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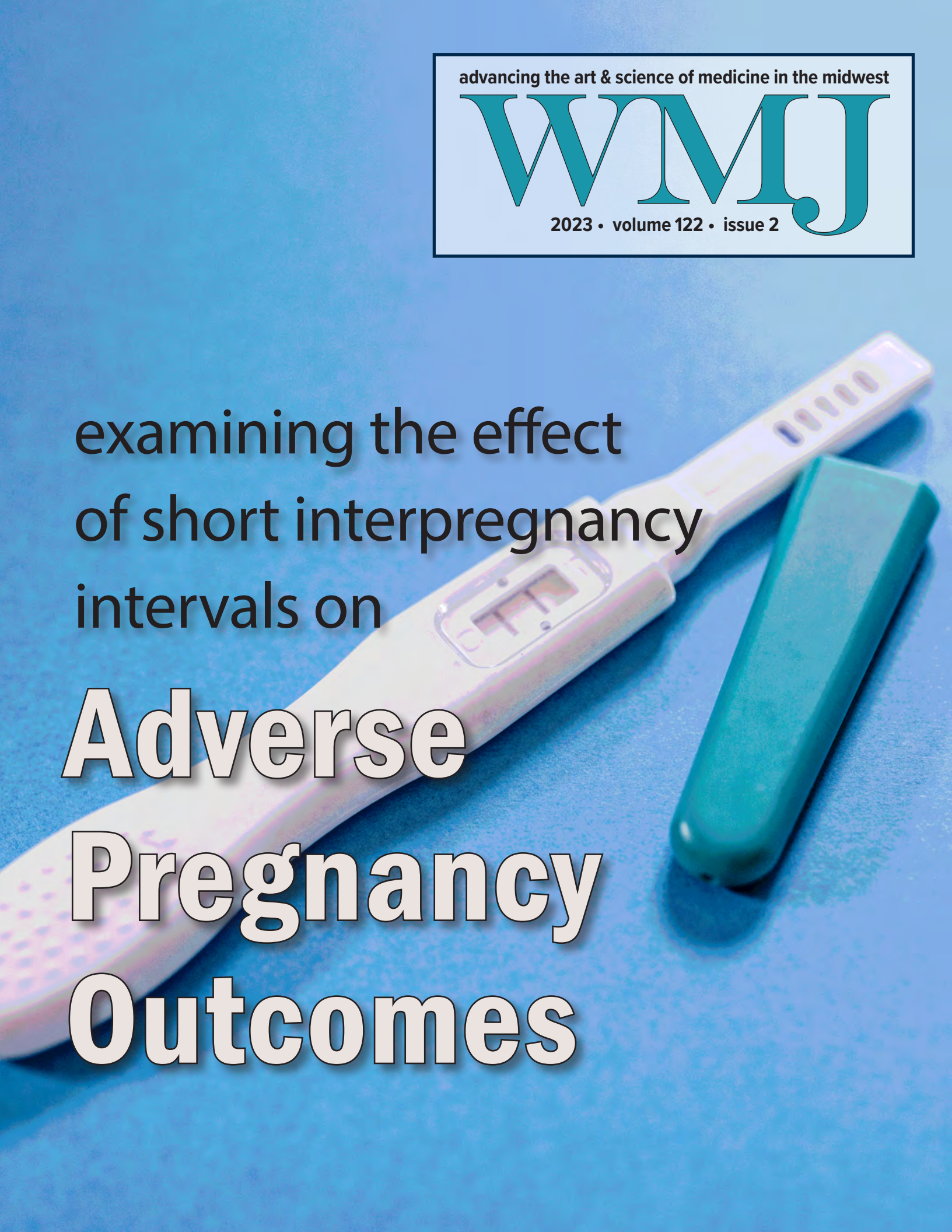

examining the effect of short interpregnancy intervals on

Adverse Pregnancy Outcomes

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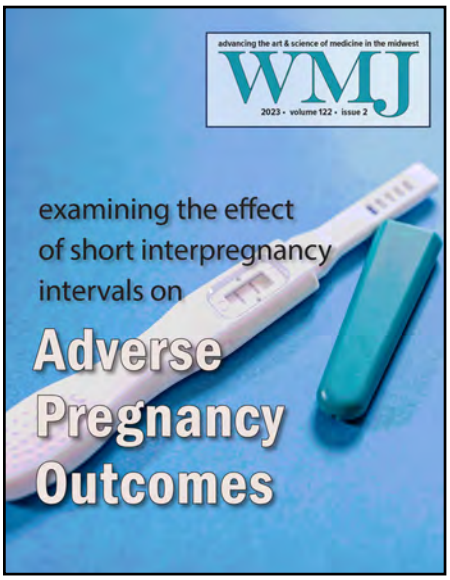

