our study worth noting. First, the generalizability of the data is limited since this is a single institution study by those who volunteered. The sample size only consisted of 26 students across 2 medical student cohorts, and there was an uneven distribution of gender and racial representation across spe-

cialties. However, despite these limitations, there was good consensus among focus group participants, and themes that emerged were consistent across focus groups as well.

We specifically explored factors that affect medical student perception of teaching physicians. Future work could build upon our findings by conducting similar focus groups at other medical schools to identify common themes across multiple institutions. The associations between a student's preferred themes and standardized exam performance could be investigated. Participants could be divided by specialty or year to determine specific differences per specialty. Specifically, we noticed that students pursuing surgery were more accepting of Vignette C, and future work could further investigate the differences between surgical and nonsurgical medical student teaching strategies. In addition, consideration of other demographic variables of the students and teaching physicians could be considered to determine how other factors impact student perceptions of teaching physicians using questions to teach. Finally, future studies that incorporate teaching physician perspectives and experiences could be valuable to help develop relevant clinical teaching tools.

CONCLUSIONS

By engaging medical students, setting clear expectations early on, empathizing with the medical student experience, and asking questions with a purpose of teaching, teaching physicians in the clinical learning environment can help foster a positive mentorship relationship with learners, and thus be less hesitant about upsetting medical students when utilizing questions as a teaching tool.

Financial Disclosures: Author EMP received some support from the Kern National Network on Flourishing in Medicine.

Funding/Support: Internal funding was provided by the University of Wisconsin Department of Ophthalmology and Visual Sciences Resident Research Fund.

Appendix: Available at www.wmjonline.org

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Brain and Body Fitness Group for Those With Dementia and Their Caregivers Through Community Partnership: A Program Evaluation

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ABSTRACT

Introduction: The growing prevalence of dementia calls for nonpharmacological interventions to reduce negative quality of life effects for those living with dementia and their caregivers. Brain and Body Fitness, a community-based collaborative group program, engages people living with dementia and their caregivers through a combination of physical, cognitive, and socialization strategies, to maximize health benefits for sustained functioning.

Methods: Using an adapted form of the Patient-Reported Outcomes Measurement Information System (PROMIS) Applied Cognition tool, ex post facto data were collected from both participants affected with Alzheimer's disease and related dementias and their caregivers during 12 biweekly sessions of the Brain and Body Fitness program conducted from 2017 through 2021.

Results: Brain and Body Fitness program participants were affected by 4 quality of life indicators: anxiety, sleep, fatigue, and depression. Data reveal significant reductions in anxiety symptoms and significant improvements in fatigue for affected participants. Anecdotally, the program demonstrates nonsignificant trends of overall mood improvement.

Conclusions: Given the positive outcomes, communities may consider adopting a similar program to provide additional support for participants.

INTRODUCTION

The use of medication to treat and/or cure underlying diseases associated with Alzheimer's disease and related dementias (ADRD) has been researched with limited potential.[1] Given the scarcity of effective medical treatments or interventions that prevent or cure ADRD, there is a need to assess the effectiveness of nonpharmacological interventions and their impact on health outcomes.

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Multiple metanalyses review the preventive and/or management effects of high and moderate physical activity for various forms of ADRD.[2-3] Additionally, the use of cognitive stimulation therapy has shown slower cognitive decline when utilized in early stages of dementia.[4] Further, socialization has been recommended for nonpharmacological treatment options for those living with ADRD to minimize loneliness, isolation, and stress.[5]

Multimodal engagement strategies combining physical, cognitive, and socialization activities have been developed. This strategy, sometimes referred to as Language-Enriched Exercise Plus Socialization (LEEPS), is a program based on a study from the University of Arizona to engage people with ADRD to potentially maximize benefits for sustained function and to slow cognitive decline.[6]

Costs of formal and informal care for those with ADRD are significant. Outside of direct care provided, there are additional costs to consider, such as time and potential loss of income for informal (nonprofessional) caregivers (eg, spouse, adult child). Nationally, the Alzheimer's Association[7] reports that over 11 million Americans provide unpaid care for people with ADRD, providing an estimated 16 billion hours of informal caregiving valued at nearly $272 billion. Without these informal caregiving efforts, many people would either not receive needed care or would be required to pay.[8] With informal caregiving also comes relationship stressors,[9] and caregivers may experience varying degrees of adverse effects on their psychosocial and physical health.[10]

Consensus on how to measure quality of life (QoL) for those

with ADRD is lacking.[11] However, 4 functional QoL and mood measures regularly appear in the literature: anxiety, depression, sleep, and fatigue. A meta-analysis by Kuring et al[12] found an association between the 4 most common forms of dementia and anxiety, yet there is not clarity on whether anxiety is a causal risk factor for, a prodromal symptom of, or comorbid with, a dementia diagnosis. These same findings were revealed for dementia and depression, though both anxiety and depression are often underrecognized and untreated in those with ADRD and their caregivers.[14] Identification of a diagnosis of depression and/or anxiety is important for treatment to begin as early as possible since meaningful clinical benefit has been shown for people with ADRD.[14]

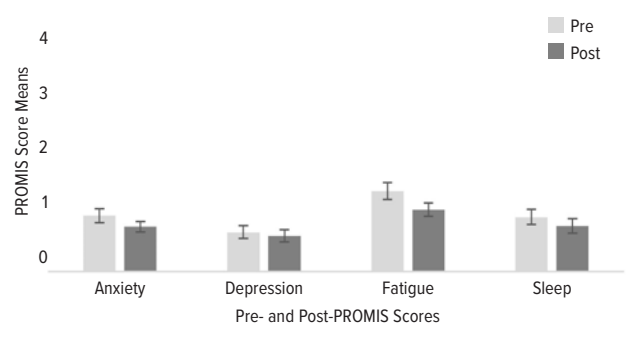
Another mood measure is related to sleep disturbance, which has a significant impact on many areas of health, including but not limited to incidence of depression, risk of infectious disease, and occurrence and progression of major medical illnesses.[15] Sleep disturbances are prevalent in people with ADRD; lack of sleep hygiene may precipitate the transfer to residential care for a person with ADRD.[16]

The final mood measure is fatigue, which also is connected to sleep disturbance.[5] Carvalho et al[5] hypothesized that fatigue may be a clinical marker for accelerated brain aging. The connection between brain aging and ADRD is noted such that fatigue, as a mood measure, may be an appropriate indicator of QoL for those with ADRD.[17]

In 2007, Arkin[6] developed a LEEPS program with success, positing that there is a clinical rationale for providing these combined interventions. La Rue et al[18] adopted this approach in 9 rural Wisconsin communities during 2010-2014 with encouraging outcomes related to stability in cognition, mood, and physical performance. See Appendix for a summary of the LEEPS program.

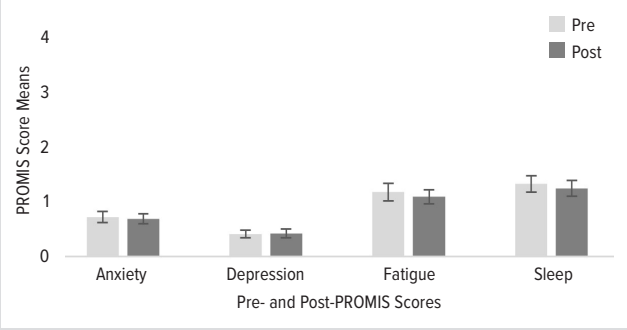
In 2017, the urban county of Eau Claire, Wisconsin, adopted and adapted a LEEPS-based program. This collaboration between the Aging and Disability Resource Center (ADRC) of Eau Claire County and the Young Men's Christian Association (YMCA) of the Chippewa Valley was named the Brain and Body Fitness (BBF) program. The BBF program is funded through grants, the ADRC, and YMCA, and there is no cost to participate. The BBF coordinator, an employee of the YMCA, utilized a LEEPS instruction manual provided by the Wisconsin Department of Health Services to develop a curriculum for BBF, modifying the LEEPS format to a group setting with multiple dyads of those with ADRD ("participants with ADRD") and their caregivers. Over the course of 12 weeks, dyads attended two 90-minute sessions per week led by the BBF coordinator and the BBF instructor, who also was employed by the YMCA. Following introductions, each session began with 10 minutes of group exercise and 10 minutes of cognitively stimulating activities for the dyads, alternating between the two activities for a total of 60 minutes.

Figure 1. Brain and Body Fitness Affected Participants' PROMIS Scores



Abbreviation: PROMIS, Patient-Reported Outcomes Measurement Information System.
Error bars represent ± 1 SD from the mean.

Figure 2. Brain and Body Fitness Affected Caregivers' PROMIS Scores



Abbreviation: PROMIS, Patient-Reported Outcomes Measurement Information System.
Error bars represent ± 1 SD from the mean.

The session concluded with 30 minutes of informal socialization. Additionally, the group occasionally met outside of class for optional events in the community to enhance socialization.

This study explored 2 research questions: (1) Does the BBF program impact functional QoL indicators for participants with ADRD? and (2) Does the BBF program impact functional QoL indicators for caregivers?

METHODS

Participant Recruitment and Data Collection

Following attainment of the Institutional Review Board approval (#202221226), this study utilized ex post facto data collected by the YMCA of the [area blinded] during the 12 biweekly sessions conducted between 2017-2021 with 3 cohorts per year. Recruitment was based on snowball sampling, and it was assumed that only those who wanted to participate in the program did so. The BBF program is advertised to the community through the YMCA and ADRC. No records are kept related to those who may decline program participation. The BBF program is targeted specifically to participants with ADRD who live in the community (rather than a congregate setting).

Data were collected from both participants with ADRD and their caregivers. Participation was voluntary and required written consent. Class sizes ranged from 6 to 25 participants. Data collected by the YMCA did not include a report of diagnosis or severity of participants' ADRD.

Measures

The YMCA of the [area blinded] obtained data utilizing an adapted form of the Patient-Reported Outcomes Measurement Information System (PROMIS) Applied Cognition tool.[19] The PROMIS tool, modified by the YMCA, included several items to assess 4 dimensions of mental health: anxiety, depression, fatigue, and sleep quality. Participants responded using a 5-point scale ranging from "0 = never" to "4 = always." Participants with ADRD and caregivers individually (with rare exception an affected partner required assistance from the caregiver) completed the modified PROMIS tool before and after participation in the group program. Cronbach's alpha analysis determined that each subscale had good to excellent reliability for both BBF participants with ADRD and their caregivers. Specifically, anxiety (ADRD $\alpha = 0.87$ pre-score; $\alpha = 0.84$ post-score; caregivers $\alpha = 0.84$ pre-score; $\alpha = 0.81$ post-score) was measured by 4 items (eg, "My worries were overwhelming"). Depression (ADRD $\alpha = 0.92$ pre-score; $\alpha = 0.95$ post-score; caregivers $\alpha = 0.90$ pre-score; $\alpha = 0.84$ post-score) was measured by 4 items (eg, "I felt depressed"). Fatigue (ADRD $\alpha = 0.94$ pre-score; $\alpha = 0.84$ post-score; caregivers $\alpha = 0.93$ pre-score; $\alpha = 0.91$ post-score) was measured by 3 items (eg, "I felt run down"). Sleep (ADRD $\alpha = 0.82$ pre-score; $\alpha = 0.90$ post-score; caregivers $\alpha = 0.89$ pre-score; $\alpha = 0.88$ post-score) was measured by 4 items (eg, "I had poor sleep quality").

Data Analysis Plan

For the primary outcomes analysis, quantitative data were available from multiple BBF cohorts from 2017 through 2021. This resulted in data from 49 participants with ADRD and 38 caregivers. Paired sample *t* tests were conducted, using 1000 bootstrapped samples for calculation 95% (CIs) calculation and effects size estimates, to compare pre-scores and post-scores on the 4 PROMIS subscales. Note that this strategy does not account for shared variance among the affected participant and caregiver dyads, although sample size precluded dyadic statistical analysis. Additionally, informal qualitative feedback to query the effectiveness of the program was solicited from the dyads via email sent by the BBF program coordinator at the conclusion of each cohort, most often with the dyads collaborating in their written feedback.

RESULTS

Regarding the first research question about whether the group program affects functional QoL indicators for participants with ADRD, results demonstrated improvements across the course of the program in anxiety ($t_{48} = 2.01$; $P = 0.049$; $d = 0.29$; 95% CI, 0.0005–0.4586) and fatigue ($t_{48} = 2.29$; $P = 0.026$; $d = 0.33$; 95% CI, 0.0478–0.4715) (Figure 1). Nonsignificant improvements were found for participants with ADRD on depression ($t_{48} = 0.65$; $P = 0.52$; $d = 0.09$; 95% CI, -0.1714-0.3344) and sleep ($t_{48} = 1.28$; $P = 0.21$; $d = 0.18$; 95% CI, -0.1041-0.4715).

Results did not suggest that functional QoL indicators for caregivers changed because of their program participation. No significant changes for caregivers were observed in anxiety, ($t_{37} = 0.29$; $P = 0.771$; $d = 0.05$; 95% CI, -0.2175-0.291), fatigue, ($t_{37} = 0.657$; $P = 0.52$; $d = -0.01$; 95% CI, -0.1992-0.3903); depression ($t_{37} = -0.07$; $P = 0.95$; $d = 0.11$; 95% CI, -.2028-0.1896), or sleep ($t_{37} = 0.72$; $P = 0.47$; $d = 0.12$; 95% CI, -0.1659-0.3501) (Figure 2). Although no statistically significant improvements for caregivers were noted, informal qualitative feedback submitted via email indicated that caregivers perceived several benefits from their participation.

DISCUSSION

The BBF group community program is unique in its format in that dyads consisting of participants with ADRD and their caregivers met collectively within the community. Originally the BBF program, hosted in Eau Claire County, began in 2014 under the name of LEEPS and was based on incorporating physical exercise, cognitive engagement, and social interaction – all of which have been shown to impart positive benefit for those with ADRD.[2-3,20] Small changes were made to the LEEPS program, and the name was changed to BBF to better capture the program's essence. Anecdotally, participation in the BBF group program positively impacts the dyads' quality of life. Notably, the means for all 4 PROMIS scores – for both participants with ADRD and caregivers – were below the midpoint on the scales, suggesting good to moderate functional QoL.

For participants with ADRD, statistically significant differences were noted as a result of BBF program participation on the anxiety and fatigue PROMIS measures, and nonsignificant trends toward differences were seen in depression and sleep. Practically, participants with ADRD reported reductions in levels of anxiety and fatigue from the beginning to end of the program. Similarly, the nonsignificant trends suggest mean differences moving in the direction of lowered levels of depression and sleep problems as well. Since anxiety and depression may contribute to decreased overall functioning and accelerated cognitive decline,[21] results illustrate the important benefits that participation in a group BBF program might have for those with dementia.

The impact of the BBF group program is encouraging for those who seek to attenuate decline in functioning. Additionally, with an estimated 65% to 70 % of those diagnosed with dementia experiencing symptoms of depression,[22] any mitigation of such symptoms is beneficial. Participation in the BBF program may provide one avenue of ADRD symptom reduction. Also encour-

aging are participants' lowered fatigue levels throughout the BBF program as increased fatigue may result in a more rapid progression of brain aging,[5] while lowering fatigue may assist in halting and/or slowing brain aging. Lastly, maintaining or improving sleep hygiene may increase the chance that a person with ADRD can remain at home for a longer period instead of transferring to a residential care setting.[16]

For BBF program caregivers, there were no statistically significant improvements on the PROMIS scales; however, qualitative feedback submitted via email indicated that caregivers perceived several benefits from their participation with their affected loved one, one of which appears to be social connections.

Social connections impact health. Holt-Lundstad noted humans are "wired" to be social, such that our brains and bodies expect proximity to others."[23(p251)] Social "disconnections" may "influence multiple health outcomes"[23(p253)] and chronic inflammation has been hypothesized as contributing to cognitive health. There is growing evidence that loneliness from social disconnection affects health as well.[24] Biddle et al noted that "older adults with less frequent social contact and community activities experience more rapid cognitive decline and increased incidence of dementia."[25] Given the increasing evidence that social connections positively impact health, the BBF group program—with its socialization emphasis—may be an important intervention for all aging adults, regardless of the presence of ADRD.

CONCLUSIONS

Given the group approach in a community setting, the Brain and Body Fitness group program is a unique multimodal intervention. The program hypothesizes that this approach of combining physical exercise and cognitive stimulation in a group setting will have positive effects on cognitive and physical health for persons with ADRD and their caregivers.

Analysis of PROMIS data indicated that participants with ADRD experienced significant decreases in anxiety and fatigue across the duration of the BBF program and slight, but nonsignificant reductions in depression and increases in sleep quality. Data did not indicate any changes of these outcomes for caregivers. However, in anecdotal communications with program staff, caregivers have reported stress relief, appreciation for social interaction, and a place where they can find support from other caregivers. It is also reassuring that reported levels of depression were very low for participants with ADRD and caregivers at both time points. It should be noted that, in the absence of a control group, we cannot be certain that the positive changes across time among participants with ADRD were due only, or primarily, to participation in the BBF program. However, the typical course of ADRD entails reductions across time. Results of this analysis are encouraging and warrant further research through continued community collaboration.

Financial Disclosures: None declared.

Funding/Support: Undergraduate student research assistant and faculty support were funded from an internal grant through the University of Wisconsin–Eau Claire's Office of Research and Sponsored Programs. The United Way of the Chippewa Valley, YMCA of the Chippewa Valley, and the ADRC of Eau Claire County provided funding and resources to support the Brain and Body Fitness program.

Acknowledgements: The UW–Eau Claire faculty researchers extend gratitude and thanks to Laurie Pettis, NBC-HWC, CIC, and Pete Fasching of the Eau Claire Area YMCA, along with Lisa Wells, MA, of the Aging and Disability Resource Center (ADRC) of Eau Claire County, for their collaborative community efforts in creating and conducting the Brain and Body Fitness program in Eau Claire County and for assisting in this mutual endeavor.

Appendix: Available at www.wmjonline.org

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A Silent Wave: Increases in Wisconsin's Alcohol-Related Mortality During the COVID-19 Pandemic

Thomas Bentley, MS; Paul D. Creswell, PhD

ABSTRACT

Background: Alcohol-related mortality is an increasing public health concern in the United States. To date, no study has considered trends in alcohol-related deaths during the full COVID-19 pandemic period.

Methods: We analyzed deaths from Wisconsin vital statistics to explore the relationship between the pandemic period and any changes in alcohol-related mortality.

Results: In Wisconsin, the pandemic period was associated with additional alcohol-related mortality above and beyond a previously reported upward trend.

Discussion: We show that the COVID-19 pandemic was associated with exacerbated alcohol-related mortality in Wisconsin. Alcohol use may need to be considered as an additional public health risk in future pandemic scenarios.

BACKGROUND

Alcohol-related mortality in the United States has increased in recent decades.[1] These increases are in contrast to the experience of European nations where alcohol-related deaths have generally been in decline.[2] Further, new evidence suggests an uptick of alcohol-related mortality at the beginning of the COVID-19 pandemic,[3,4] while findings also show a general increase in the purchasing of alcohol during that period.[5] To our knowledge, however, no study to date has considered trends in alcohol-related mortality over the full pandemic period.

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The COVID-19 pandemic was characterized by a number of factors at the individual and societal levels that may be associated with increased risks for alcohol-related mortality. These include, but are not limited to, higher anxiety and depression,[6,7] increased suicide ideation,[7] and higher levels of substance use.[7] Evidence also shows that the pandemic was associated with decreased access to health services,[8] lowered access to outpatient substance use clinics,[9] and declines in trust in physicians and hospitals.[10] While none of these factors in isolation is likely to constitute a sufficient cause of increased alcohol-related mortality at a population level, they are all components that may be associated with an increased risk of alcohol-related mortality.

Since the late 1970s, Wisconsin consistently has had some of the highest per capita levels of alcohol consumption.[11] America's Health Rankings, using data from the Behavioral Risk Factor Surveillance System, ranks Wisconsin among the 5 worst states with regards to excessive drinking by adults and seniors.[12] The prevalence of alcohol consumption and culture of drinking in Wisconsin makes it a useful case study when considering trends in alcohol-related mortality before, during, and after the pandemic.

A previous study explored alcohol-related mortality in Wisconsin before the COVID-19 pandemic and demonstrated an increasing risk of this outcome across 2 decades (2000-2019).[13] This brief report builds on that prior work and explores the potential relationship between the pandemic and changes in alcohol-related mortality. The present analysis uses Wisconsin vital records data to assess: (1) if the previously reported trends in alcohol-related mortality changed with the onset of the COVID-19 pandemic, (2) if the pandemic period was associated with higher alcohol-related mortality, (3) if demographic characteris-

tics of Wisconsin residents were associated with differences in alcohol-related mortality prior to and during the pandemic, and (4) whether any changes in trends appear poised to continue into the post-pandemic period.

METHODS

Data and Sample

We analyzed data from Wisconsin vital statistics, which are housed at the Vital Records Office in the Wisconsin Department of Health Services (DHS). The sample consisted of decedents who died from January 1, 2015, through December 30, 2023 (N=8267). Alcohol-related deaths were identified using the underlying cause of death field. This field is filled out by the medical examiner or the coroner on the death certificate. We used only deaths that were fully attributable to alcohol, and we retained deaths from both chronic and acute conditions.

Alcohol-related deaths from acute causes included excessive blood alcohol, alcohol poisoning, and alcohol-related suicide. Alcohol-related deaths from chronic causes included chronic liver disease (eg, cirrhosis), mental disorders related to alcohol, and all further health disorders owing to alcohol (ie, pancreatitis, polyneuropathy, gastritis, myopathy, cardiomyopathy, and liver disease). We included the following underlying cause of death codes from the *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM): F10, F10.0, F10.1, F102, G312, G621, G721, I426, K292, K70, K860, O354, P043, Q860, R780, T51, X45, X65, and Y15.

Table. Demographic Characteristics of Wisconsin Residents Who Died from Alcohol-related Causes in the pre-COVID-19 Pandemic Period (January 1, 2015 – December 30, 2019) vs the COVID-19 Pandemic Period (January 1, 2020 – December 30, 2023)

	Alcohol-related Deaths Pre-COVID-19	Proportion of Alcohol-related Deaths: Pre-COVID-19	Alcohol-related Deaths COVID-19 Period	Proportion of of Alcohol-related Deaths: COVID-19 Period	χ^2 test
	N = 3772	100%	N = 4495	100%	
Race and ethnicity					*P* < 0.83
Black, non-Hispanic	249	6.6%	269	6.0%	
Hispanic	138	3.7%	172	3.8%	
Other, non-Hispanic	149	4.0%	186	4.1%	
White, non-Hispanic	3236	85.8%	3868	86.1%	
Age					*P* < 0.01
0–17	103	2.7%	153	3.4%	
18–34	154	4.1%	192	4.3%	
35–44	323	8.6%	502	11.2%	
45–54	923	24.5%	910	20.2%	
55–64	1359	36.0%	1611	35.8%	
65+	910	24.1%	1127	25.1%	
Sex					*P* < 0.12
Female	1068	28.3%	1343	29.9%	
Male	2704	71.7%	3152	70.1%	
DHS region					*P* < 0.29
Northeastern	828	22.0%	1014	22.6%	
Northern	392	10.4%	504	11.2%	
Southeastern	1319	35.0%	1554	34.6%	
Southern	727	19.3%	849	18.9%	
Western	506	13.4%	570	12.7%	
Missing	–	–	4	0.1%	
Education					*P* = 0.05
High school or less	2320	61.5%	2648	58.9%	
College/Undergrad	1259	33.4%	1587	35.3%	
Graduate school	137	3.6%	170	3.8%	
Unknown	56	1.5%	90	2.0%	

Abbreviations: DHS, Department of Health Services.