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WMJ

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COVER THEME

Adverse Pregnancy Outcomes

Pregnancies occurring within short interpregnancy intervals increase the risk of adverse pregnancy outcomes, such as preterm birth, and current recommendations by the American College of Obstetricians and Gynecologists suggest avoiding interpregnancy intervals shorter than 6 months. A study in this issue of WMJ *seeks to evaluate the prevalence of adverse pregnancy outcomes among people with short interpregnancy intervals in urban Milwaukee, Wisconsin.*

Cover design by Kendi Neff-Parvin

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EDITORIAL

ORIGINAL RESEARCH

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BRIEF REPORTS

CASE REPORTS

Promoting Faculty Development Through Structured Mentoring

Dear Editor:

Mentorship plays a crucial role in facilitating professional development and career advancement. Engaging in mentorship can be mutually beneficial for mentors and mentees.[1] Various models of mentorship exist, including peer mentoring and apprenticeship. Peer mentoring offers a collaborative platform for individuals with shared interests and similar levels of training to exchange knowledge, experiences, and learning resources. Conversely, apprenticeship models involve mentors with more professional experience than their mentees.[2]

The Division of General Internal Medicine (GIM) at the Medical College of Wisconsin has 2 formalized mentoring programs: peer mentoring affinity groups and structured mentor-mentee programs. Affinity groups include research, medical education, quality improvement, and case report groups; and more than 100 faculty and advanced practice providers (APP) are part of them. To assess the effectiveness of the affinity groups, we surveyed 85 assistant professors in GIM, resulting in a response rate of 42%; 17 out of 20 faculty members (85%) who attended affinity groups indicated that they are valuable in promoting scholarship activity and faculty development.

The structured mentor-mentee program (apprenticeship model) implemented by our division enables junior faculty to choose mentors based on their area of interest and meet their mentors twice a year to discuss short-term and long-term career goals. The program has 12 mentors and 20 mentees, totaling 32 participants. The results from a survey conducted at the end of 2022 to evaluate the program's effectiveness were quite encouraging: a majority (83% of mentors and 100% of mentees) recommended the program to others. Participants noted a range of benefits, including promotion, increased scholarly productivity, greater collaboration, and leadership development. We are pleased to report that our division recently has introduced a similar mentorship model for APPs.

We have observed an exponential increase in peer-reviewed publications and presentations at regional and national meetings since the implementation of these programs. Additionally, faculty members who have participated in these programs have been appointed to several committees and have assumed leadership roles at regional and national levels. Notably, we have observed an increase in faculty members promoted to associate and full professor.

While mentorship programs cannot be one-size-fits-all and need to be tailored to address local needs, our findings underscore the feasibility of combining 2 distinct programs and their potential to foster academic excellence and success for GIM faculty. Further research is needed to identify specific factors that contribute to success of these programs and to determine their applicability in other medical disciplines.

—Sanjay Bhandari, MD; Trisha Jethwa, MD; Pinky Jha, MD, MPH

REFERENCES

1. Jha P, Quinn B, Durbin S, Bhandari S. Perceptions of junior faculty in general internal medicine regarding mentoring medical students and residents in scholarly projects. *J Gen Intern Med*. 2019;34(7):1098-1099. doi:10.1007/s11606-019-04937-4.

2. Hernandez-Lee J, Pieroway A. Mentorship for early career family physicians: Is there a role for the first five years in family practice committee and the CFPC? *Can Fam Physician.* 2018;64(11):861-862.

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8. Riley M, Ahmed S, Reed BD, Quint EH. Physician knowledge and attitudes around confidential care for minor patients. *J Pediatr Adolesc Gynecol*. 2015;28(4):234-239. doi:10.1016/j.jpag.2014.08.008

9. Duncan RE, Vandeleur M, Derks A, Sawyer S. Confidentiality with adolescents in the medical setting: what do parents think? *J Adolesc Health*. 2011;49(4):428-430. doi:10.1016/j.jadohealth.2011.02.006

10. Ford CA, Millstein SG, Halpern-Felsher BL, Irwin CE Jr. Influence of physician confidentiality assurances on adolescents' willingness to disclose information and seek future health care. A randomized controlled trial. *JAMA*. 1997;278(12):1029-1034. doi:10.1001/jama.1997.03550120089044

11. Grilo SA, Catallozzi M, Santelli JS, et al. Confidentiality discussions and private time with a health-care provider for youth, United States, 2016. *J Adolesc Health.* 2019;64(3):311-318. doi:10.1016/j.jadohealth.2018.10.301

12. Maslyanskaya S, Alderman EM. Confidentiality and consent in the care of the adolescent patient. *Pediatr Rev.* 2019;40(10):508-516. doi:10.1542/pir.2018-0040

13. High School Youth Risk Behavior Survey Data. Centers for Disease Control and Prevention. Published 2017. https://nccd.cdc.gov/youthonline/App/Default.aspx

14. Stablein T, Loud KJ, DiCapua C, Anthony DL. The catch to confidentiality: the use of electronic health records in adolescent health care. *J Adolesc Health.* 2018;62(5):577-582. doi:10.1016/j.jadohealth.2017.11.296

15. Sharko M, Wilcox L, Hong MK, Ancker JS. Variability in adolescent portal privacy features: how the unique privacy needs of the adolescent patient create a complex decision-making process. *J Am Med Inform Assoc.* 2018;25(8):1008-1017. doi:10.1093/jamia/ocy042

16. Covelli I, Ahrens K, Onchiri FM, Inwards-Breland D, Boos MD. Influence of gender and sexual identity on adolescent skin health. *Pediatr Dermatol.* 2021;38 Suppl 2:65-72. doi:10.1111/pde.14686

17. Bayer R, Santelli J, Klitzman R. New challenges for electronic health records: confidentiality and access to sensitive health information about parents and adolescents. *JAMA*. 2015;313(1):29-30. doi:10.1001/jama.2014.15391

18. Society for Adolescent Health and Medicine; American Academy of Pediatrics. Confidentiality protections for adolescents and young adults in the health care billing and insurance claims process. *J Adolesc Health.* 2016;58(3):374-377. doi:10.1016/j.jadohealth.2015.12.009

19. Alderman EM. Confidentiality in pediatric and adolescent gynecology: when we can, when we can't, and when we're challenged. *J Pediatr Adolesc Gynecol*. 2017;30(2):176-183. doi:10.1016/j.jpag.2016.10.003

Fahad Aziz, MD, FASN

Four Essential Laws of Connecting With Patients

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

A patient's relationship with their health care provider is critical to ensuring safe and quality patient care. This relationship is based on trust and a deep understanding. Learning more about a patient than what is included in their medical history is essential to establishing a connection. Health care providers should know how to connect with their patients to provide safe, high-quality, and compassionate care. Here I describe four essential laws of connecting with patients (Box).

Box. Laws of Connecting With Patients

1. Law of Compassion
2. Law of Communication
3. Law of Shared Decision-Making
4. Law of Hope

LAW OF COMPASSION

Before looking into "compassion," let's investigate sympathy and empathy and how compassion differs (Figure 1). Sympathy means understanding what the other person is feeling, while empathy is feeling what the other person is feeling. However, compassion makes us understand and feel another person's suffering and do everything to help them come out of it.

Sympathy shares similarities with compassion. Sympathy is composed of some range of feelings, while compassion, more specifically, arises in response to someone's suffering and includes a motivation to relieve the suffering. Similarly, empathy shares a few similarities with compassion; however, it does not require action or sustain itself over an extended time.[1] In other words, compassion has two components: (1) feeling someone's suffering and (2) the ability to take action to relieve them from that suffering.[2,3]

Several studies have shown that the compassion of health care providers is crucial for patient outcomes and satisfaction.[4] A clinician's compassion for their patients leads to a better connection between them, and patients have a faster recovery, significant autonomy, and less intensive care utilization.[5,6]

Practically, health care providers should take some steps to show compassion: (1) emotional presence, (2) entering the patient's world, (3) effective communication, (4) displaying understanding and kindness, and (5) taking practical steps to help them in their suffering.