Column percentages may not always sum to 100% due to rounding.

Analysis

Wisconsin vital records data provide demographic variables for decedents, including age, sex, race, ethnicity, educational attainment, geographic classification (ie, urban vs rural), and DHS region (5 regions throughout the state). For our analysis, we determined rural and urban status using the classifications created by the Wisconsin Office of Rural Health.[13] We used chi-square tests to determine if there were significant differences in deaths by demographic factors comparing the pre-pandemic period (January 1, 2015 – December 30, 2019) with the period that included the COVID-19 pandemic (January 1, 2020– December 30, 2023). We modeled age-adjusted alcohol-related mortality rates per 100 000 population for Wisconsin and the accompanying 95% CIs using a negative-binomial distribution to assess statistical significance of differences across years. For the population denominators, we used the resident population data tables available from Wisconsin Interactive Statistics on Health (WISH).[14] We completed all analyses using SAS version 9.4 (SAS Institute Inc).

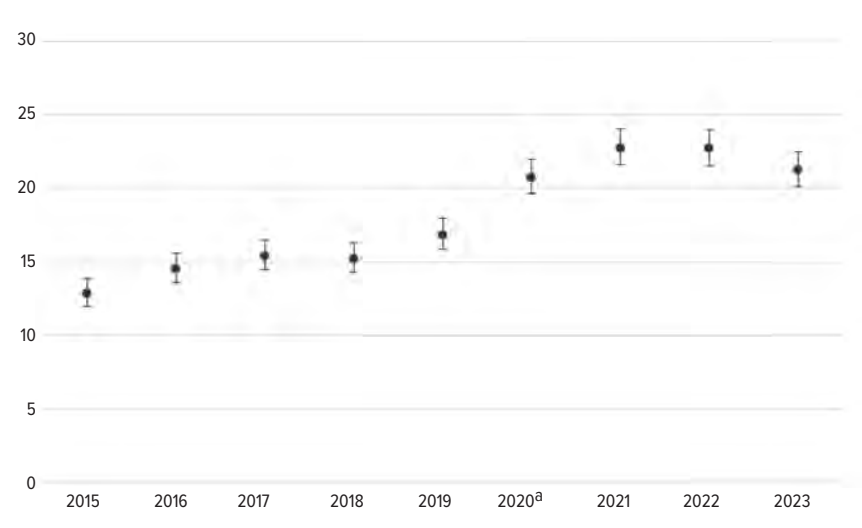
RESULTS

Demographic Analysis

The Table provides the results of the chi-square tests comparing demographics between the pre-COVID-19 pandemic period (2015-2019) and the period containing the pandemic (2020-2023). Only 1 variable had statistically significant differences across these time periods. Age was related to time period such that those aged 35 to 44 were significantly more likely to die from an alcohol-related reason during the pandemic than in the prior period, and those aged 45 to 54 were significantly less likely to die from this cause during the pandemic. Education also showed dif-

ferences, but these did not quite reach the threshold for statistical significance.

Figure. Age-adjusted Alcohol-Related Mortality Rate per 100 000 Population – Wisconsin, 2015-2023 (N = 8267)



[a]Indicates a statistically significant change over the previous year ($P < 0.05$).

Modeled Age-adjusted Mortality Rates

The Figure shows the modeled age-adjusted alcohol-related mortality rates per 100000 population in Wisconsin, with accompanying 95% CIs, from 2015 through 2023. As reported previously, the period prior to the pandemic (2015-2019) was characterized by an increasing trend in alcohol-related mortality.[13] However, our analysis shows that a statistically significant jump in alcohol-related mortality occurred with the COVID-19 pandemic. In 2019, the mortality rate was 16.9 per 100 000 population (95% CI, 15.9-18.0), whereas in 2020, the mortality rate rose to 20.8 (95% CI, 19.7-22.0). This constitutes a 23.2% increase. The rate increased another 9.6% in 2021 to 22.8 (95% CI, 21.6-24.1), though this increase was not statistically significant. The rate remained stable in 2022 and finally decreased somewhat, though not significantly so, in 2023 to 21.28 (95% CI, 20.1-22.5) – a 6.5% decline.

DISCUSSION

The COVID-19 pandemic profoundly affected people in the United States and around the world. By early 2023, COVID-19 was responsible for an estimated 14 469 deaths in Wisconsin alone.[13] Our study shows that in Wisconsin, the pandemic also was associated with higher levels of alcohol-related mortality. Similar to the findings by White et al,[3] we found an increase in alcohol-related mortality in Wisconsin going into the pandemic period from the prior year. In addition, we found that this elevated rate held through the whole pandemic and dropped off somewhat in the final year of that period – although this decrease was not statistically significant. Still, it may be that trends are edging back toward their previous trajectory. If that is the case, however, it is only partially heartening, given the 2-decade increase in alcohol-related mortality in Wisconsin that proceeded the pandemic[13] and the national trends showing increasing alcohol-related deaths overall.[3,4]

We cannot say specifically why alcohol-related mortality increased during the pandemic period in Wisconsin, but there are several factors that may have played a role. The literature shows that the pandemic was clearly stressful for people as indicated by higher reports of anxiety and depression,[6,7] suicide ideation,[7] and substance use.[7] We also know that patients had added difficulty accessing health services[8] – including outpatient substance use treatment[9] – and that trust in physicians and hospitals declined during the pandemic.[10] All of these factors may have amplified or exacerbated substance use and could have increased subsequent mortality risk. If so, this would be in keeping with evidence that shows a general trend in increased alcohol sales during the COVID-19 pandemic.[5]

We found only 1 demographic characteristic significantly associated with alcohol-related mortality during the pandemic period. A higher proportion of those aged 35 to 44 and a lower proportion of those aged 45 to 54 died of an alcohol-related reason during that time. Additional research would be needed to tease apart the underlying factors behind this association. Future work also may seek to look at additional variables that might provide information about other groups with elevated risk profiles. Our previous study indicated differential risks for alcohol-related mortality pre-pandemic by age, race/ethnicity, sex, and educational attainment.[13] However, other social determinants of health – such as decedents' usual occupation – have yet to be explored. Given the changes in work that occurred during the pandemic, this area of inquiry would be timely.

Limitations

While our findings are compelling, there are a few limitations with our analysis. First, our data are cross-sectional and, as such, we cannot say whether or not the COVID-19 pandemic was the cause – indirect or otherwise – of the increased mortality during that period. That said, however, the COVID-19 pandemic affected global society so profoundly it would prove difficult to find another parallel proximal cause. Moreover, while we have shown the association between the pandemic period and increased alcohol-related mortality, it is beyond the ability of our study to assess the multiple potential mechanisms underlying this association. It may have been stress, lack of access to

care, policy decisions (eg, changes in masking policies or stay at home orders), or a combination of factors that drove the association. We leave this for future studies to consider. Additionally, Wisconsin represents only 1 state in the union and has historically higher alcohol use than other states, making it useful to study but not necessarily representative. Future work should consider looking at these trends at a national level. Finally, it may be an additional limitation of our study that we only used fully attributable deaths from alcohol, which may underestimate the true burden.[13]

CONCLUSIONS

Increasing trends in alcohol mortality are an important area of concern for public health and the medical community. Our study shows that the COVID-19 pandemic was associated with a period of exacerbated alcohol mortality in Wisconsin. Our findings suggest that this may be a parallel risk to the public's health that should be considered in a future pandemic scenario.

Funding/Support: None declared.

Financial Disclosures: None declared.

Acknowledgments: The authors would like to acknowledge the following individuals for their assistance with the creation of this manuscript. Nathaniel Keeley, Laura Ninneman, and Xioyan Wang at the Wisconsin Vital Records Office provided invaluable assistance with the vital records data.

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Electronic Fetal Monitoring Patterns With and Without Continuous Amnioinfusion

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ABSTRACT

Background: This pre-specified analysis of a randomized controlled trial compared electronic fetal monitoring patterns among participants with and without amnioinfusion.

Methods: Data from the parent randomized trial included 26 term singleton nulliparous participants who developed risk factors for fetal neurologic injury. For this secondary analysis, the primary outcome was total deceleration area—a pattern predictive of neonatal acidemia and morbidity. Secondary outcomes included electronic fetal monitoring patterns (eg, variability).

Results: There were no differences in total deceleration area between the no amnioinfusion group and the amnioinfusion group (28 550 [8800–57 400] mm^2 [IQR] vs 31 500 [21 700–47 785] mm^2 [IQR], respectively; $P = .84$). Specific secondary outcomes differed by amnioinfusion.

Conclusions: These results highlight the need for prospective data to identify the optimal amnioinfusion administration technique that reduces morbidity.

BACKGROUND

There is no established optimal intrauterine resuscitation technique of amnioinfusion administration during labor and delivery that best reduces variable decelerations and prevents cesarean delivery.[1-5] Recent systematic reviews and meta-analyses highlight the need to study specific amnioinfusion administration techniques, such as continuous infusion, to understand how amnioinfusion administration techniques impact clinical care.[3,6,7] Randomized prospective data examining the effects of continuous amnioinfusion administration on electronic fetal monitoring patterns such as total deceleration area are limited.[3,4] Total deceleration area is an established electronic fetal monitoring pattern predictive of neonatal acidemia and morbidity leading up to delivery.[8-10] In this pre-specified secondary analysis of a pilot randomized trial, we aimed to compare electronic fetal monitoring patterns between nulliparous participants with and without a continuous amnioinfusion.

METHODS

The parent trial was conducted from June 2022 through April 2023 on the labor and delivery unit of a single tertiary care center (NCT05513690). (See Appendix for full study protocol.) Briefly, patients with singleton pregnancies at ≥37 weeks of gestation admitted for labor and delivery were eligible. Patients with major fetal anomalies, active substance use disorders, contraindications to intrauterine pressure catheter placement (eg, placenta previa), fetal growth restriction, active COVID-19, or inability to consent were excluded. Those who consented and developed intrapartum risk factors for fetal neurologic injury (suspected chorioamnionitis, persistent maternal fever, or fetal heart tracings concerning fetal acidemia) were randomized to amnioinfusion or no amnioinfusion. Study patients received standard obstetrical and intrapartum care at the discretion of their obstetrical providers, including emergent delivery if indicated. The amnioinfusion group received an intrauterine temperature probe and pressure catheter to administer a continuous room temperature amnioinfusion. The no amnioinfusion group received only the temperature probe.

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Because there is no established or optimal amnioinfusion administration technique,[4-5] we utilized our existing institutional protocol where amnioinfusion was administered with a 600 mL normal saline bolus and subsequent continuous rate of 180 mL/hour until delivery. Electronic fetal monitoring recordings were obtained with external or internal monitors, as determined clinically by the primary obstetric provider.

Electronic fetal monitoring patterns were collected in 10-minute intervals from randomization until delivery using established methods.[8] Three physicians certified in electronic fetal monitoring (JC/RF/BEP) collected patterns following delivery independently using the *Eunice Kennedy Shriver National Institute of Child Health and Human Development* definitions of electronic fetal monitoring patterns. Two of the accessors (JC/RF) were blinded to the study objective and all disagreements were adjudicated by the third (BEP). Total deceleration area also was calculated.[8-10] Deceleration area was estimated as the sum of the areas within the deceleration, and each deceleration area was estimated as .5 x duration x depth and summed as a measure of both quantity and severity of decelerations.[8-10] The Women and Infants Hospital Institutional Review Board approved this study prior to enrollment (#18008938).

For this secondary analysis, the primary outcome was total deceleration area. Secondary outcomes included category I/II/III, baseline, variability, acceleration, and deceleration electronic fetal monitoring patterns in each interval. Descriptive and bivariate analyses compared electronic fetal monitoring patterns between those with and without continuous amnioinfusion using Mann-Whitney U test or Fisher exact test accordingly.

RESULTS

Of the 26 maternal-fetal dyads randomized in the parent trial cohort, there were no significant differences in baseline characteristics, including median time from

Table 1. Cohort Characteristics

Characteristics	Amnioinfusion N = 13 (Intervention)	No Amnioinfusion N = 13 (Control)	*P* value
Maternal antibiotics	6 (46%)	7 (54%)	> .99[a]
Acetaminophen	10 (77%)	12 (92%)	.59[a]
Maternal fever > 38.0 °C	1 (8%)	3 (23%)	.59[a]
White blood cell count	22 259 ± 37 255	12 085 ± 4806	.91[b]
Prolonged rupture >18 hours	4 (31%)	3 (23%)	> .99[a]
Amnioinfusion outside protocol	0 (0%)	3 (23%)	.22[a]
Prolonged second stage	2 (15%)	2 (15%)	> .99[a]
Length of time from admission to delivery, hours	30.83 ± 18.65	30.97 ± 22.31	.79[b]
Epidural	13 (100%)	13 (100%)	> .99[a]
Stage 2 length, hours	1.77 ± 1.43	1.99 ± 2.11	> .99[b]
Estimated blood loss, mL	577 ± 385	558 ± 333	.79[b]
3rd or 4th degree laceration	2 (15%)	0 (0%)	.48[a]
Randomization to delivery, minutes	230 [90–400]	250 [120–390]	.86[a]
Mode of delivery			.29[b]
Vaginal	10 (77%)	6 (46%)	
Operative vaginal delivery	1 (8%)	1 (8%)	
Cesarean delivery	2 (15%)	6 (46%)	
Gestational age, weeks	38.7 ± 1.4	38.8 ± 1.5	.79[b]
Birth weight, grams	3138 ± 401	3323 ± 388	.14[b]

Data are mean (SD) or number (percent) or median [interquartile].

[a]Fisher exact test.

[b]Wilcoxon rank sum test.

Table 2. Electronic Fetal Monitoring Patterns by Presence or Absence of Continuous Amnioinfusion for Fetuses with Risk Factors of Neurologic Injury

Electronic Fetal Monitoring Characteristics	No Amnioinfusion N = 13; 319 Intervals	Amnioinfusion N = 13; 344 Intervals	*P* value
Primary Outcome: Total deceleration area			
Cumulative total deceleration area, mm^2	28 550 [8800–57 400]	31 500 [21 700–47 785]	.84[a]
Secondary Outcomes: NICHD definitions			
Category I	138 (43.3%)	135 (39.2%)	.29[b]
Category II	180 (56.4%)	204 (59.3%)	.45[b]
Category III	1 (0.3%)	5 (1.5%)	.12[b]
Baseline			
Beats per minute, average	135 [125–150]	145 [140–153]	< .001[a]
Normal	292 (91.5%)	306 (88.9%)	.26[b]
Bradycardia	13 (4.1%)	0 (0%)	< .001[b]
Tachycardia	14 (4.4%)	38 (11.1%)	.001[b]
Variability			
Absent/minimal	27 (8.5%)	27 (7.9%)	.72[b]
Moderate	292 (91.5%)	315 (91.6%)	.99[b]
Marked	0 (0%)	2 (0.6%)	.17[b]
Accelerations			
Number of accelerations, median	0 [0–2]	1 [0–2]	.34[a]
Present	149 (47.0%)	179 (52.3%)	.17[b]
Decelerations			
Number of decelerations, median	0 [0–2]	1 [0–2]	.25[a]
Present	145 (45.9%)	181 (52.8%)	.08[b]
Late	102 (32.0%)	106 (30.8%)	.75[b]
Variable	59 (18.5%)	94 (27.3%)	.007[b]
Early	15 (4.7%)	2 (0.6%)	.001[b]
Prolonged	11 (3.5%)	14 (4.1%)	.68[b]

Abbreviation: NICHD, National Institute of Child Health and Human Development.

Interval defined as 10 minutes of electronic fetal monitoring data from randomization to delivery; data median [interquartile range] or mean (percentage).

[a]Fisher exact test.

[b]Wilcoxon rank sum test.

randomization until delivery (250 [120–390] minutes [IQR] in the no amnioinfusion vs 230 [90–400] minutes [IQR] in amnioinfusion group; $P = .86$) (Table 1). The most common indication for randomization was minimal variability with decelerations. There was no significant difference in the primary outcome of total deceleration area (28 550 [8800–57 400] mm^2 [IQR] in the amnioinfusion group vs 31 500 [21 700–47 785] mm^2 [IQR] in the amnioinfusion group; $P = .84$). However, those randomized to continuous amnioinfusion had a higher baseline fetal heart rate (145 [140–153] vs 135 [125–150] beats per minute [IQR], $P < .001$) and fewer intervals with either bradycardia (0% vs 4.7%; $P < .001$) or early decelerations (0.6% vs 4.7%; $P < .001$). Those randomized to amnioinfusion also had more intervals with tachycardia (11.1% vs 4.4%; $P < .001$) and variable decelerations (27.3% vs 18.5%; $P < .001$). The remaining electronic fetal monitoring patterns were not statistically different (Table 2).

DISCUSSION

There was no difference in total deceleration area during labor and delivery with and without continuous amnioinfusion among term nulliparous birthing people who developed intrapartum risk factors for fetal neurologic injury. Additionally, in the parent trial, there was no difference in any clinically meaningful neonatal data, such as umbilical artery cord blood gas values of acidemia pH <7.1, base excess, lactate, and composite or individual neonatal morbidity health outcomes.[5] Continuous amnioinfusion resulted in a higher baseline, less frequent bradycardia, and early decelerations and more frequent tachycardia and variable decelerations. The clinical impact and interpretation of these differences in secondary outcomes remains challenging in the context of our secondary analysis of a pilot trial, yet the unanticipated increase in variable decelerations is noteworthy. These data suggest that amnioinfusion administration techniques (continuous vs intermittent) affect electronic fetal monitoring patterns.

Strengths of this study include the randomized prospective data with 230 minutes of continuous amnioinfusion administration technique and subsequent electronic fetal monitoring patterns. Interpretation of these data are limited by the small sample size, lack of multiparous participants, lack of comparison of continuous to bolus amnioinfusion as a control, and known prognostic limitations of electronic fetal monitoring for reducing neonatal morbidity. Amnioinfusion should continue to be administered for the approved indication of reducing variable decelerations and preventing cesarean delivery. Amnioinfusion for reducing neonatal neurologic injury remains investigational and for research purposes. Nevertheless, these data highlight that amnioinfusion administration technique impacts electronic fetal monitoring patterns currently used in labor management. These results further support the need for prospective studies to identify the optimal amnioinfusion administration technique that may reduce morbidity.

Funding/Support: This study received funding from the Foundation for Society for Maternal-Fetal Medicine (SMFM) 2021 Danielle Peress, MD Memorial Fund and Gerber Foundation Research Novice Award.

Financial Disclosures: None declared.

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A Case-Based Approach to Racial Health Disparities in Infertility Diagnosis and Management—From Reproductive Life Planning to Treating Infertility

Micaela Stevenson Wyszewianski, MD; Eliyah J. Stevenson, BS; Jayme Bosler, MD

ABSTRACT

Background: Increasing attention has been paid to medical racial health disparities, though limited attention has been paid to mitigating these disparities in access to fertility care and reproductive life planning. Workshops previously have been shown to increase physician awareness and practice improvements.

Objective: We sought to develop an education tool to provide structured, case-based learning for physicians to reflect on bias in fertility assessment and treatment and discuss changes in practice.

Methods: Authors created reproductive life planning and infertility management cases and arranged them for review informed by reproductive justice and fertility scholars. The resulting workshop was piloted to a group of 10 residents in person at a single academic institution. The cases were presented in a large group style and participants discussed cases in pairs. At the workshop's conclusion, participants were prompted to provide feedback via a survey.

Results: One hundred percent (10/10) of respondents reported that the workshop helped them think about bias in medicine. Ninety percent (9/10) of respondents reported that after the workshop, they will think differently about how they approach marginalized patients in their practice. Eighty percent (8/10) of participants reported that the workshop gave them tools on how to approach marginalized patients in their practice.

Discussion/Conclusions: Participants reported overwhelmingly that they found the workshop valuable and that it assisted them in making goals to change their practice to improve fertility care for racially marginalized patients.

BACKGROUND

While increased attention has been paid to health disparities in medicine, racial and ethnic health disparities in infertility care and management persist,[1] despite 15% of couples experiencing difficulty conceiving. Previous infertility researchers have described this as both a pipeline and education problem. Limited racial diversity in the field of infertility has been cited as a reason for ongoing racial disparities,[2] as well as Black individuals' limited reproductive health knowledge and education due to limited access to these fields. Therefore, it is difficult for this patient population to advocate for themselves, especially when no advocate exists in the medical system.[3]

Many lectures have been developed to address racial bias, but few utilized a reproductive justice framework in the field of medicine. This framework specifically utilizes a human rights framework to understand and define goals and issues related to abortion access, maternal mortality, access to children's health care, and access to economical and living resources, such as clean drinking water and clear air.[4] However, to date, there have been no published curricula or lectures that have specifically discussed the root of reproductive health disparities, including clinical decision-making, referral patterns, and managing unique challenges that Black and Brown patients pursuing fertility treatment may face. As a result, clinicians—regardless of their backgrounds—may be ill-equipped and ill-prepared to best support Black and Brown patients seeking fertility treatment.

We sought to develop an education tool to provide structured,

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case-based learning for physicians to reflect on bias in medicine and discuss how they might change their practice.

METHODS

Authors created cases based on prior experiences with Black and Brown women in the field of obstetrics and gynecology and arranged them for review informed by the work of reproductive justice and fertility scholars including Gloria Richard-Davis, Loretta Ross, Ricki Solinger, Harriet Washington, and Dorothy Roberts. The cases were expert prepared and reviewed and had not been validated previously. Reflection questions and goal-setting prompts also were developed. The cases were then arranged into a PowerPoint presentation that also could be used as a facilitator's guide to improve accessibility for educators in the future (Appendix A).

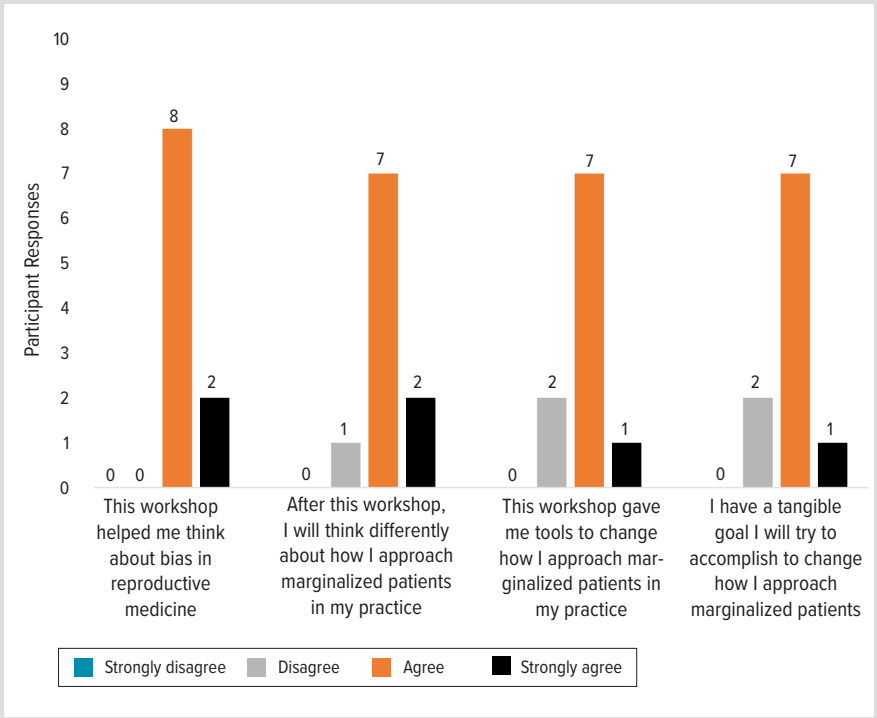
The resulting workshop was piloted to a group of 10 residents in person at a single academic institution as part of a mandatory resident didactic session. The PowerPoint slides were presented to them in a large group, and when discussions were prompted, participants were split into groups with partners seated by them physically. The workshop was 60 minutes long and the group consisted of 1 male and 9 females. Three Black and 7 White residents were present; there were no transgender residents present. Between small group discussions, participants were encouraged to share in a large group what they had discussed, and the primary author encouraged ongoing participation and reflection from other participants. After the workshop, participants were promoted to take a short survey about their thoughts on the workshop. The survey assessed participants' comfort level with the topic and whether or not the workshop improved their thinking about racial bias and approach to managing care for marginalized patients.

This project was approved as a quality improvement study by the Medical College of Wisconsin Obstetrics and Gynecology division. It was deemed not to require Institutional Review Board approval.

RESULTS

Feedback after the workshop demonstrated that participants found it valuable. One hundred percent (10/10) of respondents reported that it helped them think about bias in medicine and 90% (9/10) reported that they will think differently about how they approach marginalized patients in their practice. Similarly, 80% (8/10) reported that the workshop gave them tools for approaching marginalized patients in their practice and that they now had a tangible goal for how to approach marginalized patients they would see in the future (Figure).

Figure. Post-workshop Survey Responses



DISCUSSION

Through this workshop, we were able to gain sufficient engagement from our audience to create goals and commit participants to improving practice in the future. We also were able to have positive discussions to strategize improving access to fertility care and reducing physician-created barriers to fertility care. High levels of engagement demonstrated that the overwhelming majority of participants found that the workshop assisted in their efforts to refine their practice to help marginalized patients access fertility services. Previous reports have demonstrated that implementing similar antiracist workshops and training modules improved physician attitudes[5] and their ability to recognize racism in practice.[6] However, with this unique workshop model, we are able to engage in goal setting, which will further allow change to take place in the workplace, as participants leave with tangible goals moving forward.

The primary limitation to this study is our small sample size, which included only 10 participants. Ongoing education and research opportunities can create and evaluate an entire curriculum to address additional health disparities in infertility, such as for patients who are differently abled and those who are lesbian, gay, bisexual, transgender, and queer. Additionally, ongoing research may include assessing how implementation of larger scale workshops affect trends in care in certain areas with physician participants.

CONCLUSIONS

The resident physicians who participated in this workshop generally found it valuable and reported that it added to their ability to appropriately provide reproductive and fertility care to Black and Brown patients.

Funding/Support: None declared.

Financial Disclosures: None declared.

Acknowledgements: The authors would like to thank Ericka New, MD, at Virginia Commonwealth University for her contribution to development of these educational materials.

Appendix: Available at www.wmjonling.org

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Barriers to Completing Advance Care Planning: Insights From the Wausau Free Clinic

Grace F. Wittenberg, MD; Lauren Woyak, MD; Jeffrey Todd, MS, CMPE; Jeffrey Oswald, MD; Amy Prunuske, PhD

ABSTRACT

Background: Advance care planning (ACP) encourages individuals to express their health care wishes should they become incapacitated and to use an advance directive to designate an individual to make health care decisions on their behalf.

Methods: A survey on ACP was administered at the Wausau Free Clinic in Wausau, Wisconsin in English or Spanish to participants 18 or older from February to May 2023.

Results: Of 46 respondents, 80% had not heard of ACP. One in 10 said a physician had had a conversation with them about ACP. Health care access and lack of education were the biggest challenges to ACP.

Discussion: Most individuals who utilize the clinic were unaware of ACP. Wisconsin is not a "next of kin" state, which increases the importance of ACP completion.

BACKGROUND

Advance care planning (ACP) is the process of having important conversations to indicate one's medical wishes in anticipation of future health care decisions. The goal of an ACP session is to facilitate discussions between clinicians, patients, and their medical decision-maker surrounding the patient's desires and values related to end-of-life care.[1] An advance directive includes a living will and a durable power of attorney for health care. It is a physical, legal document that is used to inform a health care provider what treatments a patient would like if they are unable to make decisions and identifies an individual to make those decisions. An advance directive can be completed if a person is 18 years or older and in sound mind.[1] In some states, if a person has not completed an advance directive, their next of kin can make decisions for them if they are incapacitated. However, Wisconsin is not a "next-of-kin" state, meaning a court-appointed guardian makes decisions for a person if they do not have an advance directive.[2]

Approximately 1 in 3 adults in the United States have completed any type of advance directive.[3] However, a study of Hispanic and non-Hispanic White patients found that participants who identified as Hispanic were less than half as likely to have an advance directive in their medical record as their non-Hispanic White counterparts.[4] Moreover, an older study conducted in Colorado reported Hispanic patients had significantly lower rates of ACP conversations (29%) than White patients (54%).[5] In a previous study of a statewide random-digital dial telephone survey of adults 18 years or older, participants who identified as Hispanic were less likely than non-Hispanic White participants to have named a health care agent or have conversations about their end-of-life wishes with family or friends.[6]

To better understand the barriers and ethnic differences with ACP and advance directive completion, we conducted a survey at the Wausau Free Clinic, located in Wausau, Wisconsin, where the population is over 74% Hispanic and nearly 80% minority.

METHODS

An initial literature review determined barriers faced by people who are Hispanic when completing ACP and guided the creation of a 10-question survey (Appendices A and B), with questions derived from a previous survey.[7] Content of the surveys included basic demographics, respondent's general knowledge of ACP and health care power of attorney, previous conversation about

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Table 1. Demographics of Survey Respondents

Category	No. of Respondents (n)	Proportion of Total (%)
Ethnicity, proportion		
Hispanic or Latino	34	74
Non-Hispanic or Latino	11	24
Did not indicate	1	2
Age, proportion (%)		
18–24	5	11
25–34	10	22
35–44	13	28
45–54	9	20
55–64	7	15
65–74	2	4

Table 2. Barriers to Completing Advance Care Planning

Barrier[a]	No. of Respondents (n)	Proportion of Total (%)
Health care access	21	34
Lack of education	17	27
Fear	6	10
Cultural beliefs	3	5
Spiritual beliefs	4	6
Other challenges[b]	11	18

[a]This question was asked in "select all" format. Hence, there are more answers than the total number of survey respondents.

[b]Of the respondents who selected "other challenges," 1 respondent noted "reading," 1 noted "family," 1 noted "transportation," 1 noted "work," and 2 noted "time" as barriers, while 5 respondents did not comment in the provided box as to what "other challenge" they experienced regarding advance care planning completion.

ACP with physicians, desires to learn more about ACP, preferred method of information delivery, and barriers to completing ACP. To create a culturally relevant survey, the research team worked with a Spanish interpreter to review, edit, and translate the survey to match an eighth grade reading level.

After a nurse obtained patients' vital signs, an anonymous survey was administered via Qualtrics to each willing patient 18 years or older who presented at the clinic on Thursday afternoons from February to May 2023. An informational letter was included at the top of the survey and completion was voluntary. The patient completed the survey directly in English or Spanish or verbally answered the questions as read by the interpreter, depending on the respondent's literacy.

After survey completion, data were analyzed qualitatively for common themes and quantitatively with descriptive statistics using an Excel spreadsheet. The Medical College of Wisconsin Institutional Review Board deemed this project quality improvement.

RESULTS

Of the 46 respondents, 74% were Hispanic or Latino. Respondents were aged 35 to 44 years (28%), followed by 25 to 34 years (22%), 45 to 54 years (20%), 55 to 64 years (15%), 18 to 24 years (11%), and 65 to 74 years (4%) (Table 1). Eighty-five percent of the respondents had not heard of ACP; however, 65% responded "yes" to learning about ACP, 24% responded "maybe," and 15% reported they had no desire to learn about ACP. Although 70% reported they have someone in the US to make health care decisions for them, only 17% had a legal document designating that individual. Most of the respondents (72%) did not have a health care power of attorney.

Only 1 in 10 participants reported a physician has had a conversation with them about ACP. Regarding ACP education, 52% of respondents preferred 1:1 learning, 26% preferred small group learning, 7% preferred large group learning, and 15% were not interested in an ACP education session. Barriers to completing ACP included health care access (34% of total responses), followed by lack of education (27%), fear (10%), cultural beliefs (5%), spiritual beliefs (6%), and other challenges (18%). Free responses were used to describe "other challenges" and included "reading" (1 response), "family" (1 response), "transportation" (1 response), "work" (1 response), and "time" (2 responses). Five respondents did not comment in the provided response area (Table 2).

DISCUSSION

Crooks and Trotter[8] described no statistical difference in the number of informal conversations surrounding end-of-life care throughout various ethnicities, but there remains a large discrepancy in the percentage of people who go on to complete an advance directive. Our surveys replicate these findings within the Hispanic population: most respondents stated they have someone to make medical decisions for them, yet few have the supporting legal document. The lack of understanding of ACP and low completion of advance directives within the study population have significant implications within Wisconsin, which is not a next-of-kin state.[2] This process can cause distress among family members by delaying care and appointing an individual unknown to the family to make life-altering decisions for them. This delay also yields a lower quality of care for the patient.

According to our findings, noted barriers to ACP completion include lack of education, fear, differing belief systems, and health care access. Discrepancies in the language used within the documents is also a well-documented barrier to completion, which may be correlated with lack of education about ACP. Puerto and colleagues[9] identified confusion around the language used in ACP documents and differing levels of knowledge depending on the respondent's country of origin. In Spanish, there are multiple words used for "advance care planning," which creates confusion around the document's intent. Furthermore, some countries do not have ACP, making it an unfamiliar topic for immigrants. Addressing language barriers through easy-to-understand ACP materials, including using resources no higher than an eighth grade reading level, is necessary to increase advance directive

completion. Most respondents at our clinic prefer 1:1 learning, and we believe easy-to-understand ACP pamphlets meet this need. Additionally, integrating ACP conversations as an additional "vital sign" ensures the health care team has a conversation with every individual about an advance directive, even if it is short.

A smaller percentage of total respondents named fear as a barrier to ACP completion, although this was an open question without description of the specific fear. Puerto et al[9] reported that religious beliefs also may contribute to lack of ACP completion due to a belief that discussing death may "interfere with God's plan." A similar number of participants noted their cultural beliefs surrounding decision-making as a barrier. Family structure and the decision-making process in traditional Hispanic culture differs from American culture. Hispanic culture values the immediate family making shared decisions, rather than 1 or 2 appointed proxies.[8] This structure creates difficulty within Wisconsin and can lead to medical preferences not being followed. Although fear, spiritual beliefs, and cultural beliefs may be connected, it remains unclear from our survey how fear and belief systems interrelate to affect ACP completion. Nevertheless, it is important for health care providers to explain advance directives to their patients sensitively.

Survey results identifying that 1 in 10 participants have had a conversation with a physician about ACP highlights the importance of ACP education in the health care setting. Our clinic curbs financial and health literacy barriers to health care, and other free clinics could become systems to address the mismatch between informal ACP and completing advance directives. In Wisconsin there are more than 90 clinics affiliated with the Wisconsin Association of Free and Charitable Clinics, which may be an initial place to increase ACP within the state.[10] Regardless of the free clinic status, however, our findings are applicable to all health care settings given the gravity of Wisconsin not being a next-of-kin state.

Another method to reduce barriers to ACP completion includes bringing ACP conversations into non-health care settings, such as churches, community spaces, or workplaces. Overall, there is a great need for increased ACP education, cultural competency, and expanded communication to ensure peoples' wishes are honored—all in a timely fashion and without having to appoint a legal guardian from the Wisconsin court system.

Limitations

This study's sample size is small due to study time restraints, which may provide a less representative sample of the study population. Our survey specifically asked participants if physicians have had a conversation with them about ACP, although we could have asked broadly about health care providers, such as advanced practice providers. Moreover, the relatively young age of our survey respondents may have been a confounding factor. Additionally, results are taken from 1 health care partner providing services to people who are uninsured, so results may differ at other health care facilities. Lastly, although interpreters were present during survey administration, health literacy barriers may have affected participants' understanding of the survey.

Funding/Support: None declared.

Financial Disclosures: None declared.

Acknowledgements: The authors would like to thank Paula Vogt, RN, and Leslie Thiele for their ACP expertise and assistance with drafting the questionnaire and Francisco Guerrero, a Health Coverage Navigator and Spanish Interpreter for assisting in the creation of the survey, as well as the other Spanish interpreters who helped administer the survey at the WFC. They would also like to thank Kim Shibilski for helping with the administration of the project into clinic workflow.

Appendices: Available at www.wmjonline.org.

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Brain Doctors: Evaluating a Mental Health Initiative for Elementary Students

Parnika Telagi, MD; Jessica Liu, BS; Bryan Johnston, MD

ABSTRACT

Background: Brain Doctors is a community-engaged mental health education program developed using the Food Doctors model to enhance third-grade students' understanding of self and community wellness. This study serves as an evaluation of the pilot program.

Methods: Two dynamic, interactive 1-hour sessions were created, with pre-session and post-session assessments used to measure student growth. The sessions were presented at 2 elementary schools in Milwaukee, Wisconsin by medical students. Feedback was gathered through participant satisfaction surveys following each session.

Results: Student feedback indicated that most participants had a positive experience with the program. Pre-assessment (n = 116) and post-assessment (n = 125) results revealed areas of improvement and areas where performance declined.

Discussion: The elementary students' positive response demonstrated their enthusiasm for the program. This study affirmed our perception that elementary and medical students can engage meaningfully in emotional wellness education.

BACKGROUND

Children in low socioeconomic environments often face violence, trauma, and limited access to mental health resources, increasing their risk for mental health disorders and high-risk behaviors.[1,2] Protective factors, such as positive relationships and school involvement, promote well-being and help reduce risky behaviors.[3] Multi-tiered school mental health systems enhance academic and psychosocial outcomes, but their absence in many schools led to the creation of "Brain Doctors," a community-based mental health pilot initiative.[4]

Brain Doctors originates from "Food Doctors," an established nutrition education program for third-grade students at 2 urban, underserved elementary schools in Milwaukee, Wisconsin. The design, informed by a literature review of the most effective school-based nutrition education programs, emphasizes 2 key pillars: (1) interactivity and hands-on engagement, and (2) cultural relevance. Led by medical students, the curriculum has successfully strengthened student knowledge and attitudes about nutrition.[5,6] Since its inception in 2013, Food Doctors has been implemented at St. Marcus Lutheran School and Milwaukee Academy of Science, fostering strong community partnerships that allow for open dialogue. In a feedback meeting, one of the school's principals reported limited capacity to address mental health and well-being within their existing curriculum; thus Brain Doctors was developed as a pilot initiative to address this gap.

While researching similar programs, we (the authors) explored Second Step Elementary, a teacher-led curriculum fostering social-emotional learning in elementary students through 4 weekly units on growth mindset, emotional management, empathy and kindness, and problem-solving. Its effectiveness is well-documented; a 2-year randomized controlled trial showed significant improvements in social-emotional skills and reduced disruptive behaviors among participants,[7] while another study linked higher engagement to better academic performance and fewer negative classroom behaviors.[8]

Inspired by Second Step Elementary and the success of Food Doctors, we collaborated with community partners—school principals and teachers at St. Marcus Lutheran School and Milwaukee Academy of Science—to create Brain Doctors. Drawing on literature reviews, existing programming, and partner input, Brain

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Doctors was developed into two 1-hour sessions designed to fit both the school schedule and medical student availability.

This study sought to evaluate the applicability and effectiveness of the Food Doctors model in teaching mental health concepts while assessing student satisfaction.

METHODS

Program Design and Implementation

We conducted a literature review to identify age-appropriate topics and developed content focused on emotions, mindfulness, and community wellness for two 1-hour sessions targeting third-grade students (Table 1). Initially designed by medical students, the curriculum was reviewed and approved by community partners, including teachers and principals. The lessons emphasized student engagement through interactive elements, such as question-and-answer presentations and hands-on activities like yoga and the creation of worry stones. Relevant references, including Giannis Antetokounmpo, a professional basketball player for the Milwaukee Bucks, and the Berenstain Bears, were incorporated to illustrate key concepts.

Table 1. Sessions 1 and 2 Concepts and Activities

Concept	Activity
Session 1	
Identifying emotions	Students were presented with images of people and asked to identify emotions being expressed.
Expressing emotions	Students were asked to share how they express specific emotions like happiness, sadness, anger, etc. They were also asked to think about and share how others might express those same emotions.
	Students were asked to draw how they feel when they think of specific emotions such as happiness, sadness, anxiousness, etc.
Practicing mindfulness	Students were given stones and stickers to create a worry stone that could be rubbed for relaxation and anxiety relief.
	Students were introduced to different yoga poses for additional ways to practice mindfulness.
Session 2	
Navigating conflicts	Students were shown cartoon clips from popular shows and were asked to watch them from the perspective of a specific character. Later, they shared their thoughts on how their assigned character must have felt and reflected on what they would have done in a similar situation to better navigate that situation.
Uplifting community members	Students were provided with stickers that had positive expressions written on them. They were then asked to gift the stickers to someone in their life who came to their mind when they read the expression. The objective of this activity was to encourage the students to practice spreading positivity and uplifting their commnity through their actions and words.

Sessions were conducted in 3 classrooms at the Milwaukee Academy of Science and 2 at classrooms St. Marcus Lutheran School, with approximately 25 students per room. Prior to the first session, all students were sent home with a printed consent form outlining programming and research methods for review by their guardians. No guardians declined participation. Students were informed about the programming, and their participation was voluntary.

An amendment to the parent project was approved by the Medical College of Wisconsin's Institutional Review Board (#5) for this study.

Assessment

An 8-question multiple-choice assessment was created to evaluate participants' growth in program learning objectives, which included identifying emotions, acquiring basic factual knowledge about emotions, developing empathy, and resolving conflicts. We aimed to create an assessment that aligned with students' current reading levels, drawing from our experience with them in Food Doctors and our observations of their participation in its assessments, as well as acknowledging the impact of COVID-19 on academic progress. The assessment was reviewed and approved by teachers before it was administered to program participants, which occurred before the first session and after the second session.

In addition to the program assessment, participants completed a survey at the end of each session to assess satisfaction. An example question from the survey was, "Did you have fun during this lesson?" Students responded on a Likert-type scale with options including "not at all," "not really," "maybe," "a little bit," and "yes, absolutely." In addition to this sample question, there were 4 other questions regarding their level of participation, enjoyment of activities, feelings of boredom, and willingness to share what they learned with family and friends, as well as a free-response section where students could share a key takeaway from the session.

Pre-assessment and post-assessment data were analyzed at the group level, ensuring anonymity and without matching individual responses. To identify significant differences, continuous data—specifically pre-assessment and post-assessment scores, were compared between the two groups using an independent samples *t* test in RStudio (Posit PBC). Free-response data from the satisfaction surveys were analyzed thematically to identify emerging themes.

RESULTS

In the pre-assessment (n = 116), the mean percentage of correct answers was 89.3%, compared to 90.7% in the post-assessment (n = 125). A *t* test revealed no statistically significant difference between the two ($P = .43$). Analysis of individual questions showed a significant improvement in scores related to facts about emotions ($P = .03$) and a significant decline in identifying emotions ($P = .03$). Other trends, though not statistically significant,

included increased scores for empathy ($P = .09$) and decreased scores for conflict resolution ($P = .29$) (Figure).

On the satisfaction surveys, the most common response to the question, "Did you have fun in this lesson?" was "Yes, absolutely" (63%). Similarly, when asked, "Did you like how much you were able to talk," "Did you like the activities you did," and "Will you share what you learned with family and friends," the most common response to each question was "Yes, absolutely" (45%, 60%, and 55%, respectively). In response to the question, "Were you bored during this lesson," the most common response was "No, not at all" (40%).

Students' free responses when asked to identify one thing they learned were grouped into 4 key themes. Most students (52.4%) highlighted learning about experiencing, expressing, and managing emotions. Another 24.8% focused on treating others kindly. Mindfulness was a key takeaway for 8.3%, while 14.5% noted other lessons, such as understanding the brain's functions and size, as well as the role of nutrition (Table 2). Notable student quotes included, "I learned that feeling emotions is okay," "Other people have feelings," and "Treat others the way you want to be treated."

Figure. Comparison of Pre-Assessment and Post-Assessment Results

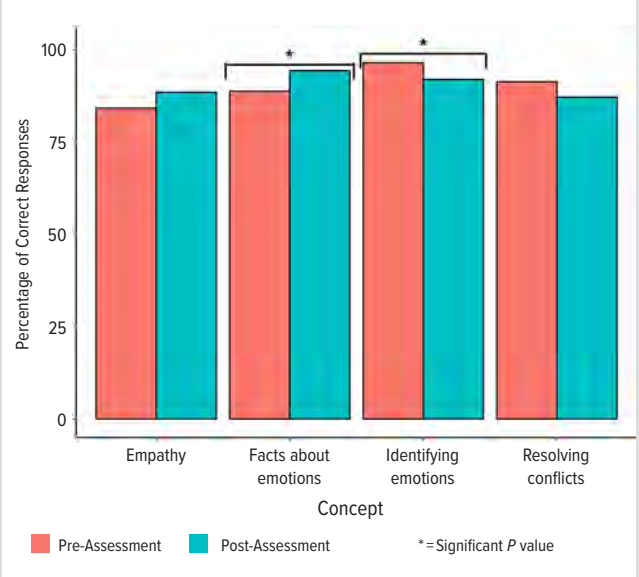

Table 2. Post-Lesson Reflection: What Is One Thing You Learned?

Response Themes	% of Students
Experiencing, expressing, and managing different emotions	52.4
Why and how to treat others kindly	24.8
Mindfulness/mindfulness activities	8.3
Other	14.5

DISCUSSION

This pilot study evaluated the effectiveness of the Brain Doctors curriculum in teaching mental health concepts and gauging student satisfaction. Although pre-assessment and post-assessment scores showed no statistically significant difference, the high baseline scores (89.3% pre-assessment and 90.7% post-assessment averages) suggest that students already had a strong understanding of the material.

Two key factors likely contributed to these high baseline scores. First, previous research highlights how media, including films and television shows, can significantly enhance children's emotional literacy and mental health awareness.[9] For example, Pixar's film Inside Out has become a popular cultural reference for emotional intelligence, introducing young audiences to the importance of understanding and managing emotions. Such media representations helped build a foundational awareness among students before participating in the program.

Second, mental health has been identified as the top health issue in Milwaukee County.[10] The elementary schools involved in the Brain Doctors program are located within this community, where the significant impact of mental health challenges may result in earlier exposure to these topics. This exposure helps normalize conversations about mental health and emotional well-being at a young age.

Most students enjoyed the lessons and activities, though opinions were mixed on participation and sharing what they learned with family. This likely reflects limitations from large class sizes, time constraints, and varying family dynamics. Nevertheless, many students were eager to participate, and community partners at the participating elementary schools highlighted the program's value. The community partners did not receive a satisfaction survey, but feedback was provided regularly with informal and formal check-ins.

Study Limitations

This study has some limitations, including the variation in student participation. As attendance for each lesson could not be controlled, there may be outlying data points, as reflected in the difference in the sample size between the pre- and post-assessments.

Discussions about mental health are crucial, as school environments prioritizing student mental health and well-being can lead to improved classroom behavior, increased school engagement, and stronger peer relationships, which are critical components of academic success.[4] In the future, we plan to address more complex emotional education topics to provide students with more tools to help them navigate emotionally challenging situations. Going forward, to adapt our curriculum, we will trial the curriculum and assessments with a small group of students to ensure they reflect the appropriate difficulty level for the students.

Overall, the elementary students' enthusiasm for the Brain Doctors programming was deeply encouraging. Feedback from

the students and community partners highlighted the value of emotional wellness education. This pilot study reaffirmed our belief that elementary and medical students can meaningfully engage in emotional wellness education and emphasizes the importance of continually adapting such programs to maximize impact.

Funding/Support: None declared.

Financial Disclosures: None declared.

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Mitochondrial Neurogastrointestinal Encephalomyopathy Presenting with Peripheral Neuropathy and Hearing Loss

Milan Patel, MD; Kaleb Keener, BS; Gina LaWall, NP; Pinky Jha, MD

ABSTRACT

Introduction: Mitochondrial neurogastrointestinal encephalopathy (MNGIE) is a rare and often fatal genetic disorder caused by mutations in the thymidine phosphorylase gene (*TYMP*), leading to mitochondrial dysfunction. Symptoms include severe gastrointestinal and neurological issues, such as dysmotility, ophthalmoplegia, leukoencephalopathy, and peripheral neuropathy. Diagnosis typically is delayed until the second decade of life, with an average lifespan of 37 years.

Case Presentation: The patient is a 20-year-old female who initially presented with progressive bilateral peripheral lower extremity neuropathy. She was treated symptomatically for years prior to the onset hearing loss, which prompted further imaging and genetic workup revealing MNGIE. She then opted to undergo liver transplant and is awaiting a donor.

Discussion: Currently, MNGIE treatment options include hematopoietic stem cell transplantation, orthotopic liver transplantation, hemodialysis, and platelet infusion. Hematopoietic stem cell transplantation treatments help restore *TYMP* gene activity, but carry with them increased risk of transplant-related morbidity and mortality. Orthotopic liver transplantation appears to have a more favorable safety profile when compared to hematopoietic stem cell transplantation.

Conclusions: This case highlights the importance of adequate monitoring and interdisciplinary thinking, especially when caring for diseases with wide clinical manifestations. A thorough review of symptomology that includes various specialists may translate to improved diagnosis and care of MNGIE.

INTRODUCTION

Mitochondrial neurogastrointestinal encephalopathy (MNGIE) is a rare and frequently deadly autosomal recessive disorder caused by pathogenic mutations in the thymidine phosphorylase gene (*TYMP*) located on the chromosome 22q13.33.[1] Mutations in the *TYMP* gene lead to a deficiency of the thymidine phosphorylase enzyme, causing an excess of thymidine and deoxyuridine leading to mitochondrial dysfunction.[2] MNGIE presents with progressive, severe gastrointestinal (GI) and neurological manifestations, including gastrointestinal dysmotility, ophthalmoplegia, leukoencephalopathy, and peripheral neuropathy. Recently, a case of MNGIE involving the reproductive system was reported, suggesting a broad scope of clinical disease with a host of unique presentations.[3] This vast heterogeneity of presenting symptoms and the rarity of MNGIE often leads to diagnosis late into the disease course—typically in the second decade of life—and early death, on average 37 years of age.[4] Temporizing treatment options, including hemodialysis, continuous ambulatory peritoneal dialysis (CAPD), erythrocyte encapsulated thymidine phosphorylase (EE-TP), and platelet infusion, have been shown to be effective before a long-term alternative can be performed. Current durable treatment options include hematopoietic stem cell transplantation (HSCT) and orthotopic liver transplantation (OLT) and are aimed at restoring thymidine phosphorylase resulting in the long-term clearance of dUrd and dThd.[4,5]

At the time of writing, less than 200 cases have been reported in the scientific literature. We present the case of MNGIE with unique presentation of bilateral lower extremity neuropathy, bilateral hearing loss, and gastrointestinal dysmotility originally attributed to primary dysmenorrhea.

CASE PRESENTATION

A 20-year-old female with past medical history pertinent for polythelia, hyperhidrosis of bilateral lower extremities, menorrhagia/

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Figure. Timeline of Pertinent Diagnostic Evaluation and Symptom Progression

August 2018: Initial Presentation
- Presents to primary care physician with foot pain
- Concerns regarding episodes of itching, hypersensitivity, and red to purple color changes mainly after hot showers

April 2019: Musculoskeletal/Abdominal Pain
- Presents to primary care physician with diffuse muscular aching after periods of prolonged activity during gym class or recreational activities
- Referral to physical therapy and rheumatology
- Also saw OB/GYN for concerns regarding abdominal pain with elevated LFT that normalized spontaneously
- Diagnosed with dysmenorrhea and had placement of hormonal IUD

June 2020: First Rheumatology Visit
- Bilateral foot symptoms with significant progression occurring daily
- Preliminary diagnosis of Raynaud's syndrome vs erythromelalgia
- Referral for genetic evaluation

November 2021: Second Rheumatology Visit and Pain Management
- Bilateral foot symptoms with even further progression with significant pain with daily activities such as putting on socks
- Progression of musculoskeletal pain and hypermobility
- *SCN9A* genetic testing negative

March 2022: Third Rheumatology Visit
- Bilateral foot pain symptoms have since coalesced with constant burning neuropathic-type pain
- Recently had abdominal pain episode similar to prior episode in 2019 with constipation and elevated LFTs
- Patient noted to have lost 10 pounds in last 3 years with fine body hair, as well as hyperhidrosis of hands and feet

April 2022: First Otolaryngology Visit
- Noted increasingly muffled hearing while in college classes with some nonpulsatile tinnitus and aural fullness
- No trauma, vertigo, dizziness, or feelings of disequilibrium
- Audiogram with "bilateral sloping sensorineural hearing loss with a very slight asymmetric component at 4 kHz and beyond, worse on the right"
- MRI showing "confluent areas of hyperintense long TR signal in the deep cerebral white matter with relative subcortical sparing"

December 2022: Otolaryngology and Neurology Visit
- Hearing loss has progressed further now requiring hearing aids with plans for future cochlear implants
- Based on MRI, leading concerns are now hypomyelinating leukodystrophy, such as Krabbe disease, metachromatic leukodystrophy, and Pelizaeus-Merzbacher disease

February 2023: Further Genetic Testing and GI Dysmotility
- Genetic testing positive for likely pathogenic *TYMP* variant suggesting mitochondrial neurogastrointestinal encephalopathy
- Placed on donor list for orthotopic liver transplantation as patient is deemed not a suitable candidate for hematopoietic stem cell transplant due to severe GI concerns and elevated LFTs
- Seen by GI with studies showing significant dysmotility with periods of intense abdominal pain likely transient pseudoobstruction
- Patient would eventually also sustain bowel perforation in August 2023

Abbreviations: OB/BYN, obstetrician/gynecologist; LFT, liver function test; IUD, intrauterine device; MRI, magnetic resonance imaging; GI, gastroenterology.

dysmenorrhea with regular cycle, body mass index less than 5th percentile, and chronic bilateral foot pain presented to her primary care physician at the age of 14 for recurrent discoloration and hyperhidrosis of her feet. She described 8 to 10 episodes per month of well demarcated bilateral erythema and edema extending to her malleoli, with associated burning and itching pain as well as hyperhidrosis. She was referred to dermatology, who discussed treatment with topical aluminum chloride as well as oral anticholinergic therapy. Workup including ferritin and thyroid panel was unremarkable.

Approximately a year and a half later, the patient reported again to her primary care physicians for progression of the same symptoms and was given a rheumatology referral. She noted at this time that the extent of the erythema and edema extended to her upper ankle/lower leg with new associated symptoms of tingling and numbness. While still generally associated with hot temperatures such as in the shower, she also noted sporadic episodes in the absence of any obvious triggers. The episodes began to increase in frequency at this time, and she reported 2 to 3 episodes per day lasting about 5 minutes at a time. She was referred to genetics for erythromelalgia *SCN9A*, *SCN10A*, and *SCN11A* gene evaluation, which was negative.

The patient was seen a year later in the rheumatology clinic with significant progression of her lower extremity discomfort. At this point, she was having pain with simple activities of daily living, such as putting on socks, which was hindering her sleep. This was in conjunction with worsening lower back pain determined to be caused by lumbar hypermobility hindering her posture, hamstring function, and core stability and affecting her ability to participate in sports or ambulate for long periods of time. She was seen by physical therapy in conjunction with pain management and was started on a course of gabapentin, diclofenac gel, and meloxicam as needed for pain. Laboratory panel at this time showed transiently elevated liver function tests that normalized without intervention.

On follow-up 3 months later, the patient noted that the diclofenac gel had minimal effect, she was starting to notice hearing loss, and she had lost 10 pounds over the course of 3 years. During the previous 2 months, she had begun to notice symmetric aural fullness and muffled hearing, as well as bilateral, nonpulsatile tinnitus. Audiogram showed bilateral sloping sensorineural hearing loss with slight asymmetric component at 4 kHz and beyond, worse on the right. Magnetic resonance imaging to evaluate for retrocochlear pathology was remarkable for confluent areas of hyperintense long repetition time (TR) signal. This was noted throughout the cerebral white matter, though prominent in the frontal and parietal lobes involving the deep white matter to a greater degree than the peripheral white matter. There were some subtle hyperintense foci in the lower pons. With these findings, a tentative diagnosis was made for a leukodystrophy vs Susac syndrome.

At this time, the patient began using hearing aids with a plan for follow-up in the neurology clinic for further evaluation of various leukodystrophies that present with peripheral myelinating defects, including Krabbe disease, metachromatic leukodystrophy, and Pelizaeus-Merzbacher disease. Additionally, mitochondrial disorders, such as mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS), which have associated hearing loss, also were considered. Genetic testing was positive for a likely pathogenic *TYMP* variant, suggesting MNGIE. Over the coming months, her hearing continued to deteriorate, with her right side requiring eventual cochlear implant and treatment with high-dose oral and local steroids.

With the tentative diagnosis of MNGIE, the patient's previous symptoms of dysmenorrhea consisting of vomiting, diarrhea, abdominal pain, and anorexia suggested the need for further evaluation of gastric motility. She was seen by gastroenterology, with labs showing elevated liver function tests and elevated total protein. She endorsed episodes of alternating constipation and diarrhea with episodes of feeling like she was choking on her food. These episodes would occur when she ate large quantities of food and were described as retrosternal fullness requiring her to eat smaller portions. Further workup, including liver biopsy, esophageal manometry, and gastric emptying, was ordered. Liver biopsy was largely unremarkable, with the most significant finding being the presence of scattered intracytoplasmic PAS-D-positive (periodic acid Schiff with diastase) globules in hepatocytes. Esophageal manometry and gastric emptying studies showed concerns for gastric dysmotility. Over the next 3 months, she had worsening earlier satiety that culminated with jejunal perforations requiring resection and anastomosis. Since surgery, she has been relatively well and is pending liver transplantation (Figure).

DISCUSSION

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is an exceedingly rare and often fatal disease, with fewer than 200 patients currently diagnosed across the globe.[1] Its diverse and often misleading presentation involving multiple organ systems makes early diagnosis extremely difficult, leading to a widely diverse presentation upon initial diagnosis. The most observed clinical features involve severe gastrointestinal dysmotility, dysphagia, nausea, diarrhea, external ophthalmoplegia, and leukoencephalopathy. Patients with MNGIE occasionally have been reported to present with neurodegenerative changes, such as peripheral neuropathy and sensorineural hearing loss, as is the case with our patient.[6] Additionally, while rare, intestinal perforations have been reported, which are likely attributable to the poor gastrointestinal motility causing regions of relatively high pressure and predisposing the patient to perforations.[7-9]

The current gold standard for MNGIE diagnostics is testing for elevated levels of dUrd and dThd in the urine and serum, as well as genomic sequencing to identify mutations in the *TYMP* gene.[10] Despite the relative availability of diagnostics, the complex clinical presentation of MNGIE often leads to unnecessary—and sometimes invasive—testing and overall diagnostic delays. In the absence of genomic testing capabilities, thymidine phosphorylase activity must be evaluated to gain insight into the presence and severity of disease.

Management of MNGIE is typically symptomatic and requires an interdisciplinary approach. Hemodialysis, continuous ambulatory peritoneal dialysis (CAPD), erythrocyte-encapsulated thymidine phosphorylase (EE-TP), and platelet transfusion have been used to temporarily lower nucleoside levels.[4] Long-term treatment options, including hematopoietic stem cell transplantation (HSCT) and orthotopic liver transplantation (OLT), aim to restore thymidine phosphorylase activity, resulting in sustained metabolic correction.[5] However, both HSCT and OLT are invasive procedures with significant risk and variable success rates.[5]

After thorough and thoughtful discussion with the multidisciplinary team involved in our patient's care and our patient and her family, an OLT was decided to be the best course of action moving forward. Despite this, these treatments are inadequate for the treatment of the GI manifestations of MNGIE, as those with already severe GI manifestations are unlikely to see significant improvement in these symptoms. The current pathogenesis is thought to be the result of mitochondrial disfunction in the interstitial cells of Cajal in the small intestine.[11] Further research into the underlying mechanism of the gastric dysmotility is needed to allow for more definitive management of MNGIE.

MNGIE also poses anesthetic challenges due to mitochondrial DNA dysfunction that may predispose the patient to acidosis by glucose loads and stressors during surgery, as well as cardiac abnormalities.[12] As such, patients should receive cardiopulmonary workup prior to surgery, as well as labs evaluating baseline glucose levels and lactic acid. Also prior to surgery, the patient's fasting glucose should be monitored closely and replenished with intravenous (IV) dextrose. The use of volatile and IV anesthetics have been shown to inhibit the electron transport chain, though short-term use of these agents are generally well tolerated despite the increased anesthetic sensitivity secondary to pathology and lower overall body weight in this patient population. The use of local anesthetics and regional anesthetics also may be an alternative in high risk or emergency cases, though they too impair the electron transport chain and carry some risk.[8,12] To date, there have been no cases of malignant hyperthermia with MNGIE.

MNGIE has an incredibly broad presentation often leading to delayed diagnosis despite evident symptomology. In our case, from presentation of the patient's symptoms of peripheral neuropathy until diagnosis was about 5.5 years. Throughout her care, she presented to us with symptoms characteristic of MNGIE, including gastric dysmotility originally thought to be dysmenorrhea,

leukodystrophy, anorexia, and progressive sensorineural hearing loss. While GI and ocular symptoms are often the most common, peripheral neuropathy and sensorineural hearing loss are often the most initial presenting symptoms.[1]

The diagnosis of MNGIE is difficult, as the patient can present with a host of symptoms that present a diagnostic hurdle. Therefore, it is important to notice early symptoms, such as hearing loss and peripheral neuropathy, in addition to more classic symptoms, such as cachexia, leukoencephalopathy, and gastrointestinal dysmotility. With symptoms being so diverse, clinicians are encouraged to explore this diagnosis in individuals with unexplained multisystem dysfunction as there is potential for these patients to be written off as having psychiatric disorders.

CONCLUSIONS

This case highlights the importance of adequate monitoring and interdisciplinary thinking, especially when caring for diseases with wide clinical manifestations. A thorough review of symptomology that includes various specialists may result in improved diagnosis and care of MNGIE.

Funding/Support: None declared.

Financial Disclosures: None declared.

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Candida Auris Total Knee Arthroplasty Infection in an Immunocompetent Individual: Case Report and Literature Review

Milan Patel, MD; Jacob Kodra, BS; Kaleb Keener, BS; Riya Singh; Pinky Jha, MD

ABSTRACT

Introduction: *Candida auris* (*C auris)*, a multidrug-resistant fungus, was declared by the Centers for Disease Control and Prevention as a serious global health threat in 2016. It is hard to identify, resistant to standard antifungal treatments, and spreads within health care settings, resulting in high morbidity and mortality in critically ill patients.

Case Presentation: We report the case of a 60-year-old immunocompetent male with a protracted course of prosthetic knee joint infections. He received medical care at several health care facilities across 2 Midwestern states culminating in wound dehiscence and *C auris* infection necessitating prolonged antimicrobial treatment.

Discussion: *C auris* has been a pathogen of increasing nosocomial transmission with particular concern for multidrug resistance. Treatment is with prompt irrigation and debridement and polyethylene exchange and systemic antifungal treatment. Local treatment with antimicrobial impregnated cement can be used to reduce treatment duration and mitigate resistance.

Conclusions: With emerging concerns and the prevalence of infection with *C auris*, there should be greater vigilance in evaluating patients with repeat surgeries and health care contacts for fungal infection.

INTRODUCTION

In the last decade, there has been growing concern over the emergence of *Candida auris* (*C auris*) as a multidrug-resistant fungal pathogen. It is often difficult to identify and deadly, with more than 1 in 3 cases of invasive *C auris* infection leading to death.[1] *C auris* was discovered initially in the outer ear canal of a hospitalized patient in Japan in 2009.[2] This multidrug-resistant pathogen has become increasingly common and now globally widespread, with reported cases in over 47 countries. In the United States alone, the percentage of clinical cases increased by 44% in 2019 and 95% in 2021.[3]

Cases of *C auris* infections most often have been reported in critically ill patients admitted to the intensive care unit (ICU) or those with severe comorbidities causing immunosuppression. Typically, like other invasive *Candida* species, *C auris* can be treated with a combination of oral and intravenous azoles, amphotericin B, and echinocandins.[4] Cases of azole-resistant strains of *C auris* have been increasingly common, thus complicating the treatment options for infections and raising concern of particularly deadly infections.

While there is some literature for the *Candida* species, there is limited literature for the treatment of *C auris* specifically. The infection risk and methodology of treatment for *C auris* identified with prosthetic joints are relatively underappreciated within the literature. Adequate understanding of *C auris* within clinical contexts is essential for the accurate treatment and prevention of this infection, ensuring the delivery of safe and effective patient care. In this case report, we present a patient with a history of right knee total arthroplasty complicated by recurrent infections, including *C auris*, leading to multiple revisions.

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CASE PRESENTATION

A 60-year-old male Wisconsinite with a past medical history of obese body habitus, hypertension, and hypothyroidism underwent right proximal tibial osteotomy in 2009 and eventual right total knee arthroplasty (TKA) in December 2015. While he initially responded well with minimal postoperative concern, an infec-

Table. Patient's Medical History Detailing Primary Medical Complaint, Treatment, and Infectious Disease Implication, 2009-2023

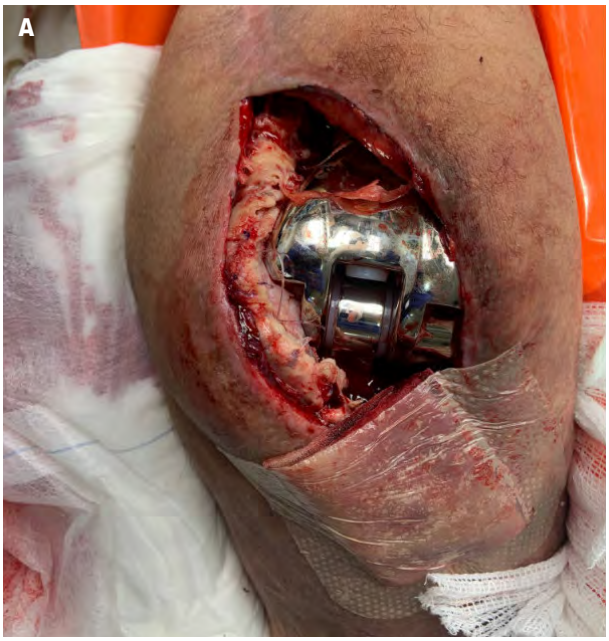
Date	Medical Complaint	Treatment	Infectious Disease Implication
5/2009	Advanced tricompartmental degenerative arthritis	Proximal tibial wedge osteotomy with allograft cellulitis treated with oral cephalexin	Postoperative overlying skin
12/2015	Progression of advanced tricompartmental degenerative arthritis now showing bone-on-bone arthritis	Right TKA	N/A
12/2015	Pruritic rash on right knee and buttock, mild erythema of knee without discharge	Methylprednisolone and cephalexin	Rash vs cellulitis of unknown origin
1/2016	Pruritic rash spread from knee to back of calf	Tramadol and continued cephalexin	Rash vs cellulitis of unknown origin
6/2016	2 weeks of fever and worsening right knee swelling that radiates to hip and is worse with movement	Inpatient vancomycin and ceftriaxone via PICC line	MSSA prosthetic knee infection
6/2016	Right knee hematoma with septic arthritis	Exploratory surgery with I&D and polyethylene exchange	MSSA prosthetic knee infection
6/2016	MSSA infection, erythema, indurated knee	Cefazolin	MSSA infection
7/2016	Improved erythema of anterior knee	Sulfadiazine cream	MSSA infection
8/2016	Septic arthritis requiring revision surgery, cellulitis of the knee	Hospitalized for 2 weeks, hardware removal and placement of antibiotic spacer	MRSA infection
1/2017	Right total knee revision	Hospitalized for 4 days, vancomycin	MRSA infection
1/2019	Serosanguineous drainage from the right knee with overlying cellulitis	Right knee debridement with flap to cover debrided tissue and suppressive vancomycin	MRSA infection
6/2020	Periprosthetic fracture of femoral component of right TKA	Scheduled for revision surgery and placed in knee immobilizer	N/A
7/2020	Revision of right total knee arthroplasty	Physical therapy, Marcaine and Kenalog injections into knee	N/A
5/2021	Fever, erythema and induration of the right knee with pain on passive movement	I&D with poly exchange and polyethylene tibial insert	*Streptococcus agalactiae* on tissue culture – ceftriaxone
4/2022	Left knee total arthroplasty	N/A	N/A
6/2022	Fever, erythema and induration of the right knee with pain on passive movement	I&D necessitating flap coverage by plastic surgery	N/A
8/2022	Right knee infection symptoms	Hospitalized for 1 week	N/A
11/2022	Patient suffers fall and has wound with bloody to purulent draining; fever	I&D with antibiotic beads and primary closure	*Enterococcus faecalis* and *Pseudomonas* on tissue culture – linezolid and levofloxacin suppression
11/2022	Infection symptoms	Daptomycin and oral linezolid	N/A
1/2023	Hospitalized; *C auris* and *Pseudomonas* coinfection	Treatment with cefepime, micafungin, and linezolid	*C auris*/*Pseudomonas aeruginosa* infection confirmed on deep and superficial tissue culture

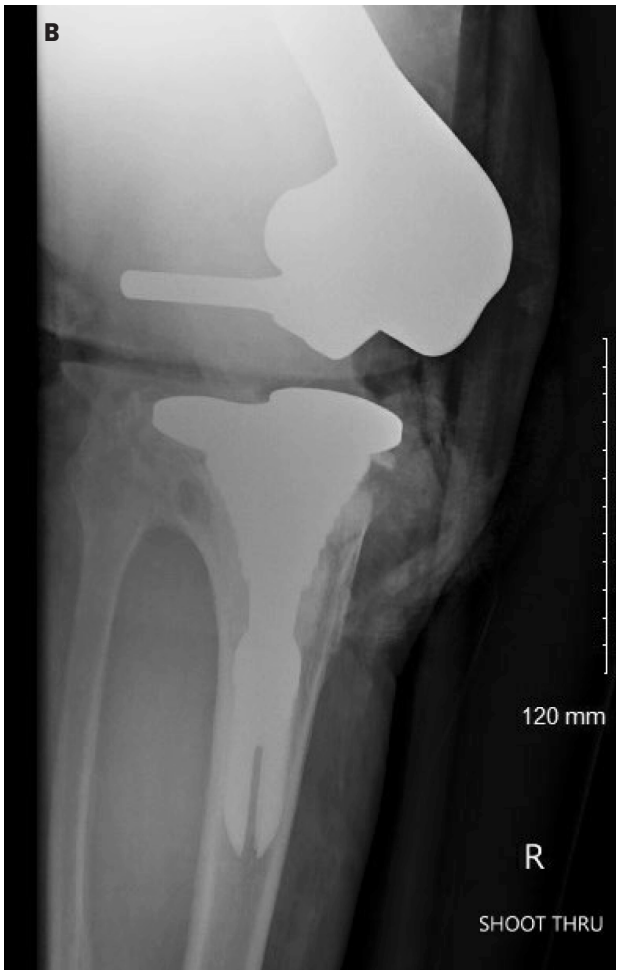
Abbreviations: TKA, total knee arthroplasty; PICC, peripherally inserted central catheter; MSSA, methicillin-susceptible *Staphylococcus aureus;* I&D, incision and drainage; MRSA, methicillin-resistant *Staphylococcus aureus*.

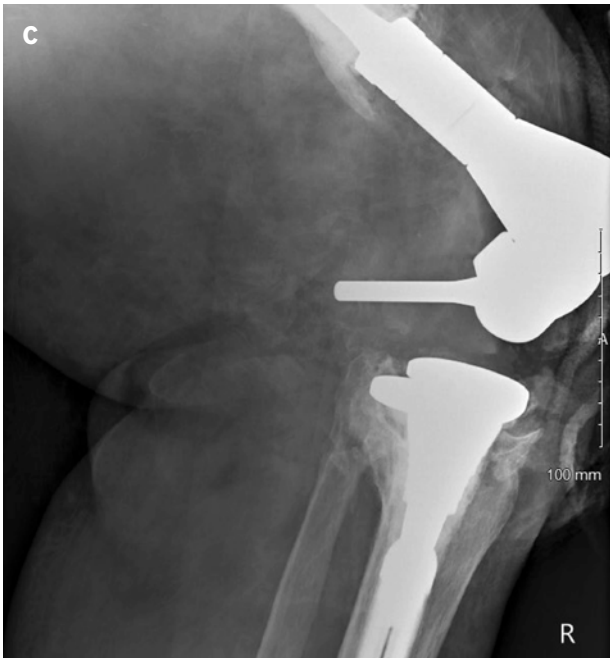
tious complications ensued 6 months status-post right TKA, including *Echinococcus faecalis*, methicillin-resistant *Staphylococcus aureus*, and *Streptococcus agalactiae* septic knee arthritis (Table). He underwent several additional years of complex care for his right TKA involving revision surgeries related to infection and hardware complications in 2019 and 2020, respectively. He was asymptomatic and underwent left TKA in April 2022. Soon after in June, he began to present with new symptoms concerning for reinfection of his right knee, for which he underwent right knee incision and drainage with polyethylene exchange. His postoperative period was complicated when he sustained a ground-level fall culminating in a laceration over his right knee requiring incision and drainage and flap coverage with long-term, broad-spectrum antibiotic treatment. He gradually improved to his baseline status of being a community ambulator with a cane.

In January 2023, the patient pivoted while taking a step in his kitchen and felt his knee "give out," leading to wound dehiscence with resultant hardware exposure and extensor mechanism lateral dislocation (Figure 1A). At this time, he had been on chronic antibiotic suppression consisting of 600 mg of linezolid twice a day and levofloxacin 750 mg daily for 2 months at the recommendation of an infectious disease specialist at an outside hospital. Further workup in the emergency department included a dose of 2 grams of cefazolin and right lower extremity radiographs (Figures 1B and 1C), at which point the patient was taken to the operating room (OR) emergently overnight for irrigation and debridement. In the OR, 2 superficial wound tissue cultures and 1 deep wound synovial tissue culture polyethylene were taken. The polyethylene was noted to have dislocated posteriorly and there was a partial avulsion of the medial tibial tubercle with the remainder of the hardware well fixed. A mixture of 2 grams of vancomycin and 3 grams of tobramycin were placed in the wound and the polyeth-

Figure 1.







A. Dehiscence Wound of Right Total Knee Arthroplasty with Exposed Hardware from Emergency Department Visit, January 2023

B/C. Anterior/Posterior (B) and Lateral (C) Radiographs of the Right Knee Status Post Ground-level Fall, January 2023

ylene was exchanged, demonstrating that the knee was stable to varus and valgus stress. The wound closed primarily with a wound vacuum set to 75 mmHg of continuous suction with overlying ace bandage, at which point he was placed in a hinged knee brace that was locked in extension.

The day after surgery, all 3 intraoperative cultures demonstrated *Pseudomonas* growth and the deep wound culture developed 2+ growth of unknown yeast. The patient was placed on 600 mg of daily oral fluconazole, 600 mg of linezolid twice a day, and 2 g cefepime three times a day in exchange for his home levofloxacin pending susceptibilities. On hospitalization day 3, the fungus was speciated to *C auris*. Fluconazole was discontinued and replaced with 200 mg IV micafungin. He was discharged on hospital day 7 on 6 weeks of IV cefepime and micafungin via a peripherally inserted central catheter (PICC) line and continued indefinitely on his oral linezolid.

Upon follow-up in February, the patient was healing well from surgery with no complications or signs of infection. A month

later, he completed his IV antibiotic course at which point his PICC line was removed. He began his current and indefinite treatment regimen of his previous 600 mg linezolid twice a day, 400 mg oral fluconazole daily and 500 mg ciprofloxacin twice a day for long-term suppression based on susceptibilities. Three months after discharge, he had had routine visits with his orthopedic surgeon and with infectious disease, with his improvement supported by decreased trending inflammatory markers and a promising clinical course.

DISCUSSION

Since its initial identification in 2009, *C auris*, a major multidrug-resistant fungal pathogen has emerged on a global scale.[1] From 2019 to 2021, *C auris* spread rapidly across the United States, with 17 states reporting their first cases.[3] During the same period, the number of clinical cases increased each year, with a 95% surge observed in 2021 alone. The number of Americans colonized by the fungus rose by 21% from 2019 to 2020 and by 209% from 2020 to 2021, despite only an 80% increase in screening measures.[3] Despite this increased prevalence, *C auris* likely remains underreported and underdiagnosed without universal screening precautions across the United States, in addition to the continued incorrect identification of *C auris* as other phylogenetically similar strains such as *Candida haemulonii* and *Rhodotorula glutinis*.[5,6] The clinical presentation of *C auris* is typically nonspecific and emulates other types of systemic fungal infections.[7] The majority of cases have been seen in adults, with those who are critically ill and, in the ICU, boasting a higher prevalence rate likely due to the concomitant presence of risk factors, such as urinary catheters, central venous catheters, malignancy, chronic kidney disease, and neutropenia. Interestingly, the COVID-19 pandemic led to multiple reported outbreaks of SARS-CoV-2 and *C auris* coinfections, specifically in patients who had received azithromycin or use of tetracycline antibiotics, as well as other second-generation tetracycline derivatives.[4] Additionally, those on long-term broad-spectrum antibiotics are also likely at greater risk of resistant fungal infection, which has been demonstrated in the intestine and was likely the driving factor in our case.[8]

Candida infections typically are treated with a combination of azoles, echinocandins, and amphotericin B. However, *C auris* has extremely variable susceptibility patterns and frequently exhibits resistance to the common treatments at the time of diagnosis.[9] National surveillance data have demonstrated that 3 times the number of *C auris* cases with echinocandin-resistant infections were reported in 2021 than the previous 2 years.[3] *C auris* displays a wide variety of resistance mechanisms. It can form biofilms, undergo filamentation, and phenotypically change between specific cell types.[4] Interestingly, *C auris* has multiple resistance mechanisms unique to *Candida* species. *C auris* can grow at high temperatures (>40 °C) and high salt concentrations (>10% sodium chloride, weight/volume). These resistance mechanisms contribute to the survival and persistence of *C auris* on organic and inorganic surfaces. This persistence may contribute to the commonly observed nosocomial transmission of *C auris*.[10] This combination of both novel and known resistance mechanisms found in *C auris* makes it an increasingly dangerous pathogen that recently has emerged on a global scale.

While reports of *C auris* infections are becoming more common, there have been few documented cases of *C auris* in joint replacement procedure–particularly in the context of complex postoperative complications. Documented fungal prosthetic joint infections (PJIs) are rare, occurring in only 0.3% to 2.3% of all infections, with *Candida* species being responsible for about 90% of all fungal PJIs, though epidemiology and etiology vary by geography.[11] There is limited literature on optimal management, and at the time of this writing, there is 1 case of a left ankle *C auris* PJI following open reduction and internal fixation for an open right ankle fracture that was successfully treated with an amphotericin B-molded cement spacer and postoperative micafungin for 2 weeks, followed by oral fluconazole.[12] At our facility, antifungal susceptibility testing for *C auris* was performed. The minimum inhibitory concentrations (MICs) were as follows: amphotericin B, 1.000 μg/mL; fluconazole, 8.000 μg/mL; micafungin, 0.060 μg/mL; and voriconazole, 0.060 μg/mL. While the antibiotic management was similar to our case, the use of amphotericin B cement spacer may mitigate the potential for further resistance by reducing the duration of azole therapy to only 2 weeks versus our case's 6 weeks. According to the Infectious Disease Society of America (IDSA), medical therapy alone is unlikely to be successful, and the addition of antifungals, such as amphotericin B and fluconazole to bone cement for osteomyelitis and loaded cement spacers for PJIs, can have some utility as an adjunctive therapy. However, this practice is controversial as cement spacers may be unable to elute antifungals at a clinically significant rate.[13,14] The current IDSA standard of treatment in most cases consists of removal of hardware and 12 weeks of antifungal therapy, followed by reimplantation with another 6 weeks of antifungal therapy.

CONCLUSIONS

This unique case presentation illustrates the evaluation, treatment, and management of *C auris* in a patient with a right total knee arthroplasty, complicated by multiple revision surgeries and significant comorbidities. The multitude of resistance mechanisms displayed by *C auris*, combined with the increased effort required for identification, makes it an incredibly challenging pathogen to treat. The complexity of care needed for *C auris* joint infections necessitates a multidisciplinary approach, including both infectious disease and orthopedic specialists. Given the alarming surge in *C auris* cases in 2021, improved detection and treatment are imperative to prevent long-term morbidity and mortality. Further research, cross-specialty collaboration, and the establishment of

screening protocols are essential to enhance future identification and management of this fungal pathogen. High clinical suspicion is particularly important in critically ill patients or those with chronic prosthetic joint infections.

Funding/Support: None declared.

Financial Disclosures: None declared.

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Locally Invasive Central Nervous System Aspergillosis Presenting as Subacute Vision Loss

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ABSTRACT

Introduction: *Aspergillus* is a ubiquitous environmental fungus that has the potential to cause a wide array of clinical illnesses, from an allergic response to invasive disseminated disease – particularly in those with immune dysfunction or underlying disease.

Case Presentation: An 83-year-old immunocompromised man presented to the emergency department with fever and subacute vision loss over 3 to 4 months after multiple prior emergency department and outpatient ophthalmology visits. After a complicated course, locally invasive central nervous system aspergillosis was diagnosed. Although the patient eventually recovered, he experienced permanent vision loss.

Discussion: This case demonstrates the importance of aggressive workup in immunosuppressed patients with onset of any concerning ocular or other symptoms. A multidisciplinary approach is necessary for optimal patient outcomes.

Conclusions: Aspergillosis has the potential to cause devastating disease and long-term consequences in immunocompromised patients. Clinicians should be alerted to the importance of early detection and intervention for this population.

INTRODUCTION

Aspergillus is a widely prevalent environmental fungus with the potential to cause an array of clinical presentations in humans, from an allergic response to invasive disseminated disease.[1] While exposure to the fungus is widespread, most people do not develop any signs or symptoms and acquire no antibody- or cell-mediated immunity.[1] However, for hosts with immune dysfunction, traumatic injury, or underlying lung disease, *Aspergillus* species have the ability to cause devastating and severe consequences.[1,2] Underlying conditions that serve as risk factors for invasive aspergillosis include severe and prolonged neutropenia, receipt of high-dose glucocorticoids, and other drugs that lead to chronically impaired cellular responses.[2-5]

Central nervous system (CNS) aspergillosis is an invasive form with high mortality that may occur through either hematogenous spread from disseminated infection or by direct extension from a locally invasive infection.[4,6] Hematogenous dissemination most frequently originates from an invasive lung infection in an immunocompromised host or those with underlying lung conditions. On the other hand, locally invasive CNS aspergillosis most commonly spreads from the paranasal sinuses in either an immunocompromised host or following cranial trauma or neurosurgery.[6,7] The clinical presentation of CNS aspergillosis is nonspecific and heterogeneous as patients may present with headache, focal neurological deficits, altered mental status, or vasculitis depending on the extent of intracranial involvement.[4-6] The most notable risk factor is persistent and significant neutropenia. In a literature review of 235 patients with CNS aspergillosis, the predisposing factors to infection included corticosteroid use (22.6%), malignancy (19.1%), and diabetes (14%).[4] Furthermore, of those with a malignancy, 75% had a hematologic malignancy.[4]

Here we present a case of CNS aspergillosis resulting in permanent vision loss in an immunocompromised patient with lymphoma-associated amyloidosis.

CASE PRESENTATION

An 83-year-old man presented to an outside emergency department (ED) with worsening vision loss in his left eye and a subjective fever. His medical history was significant for low-grade B-cell

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lymphoma with plasmocytic differentiation and associated organ-limited amyloidosis post splenectomy and partial pancreatectomy (6 years prior to presentation), bortezomib course (6 years prior to presentation) with long-term dexamethasone and pomalidomide use, diabetes secondary to pancreatectomy, and prior right eye blindness from an unrelated injury. He reported worsening of vision loss for 3 to 4 months with recent escalation to complete darkness in the left eye in the 24 hours prior to presentation. He also reported 3 ground-level falls in the prior 48 hours, which he attributed to the visual disturbances.

Moreover, the patient had been seen in the ophthalmology clinic 4 months prior to this presentation for drainage and discomfort of his right blind eye with minor discomfort in the left eye and was diagnosed with bacterial conjunctivitis. Superficial keratectomy was completed to remove the calcific densities in the right eye, and tobramycin drops were prescribed for the suspected bacterial conjunctivitis. At a follow-up appointment 1 month later, he continued to report right eye pain and headaches while noting new floaters in his left eye. An additional keratectomy was performed to further remove calcifications of the right eye. Another month later, he continued to have significant pain in the right eye and was then noted to have numbness on the right side of his nose and face. Finally, 1 additional month later, he was found to have cranial nerve 3, 4, 5, and 6 palsies, and a neurologic follow-up was recommended by ophthalmology. Within 1 week of his last ophthalmology appointment, he presented to an outside ED for complete darkness in the left eye as described above.

Upon presentation to the ED, the patient was febrile to 38.89 °C with elevated erythrocyte sedimentation rate (ESR) to 120 mm/hr and a white blood cell count (WBC) of 11 500. Magnetic resonance angiography (MRA) of the head and neck obtained in the ED demonstrated a right anterior temporal lobe abscess with associated diffuse paranasal sinus thickening and a right mastoid effusion (see Figure 1). The patient was admitted to an outside hospital for observation and underwent a lumbar puncture with cerebrospinal fluid (CSF) demonstrating >100 000 red blood cell count (RBC), 95 000 WBC, 250 mg/dL protein, and 61 mg/ml glucose consistent with a bacterial versus fungal infection. He was started empirically on vancomycin, cefepime, and metronidazole. Blood and CSF cultures were obtained, and a CSF meningitis/encephalitis panel was negative. Magnetic resonance imaging (MRI) of the brain with contrast and magnetic resonance venography (MRV) showed invasive right sphenoid sinusitis with right orbital apex and cavernous sinus involvement and a right temporal abscess. He was then transferred for admission to our hospital, a quaternary academic care center.

Upon arrival to our hospital, the patient was in no acute distress, with a mild headache and complete immobility of the right eye, which was atypical for him. He was only able to appreciate light and shadows from his left eye. On initial examination, his right eye appeared clouded with no erythema or purulent drainage, and the nasopharynx had minimal edema with no areas of necrosis. He had right eye ptosis and ophthalmoplegia, as well as loss of vision in the left eye as demonstrated by his inability to visualize finger count. He also had right-sided facial numbness in a V1 and V2 distribution, with pain to palpation along the right mandible. His labs at that time showed leukocytosis with WBC of 15 700 and thrombocytosis with a platelet count of 562 000. Neurosurgery; ear, nose, and throat (ENT); and infectious disease (ID) were consulted. The patient was transitioned to linezolid, cefepime, metronidazole, and amphotericin B. ENT performed biopsies of the right palate as well as the middle and inferior turbinates. Computed tomography (CT) sinus stealth indicated additional mucosal disease in the right maxillary sinus most consistent with invasive fungal disease (see Figure 2). The decision was made to continue the current antimicrobial regimen and monitor for improvement of symptoms and imaging findings.

On hospital day 4, preliminary culture results from the right nasal cavity indicated gram-positive rods and yeast with 1 colony of pan-sensitive *Staphylococcus lugdunensis*, and the patient was narrowed from cefepime to ceftriaxone. On hospital day 6, linezolid was discontinued since he was clinically stable. Biopsy results showed no evidence of fungal organism or neoplastic growth. On hospital day 9, he spiked a temperature up to 37.83 °C and still had no return of vision despite antimicrobial treatment. ID recommended repeat biopsy and MRI brain. ENT determined

Figure 1. Axial T2-weighted Magnetic Resonance Angiography of Head With Contrast Taken Two Days Prior to Admission

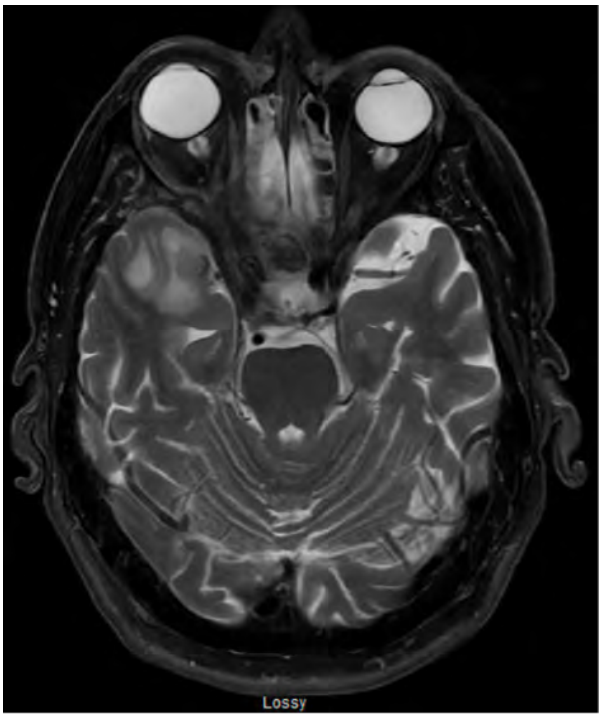

Image Shows Diffuse Paranasal Sinus Thickening and Right Mastoid Effusion.

Figure 2. Axial Computed Tomography Sinus Stealth Marker Without Contrast Taken on Day 2 of Admission

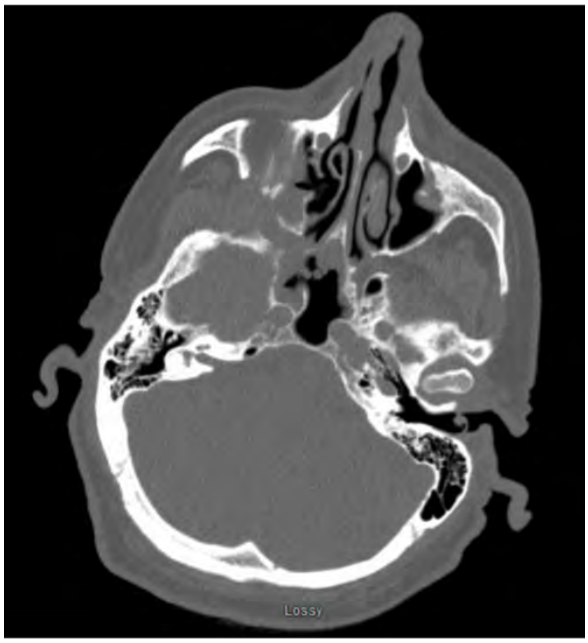

Image shows aggressive-appearing soft tissue in the right sphenoid and posterior ethmoid sinuses with progressive destruction of bone and infiltration of the soft tissues of the right orbital apex, central skull base, and right cavernous sinus.

Figure 3. Coronal T1-weighted Magnetic Resonance Imaging of Head with Contrast on Day 10 of Admission

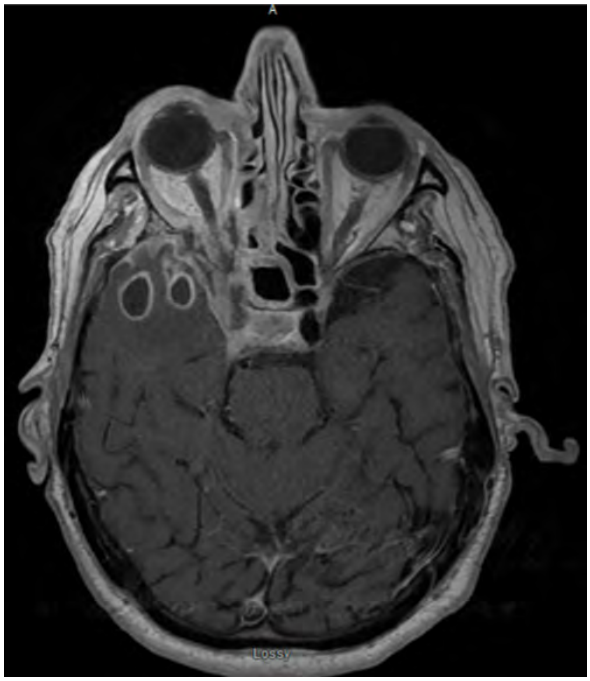

Image shows small cerebral abscesses in the right temporal pole with slightly increased surrounding vasogenic edema and similar invasive sinus disease involving the right orbital apex, cavernous sinus, pterygopalatine fossa, and retroantral fat suggestive of fungal etiology.

that there was no safe area for biopsy and recommended moving forward with craniotomy. MRI brain indicated worsening of vasogenic edema and an acute lacunar infarct in the right corona radiata most consistent with small vessel etiology but also potentially related to the ongoing temporal abscesses and fungal infection (see Figure 3). Craniotomy was performed for abscess resection on hospital day 13 and purulence was noted intraoperatively. Then, on hospital day 16, intraoperative cultures grew 1 colony of *Aspergillus* species. Amphotericin B, metronidazole, and ceftriaxone were discontinued, and the patient was then transitioned to oral voriconazole. He recovered and was discharged with oral voriconazole for an additional 6 months of treatment. Nevertheless, his vision loss was permanent at discharge.

DISCUSSION

Here we report a case of locally invasive CNS aspergillosis in an immunocompromised patient with a history of low-grade B-cell lymphoma and organ-limited immunoglobulin light chain (AL) amyloidosis who presented with subacute vision loss. Aspergillosis is known to be associated with immunosuppression, particularly in those with hematologic malignancies as well as diabetes. Therefore, this diagnosis should be suspected in immunocompromised patients who present with orbital pain or vision deficits. Although voriconazole treatment was effective in clearing the infection, the patient's vision loss could have been prevented if infection was identified and appropriate treatment was initiated earlier.

Moreover, AL amyloidosis is a potential complication of any plasma cell dyscrasia that produces monoclonal immunoglobulin light chains, and treatment involves various immunosuppressive therapies and steroids.[8] The patient in our case had a history of long-term dexamethasone use, had undergone 2 rounds of chemotherapeutic treatment, and had undergone previous splenectomy. However, this combination of therapies for amyloidosis further increased his risk of serious fungal infection.[9]

With such significant risk factors, it is vital to identify early warning signs and ensure thorough workup is completed in similar immunosuppressed patients. Our patient had presented to the ED and outpatient ophthalmology on multiple occasions for a potential eye infection in the 4 months leading up to admission. Warning signs for immunosuppressed patients should include ongoing, increasing, and new alarming symptoms. Our patient had recurring visits and, at each visit, presented with new symptoms, including extension to additional eye, headaches, floaters, and progressive numbness. Identifying these presentations in patients at risk and ensuring full workup could better detect infections prior to invasive spread in the future.

Nonetheless, laboratory tests to detect aspergillosis are lacking. CSF examination is not always helpful in the diagnosis of neuroaspergillosis, but it can aid in ruling out other opportunistic infections. CSF culture is rarely positive, and a galactomannan (GM) assay may be a useful predictor of invasive aspergillosis.[10] A study by

Chong et al reported a 93.8% positive predictive value of CSF GM in patients with cerebral aspergillosis.[10] In addition, CSF polymerase chain reaction (PCR) is another emerging tool for diagnosis of cerebral aspergillosis. A study by Imbert et al showed 75% sensitivity for CSF PCR.[11] With specificity of 98.3% reported in the same study, CSF PCR can be an alternative tool that may abate the need for tissue biopsy. In addition, tissue biopsy is not always readily available. As seen in the case presented, the first biopsy was inconclusive, and on the second attempt, the team was unable to achieve adequate tissue for biopsy prior to craniotomy. Therefore, both CSF GM and CSF PCR could be interesting diagnostics tools in the event of nonavailability of tissue biopsy and negative cultures.

Invasive aspergillosis carries a high mortality rate despite treatment.[4] In the past, amphotericin B therapy was the treatment of choice for CNS aspergillosis; however, this drug produced negligible effects.[4] Recently, voriconazole has been reported to be more effective than amphotericin B, and response rates of about 35% have been achieved with voriconazole for patients with CNS aspergillosis.[3] Of note, there is extensive variability with voriconazole due to its nonlinear pharmacokinetics, requiring therapeutic drug monitoring to achieve adequate blood trough and prevent breakthrough disease.[5] To achieve optimal outcomes, a combined medical and neurosurgical treatment should be considered in all patients with this disease as it has been shown to improve survival rates.[4] The duration of antifungal therapy is not well defined, and current recommendations are to continue treatment based on clinical and radiological improvement.[5] Also, antifungal prophylaxis has been recommended in certain high-risk groups such as transplant patients; however, future research is necessary to determine if preemptive prophylaxis has a role during immunosuppression in neurosarcoidosis or amyloidosis.[12] Moreover, the role of combination therapy in neuro-aspergillosis is an area of ongoing research and has yet to be fully elucidated. Although randomized studies are lacking, limited data from a few case reports have suggested a promising role for a combination of voriconazole with caspofungin.[13]

This case underscores the challenges associated with disseminated CNS aspergillosis in immunocompromised patients—particularly those with hematologic malignancies and long-term glucocorticoid use. The intricate interplay between immunosuppression, underlying medical conditions, and opportunistic infections like aspergillosis necessitates a multidisciplinary approach for optimal management.

Despite the effectiveness of voriconazole in treating aspergillosis, the irreversible vision loss in our patient demonstrates the critical importance of early detection and intervention. Vigilant infectious disease monitoring in immunocompromised individuals, coupled with advancements in diagnostic tools such as CSF galactomannan and CSF PCR, potentially could enhance the timeliness and accuracy of diagnosis.

As we continue to unravel the intricacies of CNS aspergillosis, future research should focus on refining combination therapies, exploring prophylactic measures during immunosuppression in conditions such as neurosarcoidosis or amyloidosis, and improving laboratory tests for early detection.

CONCLUSIONS

We present a case of CNS aspergillosis in an immunocompromised patient resulting in permanent vision loss bilaterally for this patient. This case highlights the importance of infectious disease monitoring in immunosuppressed patients, aggressive workup upon onset of any concerning signs and symptoms, and the need for a multidisciplinary approach involving infectious disease, ENT, ophthalmology, and neurology in a complex scenario to achieve the best outcomes. Collaborative efforts across medical disciplines and ongoing research endeavors will be instrumental in improving outcomes for patients facing disseminated CNS aspergillosis. The lessons learned from this case contribute to the growing body of knowledge in the field, emphasizing the continuous pursuit of advancements that can positively impact patient outcomes.

Funding/Support: None declared.

Financial Disclosures: None declared.

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An Eye for an Eye, An Ear for an Ear: A Midwestern Case Report of Vogt-Koyanagi-Harada Disease

Neil Dixit, MD; Emily Koller, MD; Nicole Avendaño, MD; Pinky Jha, MD

ABSTRACT

Introduction: Vogt-Koyanagi-Harada (VKH) disease is an autoimmune condition affecting both ocular and extraocular systems. This case highlights the need for research into the epidemiology and pathophysiology of VKH.

Case Presentation: A 23-year-old cisgender Hispanic female presented to our tertiary care center with severe headache, eye pain, vision changes, photophobia, hearing loss with tinnitus, phonophobia, nausea, vomiting, and vertigo. She was diagnosed with VKH disease.

Discussion: This report shares a case of VKH disease in the Midwestern United States. A 2023 Northwestern University study highlights the orphan nature of the disease; even with a small sample size, that study proved to be a larger cohort in studies of VKH.

Conclusions: This report contributes to the growing literature documenting VKH disease. Especially in diagnoses associated with certain racial groups, a broad differential diagnosis is essential, as delay in diagnosis may result in irreversible sequelae. Prompt coordination with colleagues may reduce subsequent morbidity and mortality.

INTRODUCTION

Vogt-Koyanagi-Harada (VKH) disease is an autoimmune, inflammatory condition characterized by a constellation of symptoms affecting the eyes, ears, integument, and meninges, classically associated with bilateral granulomatous uveitis.[1] Since the first cases of what would be eventually known as VKH were described in the early 1900s, much progress has been made in understanding its pathophysiology, course, and treatment.[1] The current understanding of VKH disease posits that a T-cell mediated autoimmune response to antigens present on melanocytes plays an integral role in the disease.[1] Early identification and treatment of VKH with combined steroidal and nonsteroidal immunosuppression is imperative to prevent chronic evolution of the disease, including permanent vision loss.[2,3] This report of a Wisconsin-based case of VKH disease highlights the need for continued research on its epidemiology and management, as well as the importance of maintaining suspicion for this disease in all patients presenting with unexplained uveitis.

CASE PRESENTATION

A 23-year-old cisgender, Hispanic female with no significant past medical history presented from an outpatient ophthalmology clinic to a tertiary care center in the northern Midwest during the late winter months. She reported 3 weeks of severe headache described as the worst of her life, eye pain, vision changes, photophobia, hearing loss with tinnitus, phonophobia, and vertigo when supine, as well as nausea and vomiting. She had presented previously to an outside hospital and initially received erythromycin ointment, followed by reevaluation and treatment with trimethoprim-polymyxin B drops. Despite these treatments, she said that her symptoms continued and only her pain improved with ibuprofen.

Admission vitals were unremarkable except for low blood pressure, which was found to be her baseline. Initial laboratory studies revealed no electrolyte or metabolic derangements, though platelet count was elevated to the mid-500 000 range (laboratory range: 165 000-366 000). Infectious workup with QuantiFERON-Tb Gold+ testing, HIV 1/2 antibody and antigen, and treponemal serology were overall reassuring. A treponemal antibody screen as well as rapid plasma reagin (RPR) were obtained to rule out ocular syphilis, as it was noted that the RPR

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test cannot safely rule out ocular syphilis, which is in line with expert opinion that suggests performing antibody testing as the initial screen for ocular syphilis.[4] Chest x-ray showed no sign of an acute cardiopulmonary process. Magnetic resonance imaging (MRI) was not performed, though computed tomography (CT) head without contrast from the month prior to admission showed no intracranial abnormality.

Ophthalmology and otolaryngology were consulted given vision and hearing impairment. Ophthalmology exam also revealed keratic precipitates and vitritis bilaterally. On the initial ophthalmology exam, visual acuity was 20/200 in the right eye (OD) and only for hand motion in the left eye (OS), with pinhole visual acuity as follows: OD 20/70-1, OS 20/400. Maximum noted intraocular pressure (IOP) on admission was OD 20 mmHg and OS 28 mmHg, both of which are elevated. Over the admission, IOP ranged from OD 13 to 22 and OS 15 to 28. Further ocular study showed choroidal thickening on B-scan ocular ultrasound, hyperreflective vitreous opacities and paracentral acute middle maculopathy (PAMM) lesions on optic coherence tomography (OCT) and optic nerve leakage on fluorescein angiography. Serous retinal detachments were not commented on by ophthalmology in this case, though these findings are commonly found on OCT in VKH disease.[5] Otolaryngology, on exam, found Weber test lateralized to the left, and Rinne test with air conduction favored over bone conduction bilaterally, consistent with sensorineural hearing loss.

Based on the patient's clinical presentation and negative workup for alternative etiologies adequately explaining her constellation of symptoms, the diagnosis of VKH disease was made, though the differential diagnosis included infectious conditions and other autoimmune conditions such as sarcoidosis, Cogan syndrome, and Susac syndrome.

The patient was started on intravenous (IV) methylprednisolone with improvement of ocular and meningismus symptoms by day 4, followed by a 24-hour trial period of oral prednisone prior to discharge. For the ocular manifestations of VKH disease, she was started on several bilateral eye drops: prednisolone every 2 hours, dorzolamide hydrochloride-timolol hydrochloride twice daily, and cyclopentolate twice daily. There was improvement in the visual acuity to 20/20 in each eye and in her IOP to OD 13 and OS 15. Auditory symptoms had improved somewhat, though outpatient follow-up with otolaryngology was necessary to monitor for ongoing hearing loss.

On outpatient follow-up with ophthalmology 5 days after discharge, elevated IOP and PAMM lesions noted on OCT were both observed to have improved. The patient began a prednisone taper and started difluprednate eye drops to alleviate the improved, though ongoing uveitis. At this follow-up visit, ophthalmology planned to start the patient on immunomodulatory therapy if ocular inflammation recurs, which is of high likelihood in VKH. Otolaryngology follow-up was significant for ongoing tinnitus, torsional nystagmus with left-sided Dix-Hallpike maneuver, and left benign paroxysmal positional vertigo. The Epley maneuver was performed twice and a referral for a vestibular evaluation was placed. MRI of the head was ordered to rule out intracranial pathology for her otolaryngological findings.

DISCUSSION

We describe the case of incomplete VKH disease in a patient who presented with vision loss, hearing loss, and symptoms of meningismus.

The first probable descriptions of VKH date to the early 20th century.[1] In 1906, Swiss ophthalmologist Alfred Vogt described a case in which his patient was noted to have eyelash whitening (poliosis), as well as concomitant intraocular inflammation.[1] Several years later in Japan, ophthalmologists Jujiro Komoto and Yoshizo Koyanagi both noted a similar presentation in a handful of their patients, publishing their findings in a German and Japanese medical journal, respectively.[1] In 1929, Koyanagi published a report detailing 16 additional cases where he described the natural course of what would eventually be termed Vogt-Koyanagi-Harada disease.[1] Koyanagi noted that there was no current treatment.[1] Japanese ophthalmologist Einosuke Harada observed a similar constellation of symptoms in several of his patients, which he described in the mid-1920s and referred to as Harada's disease.[1] Recognizing the similarities among cases reported in Switzerland and Japan, Professor Jean Babel of Geneva proposed the name Vogt-Koyanagi syndrome.[1] In 2001, the disease became formally known as Vogt-Koyanagi-Harada disease.[3]

Vogt-Koyanagi-Harada disease affects individuals during the second to fifth decade, especially females with high melanin pigments in their skin.[6] The prevalence of the disease varies widely across the world, and it is considered rare in the United States.[3] In India, VKH disease is the most common cause of panuveitis, with prevalence 21.08%; in Japan, its prevalence is 6.7% to 11%, with an incidence of approximately 800 new cases each year.[7] VKH is reported at higher rates among those of Asian, Hispanic, Middle-Eastern, First Nation, Metis, and Inuit origin.[8] In a recent study on demographics of patients diagnosed with VKH disease at Northwestern University, more than 50% of patients self-reported as non-Hispanic White or Black/African-American.[8]

Though our patient identified with an ethnic group classically associated with VKH disease in the literature, it is essential to assess the clinical picture and not discount the diagnosis of VKH based on a patient's race or ethnicity, as doing so may lead to delayed diagnosis and treatment.[8] The authors suggest that the low prevalence of VKH may be attributed to this condition being underrecognized and underreported.[8]

The underlying mechanism of this disease is thought to be the result of autoimmune processes. Specifically, CD4+ and Th17 T cell-directed responses toward melanocyte-specific antigens

derived from tyrosinase peptides and melanocyte-specific antigens are thought to play a major role in its pathophysiology.[3,9] This autoimmune mechanism raises concern for viral triggers of the disease. VKH disease following both infection and vaccination has been reported for multiple infectious agents, including COVID-19, tuberculosis, and influenza A, among others.[9] The relationship between VKH and viral triggers is of particular interest in the wake of the COVID-19 pandemic caused by the SARS-CoV-2 virus and related vaccination.[9] Though reports of VKH disease following COVID-19 infection and vaccination exist, there has not been an identifiable change in VKH epidemiology following the pandemic.[9] For VKH following either COVID-19 vaccination or infection, there may be a relationship with the HLA class II antigen, namely HLA-DR4, though the exact nature of this possible genetic susceptibility to VKH remains to be fully elucidated.[9] Molecular mimicry, as well as adjuvants and additives in the vaccine formulations, also have been posited to play a role in precipitating VKH following vaccination.[9] Though it remains one of the most common causes of uveitis following infection, the unlikely possibility of VKH disease following vaccination against SARS-CoV-2 should not preclude vaccination.[9]

Multiple attempts to classify the signs and symptoms into standardized diagnostic criteria have been made.[3,6] The Revised Diagnostic Criteria developed in 2001 stratify the disease into "incomplete," "complete," and "probable" VKH.[3] Incomplete VKH disease requires the lack of ocular trauma, no findings suggestive of other ocular disease, and bilateral ocular involvement, with either neurological and auditory findings or integumentary involvement.[3] Complete VKH requires all of the previous criteria to be met.[3] Probable VKH does not require neurological, auditory, or integumentary involvement.[3]

There is no definitive laboratory test for diagnosing VKH disease.[3] As a result, the diagnosis is based on the clinical presentation and exclusion of history of ocular trauma or surgery, followed by ophthalmological examination and evaluation to rule out any infectious or other causes of ocular pathology.[3] Though not routinely performed in the United States for this indication, cerebrospinal fluid may be collected via lumbar puncture to assess for pleocytosis—namely in Japan and Europe—though this remains a controversial component of evaluation.[3]

The ocular and integumentary findings in VKH will vary depending on the stage of disease at presentation. VKH may present in 1 of 4 phases: prodromal, uveitic, convalescent, and recurrent.[3,6] In its earlier phases, typical optical findings include optic disk hyperemia, bilateral granulomatous panuveitis, and serous retinal detachments.[8,10] Meningismus signs, such as the headache, nausea, vomiting, and photophobia seen in our case, present in the prodromal phase of VKH.[1] As the disease progresses to the convalescent phase, ocular findings include depigmentation of the retina (ie, the classically associated "sunset glow fundus") and chronic anterior uveitis, while integumentary findings include vitiligo and poliosis.[8,11]

Several imaging modalities—namely optical coherence tomography (OCT) and fluorescein angiography (FA)—are used to diagnose VKH. Indocyanine green angiography also has been used.[5] Optic coherence tomography (OCT) has been studied as an optic imaging tool to assist in VHK diagnosis.[5] OCT can show subretinal hyperreflective opacities as well as choroidal thickening in the acute phase of VKH.[5] Fluorescein angiography shows leakage in VKH, which correlates with the subretinal and intraretinal fluid collection noted on OCT.[5] Other long-term, extraocular findings include pigmentary changes of the integument, such as poliosis, alopecia, or vitiligo, that occur after the onset of uveitis.[12]

Ocular outcomes may improve with rapid initiation of treatment in the acute phase of VKH, though more research is needed to elucidate the role of treatment timing and stage of disease at presentation in preventing ocular and extraocular manifestations of the disease.[13] Our case of VKH disease demonstrates the importance of multidisciplinary approach, where the primary care team coordinates care with colleagues in otolaryngology, neurology, ophthalmology, and dermatology to ensure prompt diagnosis and treatment.

High-dose, systemic corticosteroid therapy with eventual transition to nonsteroidal immunosuppression, such as mycophenolate mofetil, and steroid taper, is the mainstay of treatment for patients with acute VKH disease.[3] Treatment with both prolonged oral corticosteroids and IV methylprednisolone bolus for 3 to 5 days has been shown to provide similar visual recovery and final visual acuity in patients who experienced vision loss; however, Accorinti et al found in patients initially treated with IV corticosteroids, long-term recurrence of the disease and risk of requiring further intervention was lower when compared to patients initially treated with oral corticosteroids, possibly due to a longer follow-up period in their study.[14] While early treatment is essential in the proper management of VKH disease, patients may require long-term immunosuppression with immunomodulators.[5] There is evidence that both mycophenolate mofetil and corticosteroids may be efficacious in the treatment of acute VKH with reduction in recurrent inflammation compared to treatment with only corticosteroids.[3] There is ongoing research examining the possible role of biological response modifiers in long-term treatment for VKH, with case reports suggesting response in immunosuppression-resistant cases.[3,5]

The prognosis and complications associated with VKH depend largely on when the diagnosis is made and treatment is initiated.[3] There has been suspicion that VKH has a window of opportunity to initiate treatment following disease onset for best outcomes.[14,15] Other factors that affect prognosis include age at onset of disease, duration of disease, number of recur-

rent episodes of inflammation, and number of complications associated with disease.[12] One study showed that treatment with high-dose corticosteroid combined with immunomodulators initiated within 3 months caused a significant reduction in risk of progression to chronic recurrent uveitis.[16] Another study showed that if treatment with mycophenolate mofetil and systemic corticosteroids is initiated within 2 to 3 weeks from symptom onset, progression to chronic recurrent granulomatous inflammation and development of "sunset glow fundus" can be prevented.[17] Herbort et al suggested that aiming for adequate treatment with both steroidal and nonsteroidal immunosuppression within 2 to 3 weeks of symptom onset and monitoring for findings of subclinical choroiditis via indocyanine green angiography with the intention to increase therapy if necessary can induce cure prior to depigmentation of the retina.[15] If VKH disease is left untreated, recurring granulomatous anterior uveitis, stromal iris atrophy, posterior synechiae, and Busacca nodules may occur.[6,18] Additionally, the development of posterior subcapsular cataracts, glaucoma, and subretinal fibrosis can occur, leading to permanent and complete vision loss.[6,18]

This case highlights the importance of considering a broad differential, especially with regard to diagnoses typically seen in specific racial or ethnic groups, as delay in diagnosis and treatment may result in irreversible disease progression. This case also emphasizes the importance of the primary medicine team acting as a facilitator of communication between consulting subspecialties, ensuring prompt diagnosis and adequate management to improve outcomes. Given the rarity of this condition, the majority of studies on VKH necessarily draw from small sample sizes, which hampers the generalizability of the research findings. Finally, this report illustrates the necessity of both continued research to help better understand the epidemiology and demographic patterns of this disease and a multidisciplinary approach to management.

CONCLUSIONS

We present a clinical case of Vogt-Koyanagi-Harada disease–a rare, inflammatory, autoimmune disorder–to increase awareness of this condition among health care professionals. Early recognition and treatment can prevent long-term morbidity, including permanent vision loss. This report aims to encourage further research by adding to the existing literature on VKH disease.

Funding/Support: None declared.

Financial Disclosures: None declared.

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Intentional Hydroxychloroquine Overdose Leading to Severe Hypotension and Multiorgan Failure

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ABSTRACT

Introduction: The use of hydroxychloroquine for treating malarial infections and certain autoimmune diseases is well established, but data on hydroxychloroquine overdose and management are relatively scarce. Given its increased use in recent years and because life-threatening symptoms can occur within hours of ingestion, it is important to understand its potential for toxicity and available treatment options.

Case Presentation: We present a case of a 43-year-old male with intentional overdose of 6 grams hydroxychloroquine, along with 6 grams trazodone and 30 grams metformin. He presented in respiratory failure, later developing severe hypokalemia and electrocardiogram abnormalities. He was managed with activated charcoal, intravenous 20% lipid emulsion, intravenous epinephrine, intravenous diazepam, and intravenous sodium bicarbonate, which resulted in clinical improvement. Unfortunately, aspiration pneumonia and severe hypotension led to fatal multiorgan failure.

Discussion: This case highlights the potential treatment options for hydroxychloroquine overdose, given its more recent use in the treatment of COVID-19 and increased incidence of toxicity.

INTRODUCTION

Hydroxychloroquine's role in malarial infections and certain autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis, is well established. Additionally, hydroxychloroquine has been used more frequently in recent years, given its off-label use in treating coronavirus disease 2019 (COVID-19). Despite its increased use, data on hydroxychloroquine overdose and management are relatively scarce. As life-threatening symptoms can occur within hours of ingestion, it is important to know about the potential for toxicity and available treatment options.

Based on the American Association of Poison Control Centers 2022 annual report, of the 2 065 875 human exposures, hydroxychloroquine toxicity was found in 7 cases.[1] This is an increase from the 2021 report of 2 851 166 human exposures with 5 hydroxychloroquine toxicity cases leading to death.[2]

The surge in COVID-19 cases in 2020 created a desperate search for potential treatment options, and it was hypothesized that hydroxychloroquine, among other treatment options, could be helpful.[3] The US Food and Drug Administration (FDA) approved emergency use of hydroxychloroquine for COVID-19 in 2020, later ending this approval when hydroxychloroquine was shown to be ineffective.[4] Later, the World Health Organization released a statement recommending against the use of hydroxychloroquine in the treatment of COVID-19.[4,5] Despite this, it is still used intermittently as an off-label treatment option, which may be a reason for the slight increase in toxicity cases.

We present a case of an intentional multidrug overdose that included hydroxychloroquine in which treatment attempts were not successful.

CASE PRESENTATION

We present a case of a 43-year-old, 160.2 kg male with an intentional overdose of 6 grams hydroxychloroquine, along with 6 grams trazodone and 30 grams metformin. These amounts were estimated based on pharmacy records of his most recent

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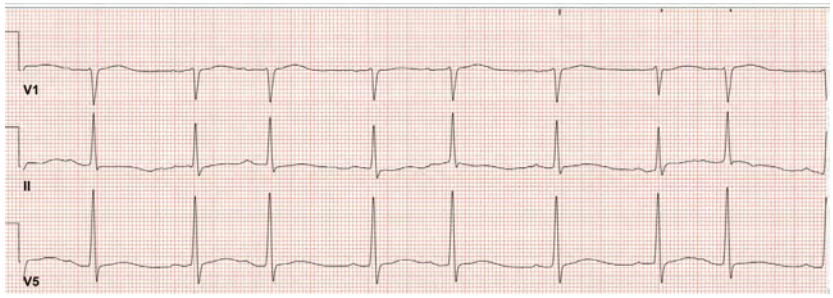
refill, the remaining amount of medication left in the prescription bottles, and information provided by his family. It was unknown how much time elapsed between ingestion and presentation. On presentation, he was obtunded and was intubated in the emergency department for acute hypoxic respiratory failure. Initial laboratory results showed an anion gap metabolic acidosis, a lactate level of 4.2 mmol/L, and electrolyte levels within reference range, including a potassium level of 3.8 mmol/L. Within 4 hours of admission, he developed severe hypokalemia of 1.7 mmol/L and his lactate peaked at 19.1 mmol/L. His anion gap peaked at 27 with bicarbonate as low as 12 mmol/L. His electrocardiogram (ECG) (Figure 1) demonstrated prolonged PR interval, QRS complex, and corrected QT interval (QTc). The regional poison control center was consulted and actively followed the patient.

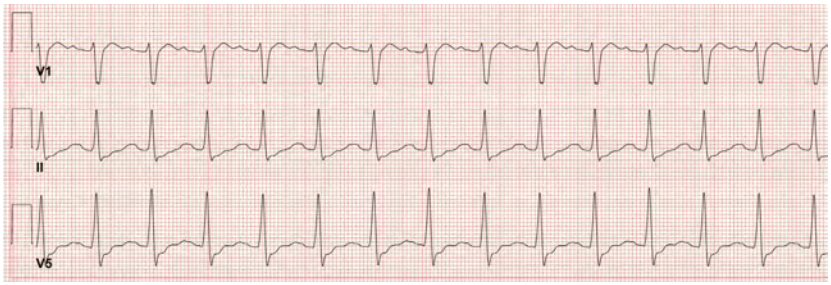
Based on limited case reports, the patient was given activated charcoal via nasogastric (NG) tube followed by intravenous (IV) 20% lipid emulsion within 1 hour of arrival. He was treated with IV epinephrine and IV diazepam 1 mg/kg/day after loading 1 mg/kg. IV sodium bicarbonate drip was started to treat the prolonged QRS interval, and a dose of calcium gluconate was given to treat the prolonged QTc interval. This was effective initially, as demonstrated by his improved ECG (Figures 2 and 3). His refractory hypokalemia was treated successfully with aggressive replacement of both oral (via NG tube) and IV potassium, fluctuating between 20 to 60 mEq doses based on his potassium levels, which were checked hourly with a goal of maintaining levels above 4 mmol/L. IV potassium was replaced with a central line for quicker replacement due to refractory and severe hypokalemia. This was stopped when the patient developed hyperkalemia with potassium at 5.4 mmol/L. His pH, anion gap, and bicarbonate showed slight improvement but did not normalize. His lactate trended down slightly to 14.6 mmol/L.

Figure 1. Electrocardiogram at Presentation



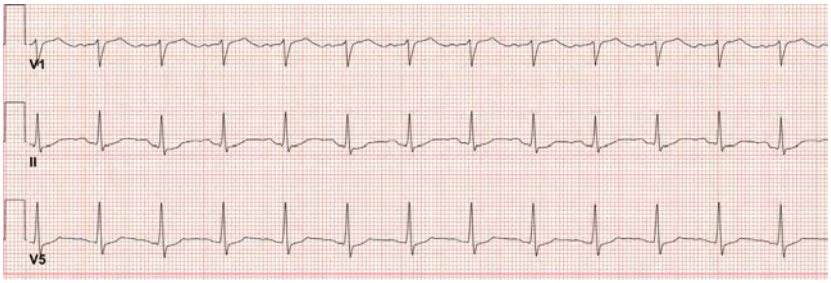
Electrocardiogram showing QRS duration of 130 ms, corrected QT interval of 538 ms, PR interval of 204 ms, ventricular rate of 65 beats/minute and nonspecific T wave changes.

Figure 2. Electrocardiogram Four Hours After Presentation



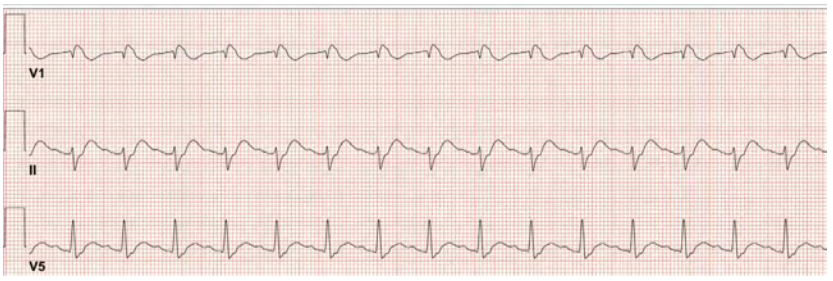
Electrocardiogram showing QRS duration of 138 ms, corrected QT interval of 587 ms, PR interval of 136 ms, ventricular rate of 106 beats/minute, and mild ST segment depression.

Figure 3. Electrocardiogram 18 Hours After Presentation



Electrocardiogram showing QRS duration of 108 ms, corrected QT interval of 486 ms, PR interval of 182 ms, ventricular rate of 96 beats/minute, and normal sinus rhythm.

Figure 4. Electrocardiogram 40 Hours After Presentation



Electrocardiogram showing QRS duration of 138 ms, corrected QT interval of 587 ms, PR interval of 136 ms, ventricular rate of 106 beats/minute, and mild ST segment depression.

The patient started to show clinical improvement with normalizing vitals and improvement in his ECGs, but within 40 hours of presentation, he developed aspiration pneumonia secondary to his altered mental status. His ECG (Figure 4) began to show prolongation in QRS and QTc intervals, and he developed severe hypotension leading to multiorgan failure, which ultimately was fatal. Given the long half-life of hydroxychloroquine and his recent consumption, his decline was attributed to multidrug ingestion.[6]

DISCUSSON

Hydroxychloroquine is toxic at daily doses greater than 400 mg and cumulative doses greater than 1000 grams.[6,7] Severe intoxication is defined as ingestions in excess of 4 grams, which can lead to hypotension or fatal ventricular arrhythmias.[8] The most common signs of toxicity are cardiovascular collapse, central nervous system and respiratory depression, convulsions, coma, nausea, vomiting, hypokalemia, hypotension, and widening of the QRS and QT intervals.[8]

Intracellular shift of potassium can be severe, and aggressive replacement is the mainstay of treatment. In our case, the patient originally showed a normal potassium level, which then changed to severe hypokalemia as the case progressed. This is likely due to the transient effect of the intracellular shift once hydroxychloroquine levels start to drop.[8] It also could be due to his treatment with epinephrine and bicarbonate, which both can increase the intracellular shift of potassium.[9,10] Once the potassium was corrected, the patient started to improve despite originally presenting with a prolonged PR, QRS, and QTc interval, reinforcing that the management of potassium remains important in the overall treatment of overdose with hydroxychloroquine.

Diazepam, epinephrine, and lipid emulsion were administered for neurocardiac protection, although evidence is limited. The suggestion for diazepam comes from several past studies that noted limited cardiovascular toxicity with co-ingestion of both chloroquine and diazepam.[8] It has since become an additional treatment option for hydroxychloroquine toxicity for its potential to prevent cardiovascular toxicity. Epinephrine is used frequently to treat resultant hypotension due to the toxicity of hydroxychloroquine. This was used in our case to prevent cardiovascular collapse.

Our patient was treated with activated charcoal in an effort to achieve gastrointestinal decontamination, despite an unknown time from ingestion to clinical presentation. This decision was based on limited case reports of hydroxychloroquine toxicity available and studies reporting that activated charcoal binds well to hydroxychloroquine when administered shortly after ingestion.[10,11] Of note, there also have been reports of limited effectiveness of activated charcoal. Specifically, it has been associated with increased frequency of speech impairment, coma, and aspiration—even when given via nasogastric tube.[12,13] Our patient presented with altered mental status and was intubated prior to administration of activated charcoal, limiting his aspiration risk. However, he was found to have severe hypotension secondary to his multidrug toxicity as the case progressed.

Finally, lipid emulsion has long been considered a treatment option for toxicity involving various substances. In this case, it was administered specifically due to the limited number of case reports available describing chloroquine and hydroxychloroquine toxicity.[14-16] It also has been postulated as a treatment option in trazodone overdose.[17] Although the mechanism remains debated, one hypothesis suggests the existence of a lipid compartment within the blood and highly perfused organs. This compartment may sequester lipid-soluble drugs within the vascular space, thereby dissolving the substance and reducing its availability for tissue toxicity.[18] In addition to this effect, lipid emulsion may enhance cardiac contractility, which would counteract the cardiac depression seen in hydroxychloroquine overdose.[18] Specific indications to use lipid emulsion therapy include hemodynamic instability that persists despite other resuscitation measures such as fluid replacement, inotrope support, and vasopressor administration—factors that contributed to the decision to initiate this treatment in the present case.[19]

There is limited literature available on trazodone overdose, with only a few case reports suggesting the use of lipid emulsion and diazepam for neuroprotection—an approach that parallels treatment strategies for hydroxychloroquine toxicity.[17,20] In contrast, metformin overdose has been studied more extensively. Metformin is known to cause metabolic lactic acidosis in both therapeutic and toxic doses.[21] Previous studies have demonstrated that metformin concentration greater than 50 μ/mL are associated with a 38% mortality rate.[21] Standard treatment typically includes renal replacement therapy or IV sodium bicarbonate[21] to treat the acidosis.[22] Additional treatment options include prevention of complete drug absorption through activated charcoal or gastric lavage.[22] In the present case, we administered IV sodium bicarbonate, which appeared to mitigate the toxic effects associated with metformin exposure.

CONCLUSIONS

Although this case ended in a fatal outcome, it offers valuable insights into the management of hydroxychloroquine toxicity—a relatively rare clinical presentation. Potassium replacement—administered both orally and via IV—played an integral role in the case and contributed to temporary clinical improvement. The replacement of potassium remains the mainstay of treatment, supported by adjunctive therapies such as diazepam, epinephrine, and lipid emulsion to assist with cardiac and neurologic protection. Additionally, sodium bicarbonate proved beneficial in managing this multidrug ingestion, particularly in treating the metabolic acidosis associated with metformin toxicity. It is important to note that these findings are based on a single patient and further research is needed to make definitive conclusions.

Funding/Support: None declared.

Financial Disclosures: None declared.

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Subacute Combined Degeneration of the Spinal Cord From Nitrous Oxide Abuse

Lauren Beranek, MD; Satchel Beranek, MD; Benjamin Kaster, MD

ABSTRACT

Introduction: The recreational use of nitrous oxide is surging in popularity, with nearly 13 million Americans aged 12 and older reported to have misused it, according to a 2019 survey by the Substance Abuse and Mental Health Services Administration. Prolonged use has been linked to significant neurological deficits, potentially leading to lifelong issues if not treated early.

Case Presentation: We present a case of a 38-year-old male with significant neurologic deficits attributed to prolonged nitrous oxide abuse, resulting in subacute combined degeneration of the spinal cord. This condition is characterized by demyelination of dorsal and lateral columns.

Discussion/Conclusions: The growing recreational use of nitrous oxide, facilitated by its easy availability and lack of regulation, highlights the importance of clinician vigilance in managing associated risks. Neurological symptoms from vitamin B12 deficiency are particularly worrisome. Early intervention is crucial to prevent potential long-term consequences.

INTRODUCTION

Vitamin B12 is a necessary coenzyme in biochemical processes in the human nervous system. It plays a crucial role in the formation of the myelin sheath, insulating neurons and allowing for efficient transmission of impulses down their axons.[1] Deficiencies in vitamin B12 can lead to loss of neuronal myelination, resulting in motor and sensory neurological symptoms.[1] A well-balanced diet will provide adequate vitamin B12 as it is naturally found in fish, meat, eggs, and dairy products.

Nitrous oxide is a colorless and odorless gas that has a long history of medical use for anesthesia and anxiolytic purposes.[2] It also has been used as a recreational substance for many decades, producing a short-lived euphoria (around 1 minute) when inhaled.[2] Street names for nitrous oxide include laughing gas, nitro, NOS, nangs, whippets, hippy crack, canisters, and balloons. It remains legal and loosely regulated in many countries, including the United States, where it is readily available in stores and online. It is often sold under the guise of use in the food industry as a propellant and bacteriostatic agent in whipped cream and is available in small single-use canisters or larger bottles that can hold multiple "doses." Statutes on possession limits and intentional inhalation differ depending on local jurisdictions. As of 2020, the National Survey on Drug Use and Health reported a 4.7% lifetime prevalence in those 12 years old and older of recreational nitrous oxide in the US.[3]

The detection of nitrous oxide use is usually not feasible in a clinical setting due to its short half-life in the blood (5 minutes).[4] It is not commonly reported on serum or urine drug screens. Clinicians should instead focus on taking a thorough substance use history, especially in patients who present with neurological findings. Clarifying the quantity and duration of use is important as there is a dose-dependent relationship with adverse neurological effects.[5]

Vitamin B12 Measurement

Vitamin B12 levels are most commonly measured using a chemiluminescence assay; however, this does not always reflect actual total body B12 stores but rather the protein-bound B12 in the serum.[6] It is possible to have B12 deficiency despite having a normal value on a serum B12 assay. Therefore, other biomarkers in the cyanocobalamin metabolism pathway are used to help quantify actual B12 stores. Methylmalonic acid (MMA) is a useful test and

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may be elevated in a setting of true B12 deficiency, as B12 is a necessary cofactor for its conversion to succinyl-COA.[6] MMA can be a useful test when serum B12 levels are normal but suspicion of deficiency remains high.

Nitrous Oxide Mechanism of Reducing B12

Vitamin B12 plays a crucial role in cellular DNA production by serving as a co-factor for enzymes of methionine synthase and methyl-malonyl CoA mutase. Methionine synthase carries out the conversion of homocysteine to methionine. Methionine is then converted to S-adenosyl methionine, which serves as a methyl group donor to myelin basic protein (MBP). Without methylation of MBP, the myelin sheath is more susceptible to damage. The second enzyme, methyl-malonyl CoA mutase, is directly involved in myelin production. Therefore, B12 deficiency may impair new myelin production and leave existing myelin more prone to insult.[6]

B12 deficiency in nitrous oxide poisoning has a unique mechanism as it represents a functional deficiency. Nitrous oxide acts on the cobalt atom in vitamin B12, causing it to become irreversibly inactivated and unable to serve as a cofactor in the processes described above.[6] The risk of neurologic symptoms from nitrous oxide abuse is dose-dependent and more likely to occur with long-term use.[5]

Subacute Combined Degeneration

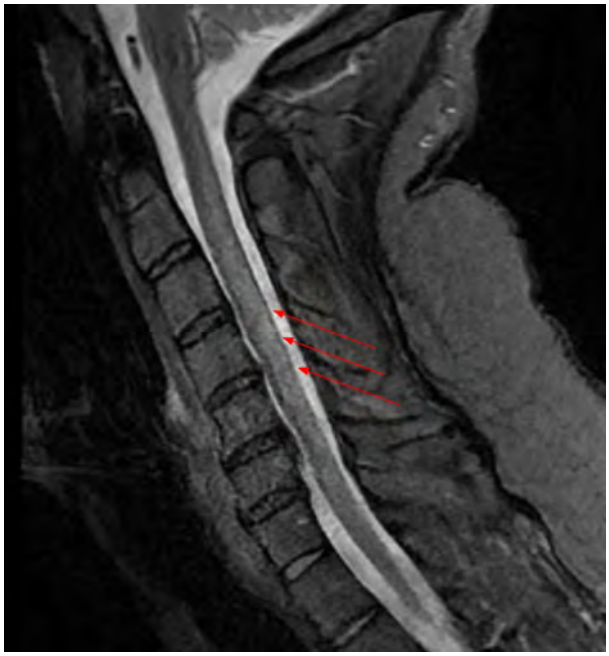
Subacute combined degeneration is a neurological syndrome that arises as a complication of vitamin B12 deficiency. The signs and symptoms stem from demyelination of neurons in the spinal cord.[6] Subacute combined degeneration is preferential to the dorsal and lateral columns of the spinal cord, and the clinical syndrome presents accordingly. Involvement of the dorsal column leads to paresthesias (often the earliest sign) and impaired proprioception and vibratory sensation. Both the upper and lower extremities can be affected. Balance also may be impaired secondary to proprioception. The lateral column carries the corticospinal tract, which is responsible for motor function of the limbs. Demyelination at this site can manifest as muscle weakness, and upper motor neuron signs, such as spasticity and hyperreflexia, may be present.[6] Normocytic or macrocytic anemia also may be present; therefore, the absence of macrocytic anemia does not rule out subacute combined degeneration.[7]

Prognosis

Generally speaking, treatment of subacute combined degeneration with B12 replacement will arrest the progression of the disease and lead to partial reversal of the neurological complications. A small retrospective review of 57 patients showed that 86% of patients had symptom improvement with B12 replacement, but only 14% had complete resolution of their symptoms.[8]

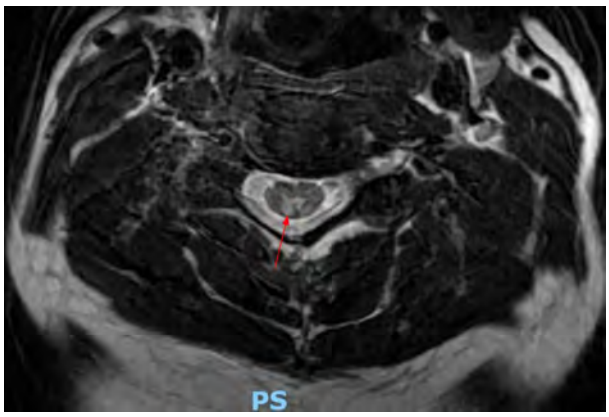
We present a case of a patient with significant neurologic deficits attributed to prolonged nitrous oxide abuse, resulting in subacute combined degeneration of the spinal cord.

Figure 1. Magnetic Resonance Imaging of the Dorsal Spine



Hyperintense T2 signal in the dorsal spinal column extending over several levels of the cervical spine.

Figure 2. Magnetic Resonance Imaging of the Cervical Spine



Classic subacute combined degeneration findings of hyperintense T2 signal affecting the dorsal columns.

CASE PRESENTATION

A 38-year-old male with a past medical history of polysubstance abuse presented to the hospital with altered mental status, psychosis, and generalized weakness. He reported using nitrous oxide multiple times daily over the past several months. He also used recreational cannabis during that time period. He had a history of alcohol dependence with previous withdrawal seizures, but he was not using alcohol in the months leading up to his presentation. Initially, the patient's altered mentation, agitation, and psycho-

sis prevented a comprehensive neurological evaluation. He experienced visual hallucinations and was very irritable for the first few days of his hospitalization, which led to the administration of antipsychotic medications. As his mentation cleared, his weakness became more apparent, and a neurological workup was initiated. Imaging and laboratory workup were performed over the course of his hospitalization. His vitamin B12 on admission was low at 204 (reference range 232-1245) and MMA was significantly increased at 14.37 (reference range 0.00-0.40). He had a mild normocytic anemia with a hemoglobin of 11.7 and a mean corpuscular volume of 94.9 (reference 81.5-99.0).

Neurological exam performed on day 6 of hospitalization was significant for bilateral lower extremity weakness, impaired vibration and proprioception below the waist, and patellar and achilles hyperreflexia. His sensory deficits were symmetric and in a graded fashion proximal to distal. He had a positive Babinski sign and multiple beat clonus in his bilateral ankles. There were findings of upper extremity weakness as well, with 3/5 strength of intrinsic finger muscles and 4/5 wrist extension and grip. He had no cranial nerve deficits, dysarthria, ataxia, or dysmetria.

The patient's symptoms were suspicious for a spinal cord etiology, prompting cervical and thoracic spine magnetic resonance imaging (MRI). The MRI revealed an abnormal T2 hyperintense signal in the dorsal spinal cord consistent with subacute degeneration seen in nitrous oxide abuse (Figures 1 and 2). The patient initially required a mechanical lift for transfer. He was able to stand for short periods of time but could not ambulate and needed assistance with activities of daily living, including dressing and toileting.

Follow-up and Outcome

The patient was treated with intravenous B12 at a dose of 1000 mcg every other day along with high-dose folic acid (4 mg daily). He worked intensively with physical and occupational therapy. Over the course of 6 weeks, he gradually regained both motor and sensory function. At the time of his discharge, he was able to ambulate with the assistance of a 4-wheeled walker and subjectively regained most of his lower extremity sensation. His upper extremities improved more quickly and, at discharge, he had full use and normal sensation. Additionally, his serum B12 levels measured above the upper limit of normal and his MMA had normalized. He was discharged on 1000 mcg of oral B12 and 800 mcg of folic acid daily and was set up with outpatient neurology, physical therapy, and addiction medicine.

The patient was discharged from physical therapy after approximately 3 months due to financial constraints. He did show improvements in lower extremity strength during the course of physical therapy, ambulating with a cane at the time of discharge rather than a 4-wheeled walker and able to independently perform activities of daily living. He self-increased his oral B12 to 2000 mcg once a week, which was continued due to patient preference and low risk for toxicity. Additionally, he continues to take folic acid 800 mcg daily and is actively working with addiction medicine for his polysubstance abuse.

DISCUSSION

Subacute combined degeneration of the spinal cord (SCD) is a demyelinating condition of the dorsal and lateral columns of the spinal cord commonly seen in vitamin B12 deficiency. Due to nitrous oxide's effect on vitamin B12 activation, nitrous oxide misuse is a rare, yet possible cause of SCD. Patients with SCD may present with numbness, weakness, impaired vibration and proprioception, psychosis, normocytic or macrocytic anemia, and upper motor neuron symptoms.[9] Additionally, in patients with polysubstance abuse, as seen in this case, symptoms initially may be masked by substance intoxication making diagnosis challenging. Given the rise in recreational use of nitrous oxide, it is now essential to include questions about this substance in drug screenings. Important questions to ask include the quantity and duration of misuse as there is a dose-dependent relationship with adverse neurologic effects.[5] A thorough social history can help identify medical issues related to B12 deficiency and potentially prevent SCD if patients are educated properly.

Diagnostic workup includes a thorough neurologic examination, metabolic panel, complete blood cell count, B12 and methylmalonic acid, and MRI of the spinal cord. Of note, testing for nitrous oxide misuse is challenging as it does not commonly appear on urine or serum drug tests due to its short half-life.[4] Once a diagnosis is made, treatment typically involves aggressive supplementation of B12 to prevent irreversible neurological deficits and intensive physical therapy. Recommended dosing regimens in the acute setting include parenteral 1000 mcg of vitamin B12 every other day for at least 2 weeks, followed by B12 injections 3 times weekly for another 2 weeks. While parenteral administration is strongly preferred, oral 1000 – 2000 mcg daily B12 supplementation may be used as an alternative.[7] For reversible causes of B12 deficiency (ie, drug-induced), supplementation is required only until the deficiency is corrected and offending substance stopped.[6]

CONCLUSIONS

We present a case involving a patient with polysubstance abuse who presented with a complex combination of vague neurological symptoms, psychosis, and altered mentation. Upon further examination and history, it was discovered that he had recently misused nitrous oxide, leading to symptoms consistent with SCD. Although rare, SCD has been associated with nitrous oxide misuse. Key factors in reaching an accurate diagnosis included considering the patient's age and social history, conducting a thorough neurological examination, and understanding that normocytic anemia does not exclude B12 deficiency/inactivation. Early intervention, as this case highlights, is crucial to prevent potential long-term, life-changing consequences.

This case emphasizes the potential severity of SCD from nitrous oxide abuse, as this patient's neurological symptoms were more severe than most contemporary case reports on this condition. It also highlights the importance of including screening for nitrous oxide misuse when taking a patient's substance use history, especially in patients with neurological symptoms.

Funding/Support: None declared.

Financial Disclosures: None declared.

Acknowledgments: A statement of informed consent was received by the patient.

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Statistical Thinking in Medicine, Part 6: Creating Evidence (or What to Know Before Visiting a Statistician)

Robert A. Calder, MD, MS; Jayshil J. Patel, MD

What is evidence-based medicine? What are the different levels of evidence? Is a testimonial for some treatment considered evidence? How do we know when we have sufficient evidence to draw sound conclusions? For example, is there sufficient evidence to conclude cigarette smoking causes lung cancer? How can we apply evidence to the individual patient? These are the key questions that we will explore in this last part of our series.

What is "Evidence-Based Medicine?"

By the early 1980s, evidence in medicine was mounting and physicians asked, "How do I sift through the heap of evidence?" Thus, evidence-based medicine pioneer David Sackett introduced the concept of critical appraisal – or the systematic evaluation of clinical research evidence to assess relevance, validity, and applicability to patient care. As it turns out, the term "evidence-based medicine" was an extension of critical appraisal and was used by David Eddy in the late 1980s[1] and popularized by Gordon Guyatt and colleagues in a sentinel publication in 1992.[2]

When the term "evidence-based medicine" came into use, many health care professionals were offended by it, thinking that we have always used evidence in the practice of medicine. In 1980, I (RAC) clearly recall a situation that I thought represented the use of evidence, but, in retrospect, it did not. It was late one Sunday night in the third year of medical school when I was called to a patient's bedside, and my resident told me to put a nasogastric tube into "Mr. Smith" and irrigate his stomach with iced saline to treat his bleeding gastric ulcer. I recall being happy to do this because I thought that iced saline would cause arterioles to constrict, stopping the bleeding. I also had great confidence in whatever my resident told me to do ("eminence-based" medicine). However, I didn't realize that no randomized controlled study had ever shown this approach to be beneficial for treating bleeding gastric ulcers. Now, I recognize what I did was because of my understanding of pathophysiology (arterioles bleeding that could constrict in the face of iced saline) and "expert opinion" (my resident's order). Such a patient would be treated much differently today because of evidence showing that a bacterium, *Helicobacter pylori,* contributes to ulcer formation and that an antibacterial regimen and gastric acid control are much more effective treatments. It is surprising that much of what we still do in medicine today is based on pathophysiology and expert opinion rooted in tradition, eminence-based medicine, or pathophysiologic rationale rather than high-quality evidence from randomized controlled clinical trials.[3]

Pyramid of Evidence

Evidence in medicine has been likened to a pyramid, with the highest quality evidence at the top and the lowest quality on the bottom. At the top are systematic reviews including one or more meta-analyses of several well-done clinical trials all studying the same outcomes. Below systematic reviews are randomized controlled clinical trials (which vary in quality), followed by prospective epidemiologic studies and retrospective studies (observational studies), then basic research, and finally, expert opinion, case studies, and case reports (clinical experience). Note that "testimonials" from individual users of a treatment are not included in this list.

Randomized controlled trials are the "gold standard" in clinical evidence because when a treatment is randomly and blindly allocated (allocation-concealed) to subjects, and when neither the subjects nor the clinicians know who received which treatment (double blind), the only difference between the groups is the treatment in question. Other factors that could influence the outcome, such as age, sex, race, bias on the part of the investigators, patient expectations, and other confounding factors, are all randomly distributed between the two

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treatment groups, leaving treatment allocation as the only difference. Furthermore, analyzing all participants in a randomized controlled trial according to their original group assignment—regardless of what occurs after randomization—is known as an intention-to-treat analysis, and it strengthens the validity of the study. When such trials are combined in a valid meta-analysis, statistical power is increased and conclusions are strengthened.

Interventional Studies

Broadly speaking, clinical trials can be divided into interventional and observational studies according to whether the investigators are doing something (intervening) or observing, letting "nature take its course." Interventional studies include randomized controlled studies, non-randomized studies, and non-inferiority studies. Non-randomized studies are sometimes conducted to allow compassionate use of a new treatment. Non-inferiority studies are conducted to determine whether some new treatment is not worse than a standard treatment by more than some certain amount. These studies are conducted more often today when it would be unethical to compare a new treatment with placebo when a well-established treatment is widely available. It is also important to demonstrate that a new treatment, which may have some specific advantages, is not inferior to the standard treatment with respect to important side effects, such as cardiac adverse effects.

Observational Studies

Observational studies frequently are subdivided into case-control, cohort, and cross-sectional studies. Case-control studies begin by identifying "cases," ie, those who meet some illness definition versus controls who do not meet the definition. Then, various "exposures" are identified to determine whether one or more exposures are more likely to have occurred in those who are cases versus controls. For example, if all the individuals who acquired norovirus on a cruise ship slept in a specific area of the ship and none of the controls did, that would be important evidence to consider when determining the cause of the outbreak. Case-control studies are valuable when studying rare diseases.

Cohort studies begin with "exposed" and "unexposed" groups that are followed forward in time to determine who develops a given disease of interest. Cohort studies can be done prospectively (such as the Framingham study4) or "historically" as when a group of exposed people is identified via health records and then evaluated again at some future date to determine which of the "exposed" and "unexposed" developed disease. Cohort studies are useful when the exposure of interest is rare (eg, asbestos exposure).

Cross-sectional studies assess the prevalence of an exposure—such as COVID vaccination—and an outcome—such as hospitalization—at a single point in time. Because data are collected simultaneously, these studies can determine only the prevalence of exposure among those with and without the outcome. Prevalence reflects both the incidence and duration of a condition (prevalence = incidence × duration). As a result, individuals with longer disease duration are more likely to be captured in cross-sectional studies, since duration significantly influences overall prevalence.

How Do We Decide Which Statistical Test to Use?

Over the past 100 years, many statistical techniques have been developed. How do we decide which of these techniques is most appropriate to evaluate the evidence we plan to collect? It is obviously not appropriate to run every statistical test we can think of and then report the one with the lowest *P* value—a problem called multiple comparisons that inflates the type I error rate. The evaluation plan for our data should be determined before the first subject is enrolled into a study.

What Type of Study Are You Planning?

The first consideration is what question you are trying to answer. From there, you can ask what type of study will best answer that question. For example, if you want to know if exposure "x" increases the risk of outcome "y," then a cohort study design will answer that question. Does your question require you to design a retrospective study? If so, certain statistical measures, such as the odds ratio, will be most appropriate, comparing the odds of disease in groups with various exposures.

Are you planning a prospective study? If so, then the relative risk can be calculated since you will be collecting "incidence" data, and you can compare the incidence of disease in exposed versus unexposed groups.

Do you seek to know if a new intervention improves an outcome compared to existing standard of care interventions? If so, then a randomized controlled clinical trial would provide the strongest evidence to answer the question. Furthermore, if you intend to have "time-to-event" as an outcome measure, such as the time between entry into the study until some "cardiac event" occurs, you will want to consider using the Kaplan-Meier method for estimating survival functions (comparing who does and who does not develop disease) and perhaps comparing the hazard rates for various treatments using Cox Proportional Hazards analysis.[5] The hazard rate (discussed in part 2 of this series) reflects how likely a given event is to occur. The higher the hazard rate the lower the survival rate, similar to a teeter totter.6 When the hazard rate is high, the survival rate is low and vice versa. To recap: the Kaplan-Meier method estimates the probability of "survival" (not having an event), and the hazard ratio represents the ratio of the hazard in one group (such as the treatment group) versus another group (such as the control group).

What Type of Data Will You Have?

The type of data you plan to collect—regardless of study design—directly influences the statistical tests you can appropriately use. Ask yourself if the data will be numerical or categorical. If numerical, is it continuous (eg, systolic blood pressure measured to 3 decimal places) or discrete (eg, achieving a blood pressure target: yes or no)? If categorical, is it nominal (eg, blood type: A, B, AB, O) or ordinal (eg, cancer stage I to IV)? When working with ordinal data, it is important to choose statistical methods that preserve the natural order of the categories (Table 1).

How Do You Determine Sample Size?

Finally, once you have decided which statistical test to use to evaluate your data, how do you

determine an adequate sample size? Although the full methodology is beyond the scope of this discussion, sample size calculations are influenced primarily by 4 factors (Table 2).

First, consider the minimum difference between groups that you consider clinically meaningful. The smaller this difference, the larger the sample size you will need to detect it. Conversely, if you aim to detect a very large difference, a smaller sample may suffice.

Second, consider the alpha level (α)—the probability of a "false alarm" (type I error). The smaller you set alpha, the larger the sample size required, because you're demanding stronger evidence to declare a result statistically significant.

Third, decide an acceptable beta level (β)—the probability of "missing the boat" (type II error). A smaller beta (eg, 10%, corresponding to 90% power) requires a larger sample size than a higher beta (eg, 20%, or 80% power), because greater power increases your ability to detect a true difference.

Fourth, consider the precision of your outcome measurement. More precise measurements—such as blood pressure recorded to 3 decimal places via arterial line—reduce variability and allow smaller differences to be detected with fewer participants. In contrast, less precise methods—such as using a blood pressure cuff accurate to only +/- 2 mmHg—increase variability and require a larger sample size to detect the same effect.

Table 1. Types of Data

Data Type	Subtype	Description	Example
Numerical	Continuous	Can take any value within a range	Blood pressure (eg, 132.7 mmHg)
	Discrete	Countable values; no intermediate values	Reached blood pressure goal (yes/no)
Categorical	Nominal	Unordered categories	Blood group (A, B, AB, O)
	Ordinal	Ordered categories	Cancer stage (I, II, III, IV)

Table 2. Factors to Consider When Determining Sample Size

Factor	Description	Effect on Sample Size
1. Clinically meaningful difference	Smallest outcome difference worth detecting	Smaller differences → larger sample size
2. Alpha (α) – Type I error	Probability of a false positive (eg, 0.05 vs 0.001)	Smaller α → larger sample size
3. Beta (β) – Type II error	Probability of a false negative; Power = 1 – β	Lower β (higher power) → larger sample size
4. Measurement precision	How accurately the outcome is measured	Greater precision → smaller sample size

Statistical Pitfalls

Scientific studies can encounter numerous challenges—from choosing the right participants to correctly analyzing data. This discussion will highlight 2 major concerns.

Bias

Bias is any effect tending to produce results that depart systematically from the true values.[7(pp10)] Bias must be systematic and not random. If it were random, it would have no overall effect, since one group would be affected as much as any other.

A famous example of bias comes from the work of Abraham Wald.[8] Wald, a Hungarian mathematician who escaped the Holocaust and later supported the Allied war effort in the United States, was tasked with improving aircraft survivability. The US Army Air Force collected extensive data on where bullet holes were found on planes that returned safely from bombing runs over the English Channel. After analyzing these data, Wald famously asked a crucial question: Where were the bullet holes on the planes that didn't return?

Wald concluded that armament should be increased in those areas—because the planes that came back showed where they could sustain damage and still fly home. Stated differently, the planes that made it back to England just demonstrated where an airplane could take a hit and still make it back to base. This is a great example of survivorship bias: focusing only on surviving examples can lead to misleading conclusions. Survivorship bias is just one of many biases that can affect studies--especially observational ones—where biases are not evenly distributed between treatment groups.

Confounding

Confounding is a special type of bias. A confounder is a factor that distorts the apparent magnitude of the effect of a study factor on risk.[7(pp21)] Such a factor is a determinant of the outcome of interest and is unequally distributed among the exposed and unexposed groups. For example, in 1973, a study associated coffee drinking with myocardial infarction (MI).[9] At that time, smokers were more likely to drink coffee than nonsmokers. Since smoking is a cause of MI and because it was unequally distributed in the exposure groups (coffee drinkers and non-coffee drinkers), it gave the illusion that coffee drinking was linked to MI.

In general, confounding is controlled by "stratification," an analysis technique beyond the scope of this discussion. In essence, the data are divided into "strata" with and without the putative confounder and then reanalyzed to see if the original relationship still exists (eg, coffee drinking and MI).

Association, Correlation and Causation

Association, correlation, and causation have distinct and specific meanings, yet often they are confused or used interchangeably, leading to misunderstanding and misinterpretation of study results.

Association

An association means that events are occurring more often together than expected by chance.[7(pp5)] This does not imply, however, that one event causes the other.

Correlation

Correlation measures the strength and direction of a linear relationship between two variables.[7(pp23)] For example, when one variable increases, the other tends to increase as well, forming a pattern that fits a straight line.

The correlation coefficient quantifies the linear relationship. However, two variables may be related without a linear pattern. For instance, the velocity of a falling object is related to the height from which it was dropped, but the relationship is nonlinear due to acceleration from gravity. Importantly, correlation does not imply causation. Two things may appear to be related, but that does not imply one causes the other.

Causation

What does it mean to state that something causes something else? What does the term "cause" mean? Perhaps this can best be described with a story.

One of us (RAC) was married several years ago and brought a nice alarm clock into our home, which was in a high-rise condo. Every day at 5:30 AM, the alarm went off. When it went off in the summer months, the sun was rising. It was a nice clock, but the clock did not cause the sun to rise. Nevertheless, there was a strong correlation between the alarm going off and the sun coming up during the summer. Now, suppose in December when the alarm went off, I became upset because the sun was not rising and, as a result, threw the alarm clock out the window (of the high-rise condo), and it fell to the ground and broke into 100 pieces. Did I cause the alarm clock to break by throwing it out the window?

Thinking about this more carefully, was tossing it out the window a necessary cause (that must be present for the outcome to occur)? No, I could have broken the alarm clock any number of creative ways, such as hitting it with a hammer or throwing it against the wall. Therefore, throwing it out the window was not a necessary cause.

Was throwing it out the window a sufficient cause (that alone can produce the outcome)? It was not, since in December in Wisconsin it could have landed in a snowbank and not been damaged at all. Therefore, throwing it out the window was not a sufficient cause for breaking the alarm clock.

Instead, it was a contributory cause (that increases the likelihood of the outcome to occur). I contributed to breaking the clock by throwing it out the window. In medicine, when we say one factor causes another, we usually mean it is a contributory cause – one that plays a meaningful role. Generally, for a cause to warrant study and intervention, it must be significant enough to justify taking action.

"Criteria" for Causation

How can a contributory cause be determined? In 1965 Sir Austin Bradford Hill presented 9 criteria for determining causation in medicine (eg, smoking and the development of lung cancer):[10]

1. **Strength.** The stronger an association, the more likely it is to be causal. For example, doctors in England who smoked in the early 1950s were up to 30 times more likely to develop lung cancer.
2. **Consistency.** The same association was observed across all settings.
3. **Specificity.** This criterion implies a one-to-one relationship, a concept rooted in Koch's postulates. However, it was not fulfilled by smoking and lung cancer – smoking causes multiple diseases, including myocardial infarction, chronic obstructive lung disease, and bladder cancer. Therefore, not every criteria must be met for a factor to be considered a cause.
4. **Temporality.** This indispensable criterion implies the cause precedes the effect. For example, it must be shown that smoking comes before lung cancer.
5. **Biological gradient (dose-response).** The risk of lung cancer increases with the amount of smoking – a strong criterion for causation – because it is unlikely that such a consistent dose-response relationship would occur by chance alone if there were no true cause-and-effect link.
6. **Plausibility.** Is it biologically plausible that inhaling known carcinogens into your alveoli can cause cancer? Yes, it is. However, it is important to recognize that our understanding of many cause-and-effect relationships is incomplete. A lack of current explanation does not rule out a true biological connection.
7. **Coherence.** The cause-and-effect interpretation should align with what we know about the disease. For example, cigarette sales and lung cancer rates have shown a strong association, accounting for the expected time lag in cancer development.
8. **Experiment.** Removing the cause should reduce the effect. Smoking cessation lowers the risk of developing lung cancer.
9. **Analogy.** If experimental animals develop lung cancer when exposed to cigarette smoke, it is reasonable to infer that humans might as well, based on this similarity.

Conclusion

Evidence goes beyond pathophysiology and expert opinion, with its strength depending on study design. The results of well-designed randomized controlled trials offer more robust evidence than a case report, case series, or an observational study. The choice of statistical tests should align with the study design and data type. Common challenges include bias and confounding, among others. Most associations are not causal, and Austin Bradford Hill's criteria provide a useful framework for evaluating causation.

Funding/Support: None declared.

Financial Disclosures: None declared.

Acknowledgement: If you would like to study the issues covered in these 6 articles in more depth please see www.biostatisticstools.com.

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Part 5: Descriptive Statistics Practice Questions and Answers

1. What is the mean of the following numbers: 1, 2, 3, 4, 7, 8?

   The sum of these 6 numbers (1, 2, 3, 4, 7, 8) is 25. The mean is 25/6 = 4.167

2. What is the median of the following numbers: 2, 5, 9, 16, 22, 25?

   The median of these numbers (2, 5, 9, 16, 22, 25) is the average of the middle 2 numbers (9 and 16). Therefore, the median is (9 + 16)/2 = 12.5

3. If the mean systolic blood pressure of all patients in your practice is 130 mmHg and the standard deviation is 6 mmHg, what percent of your practice would you expect to have systolic pressures above 142 mmHg assuming the systolic pressures follow a normal distribution?

   Since the population standard deviation is 6 mmHg, and the mean is 130, 142 is 2 standard deviations above the mean. In a normal distribution, 95% of values are within 2 standard deviations of the mean (2.5% above and 2.5% below 2 standard deviations).

4. Suppose you record the blood pressures of the next 9 patients in your office and calculate the mean systolic pressure of that sample to be 134 mmHg. Would that mean surprise you? What is the standard error of the mean for this random sample of 9?

   For a sample size of 9, the standard error of the mean (SEM) is the population standard deviation (6) divided by the square root of the sample size (square root of 9 is 3). Therefore, the SEM is 6/3 = 2. Since 134 is 2 standard deviations above the mean, it would not be terribly surprising (P = 0.05).

5. What would the standard error of the mean be for a random sample of 36 of your patients?

   For a sample of 36, the SEM would be 6/(square root of 36). Therefore, the SEM for a random sample of 36 would be 1.0. Note that to cut the standard error in half (from 2 to 1), the sample size must increase 4 times (from 9 to 36).

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The *WMJ* would like to thank everyone who served as a manuscript reviewer in 2024. Manuscript review is an important collegial act and is essential to the integrity of *WMJ*. We are grateful for the assistance of these individuals in ensuring authors receive objective and insightful feedback on their work.

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