While caring for patients, focusing on human connection is the key to forming a good relationship. Expressing compassion while caring for patients makes them feel more comfortable discussing what they are experiencing. It ultimately builds a relationship that is based on trust.

LAW OF COMMUNICATION

Also critical to connecting with patients is effective communication, which includes four key elements (Figure 2):

1. Listening: Listening is essential for any communication. There's an old saying: "Fifty percent of medical problems would be cured if your physician just listened to your problems." The principles of effective listening to patients are:

- Listen with ears open.
- Understand each word.
- Understand the meaning of each word.
- Understand the meaning between the lines.
- Understand body language.
- Avoid multitasking while listening.
- Avoid interruptions.

By following these principles, our patients understand that we care and understand their concerns.

2. Asking questions: Asking questions to better understand the patient's issues is also essential to communication. Asking questions can help clinicians to dig deeper and learn more about any problems. Further, asking questions helps patients understand that their clinician has a genuine concern for their medical issues.

3. Sharing opinions: Sharing expert and honest opinions with patients helps the clinician to strengthen their connection. Detailed medical information should be communicated understandably to patients. Outstanding clinicians use paper and pen or whiteboards to discuss complex medical issues, and they should share the logic behind their decisions and the possible outcomes of those decisions.

4. Answering questions: Another critical component of communication with patients is giving them time to think through the issue,

Figure 1. Staircase to Compassion

Figure 2. Components of Effective Communication

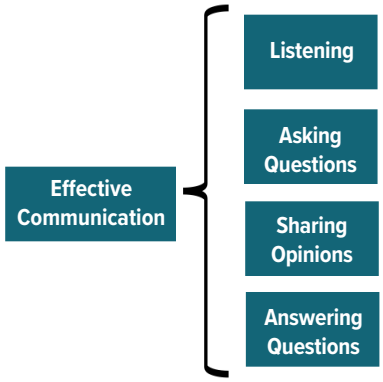
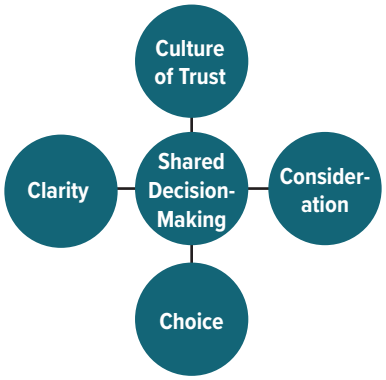


Figure 3. Shared Decision-Making



after which clinicians should make themselves available to answer any questions. It's important to remember that all questions are valid. Patients should be encouraged to ask anything, no matter how minor or straightforward it may seem. Making patients feel comfortable and answering their questions helps them develop confidence in their clinician.

LAW OF SHARED DECISION-MAKING

Shared decision-making is a process in which the health care provider and patient work together to make the best decision for that patient, and it is a crucial component of connecting with patients. Difficult medical decisions are more manageable when the patient understands the problem and shares in the decision-making. It's human nature to accept the decisions in which we have ownership.

A detailed account of shared decision-making is given in a previous editorial.[7] In short, shared decision-making is critical for creating genuine clinician-patient relationships and is associated with better patient outcomes and satisfaction.

To develop shared decision-making, I proposed the 4C model (Figure 3):

Step 1: Develop a Culture of Trust: With integrity, compassion, kindness, and humility, physicians develop a relationship of trust with their patients. In this culture of faith, a difficult decision can be made quickly.

Step 2: Bringing Clarity: Adding clarity to the patient's challenging medical issues always makes it easier for them to understand their medical problems and share in decision-making.

Step 3: Consideration: After better understanding the medical issues, physicians should explain all the possible treatment options, including the pros and cons of each.

Step 4: Choice: Finally, with a better understanding of the medical issues and possible treatment options, patients should be encouraged to make their decision. Ownership of the decision leads to better adherence to the treatment plan.

LAW OF HOPE

"Hope is life." Hope is essential to a patient's quality of life. It is well-known that people with higher hope show better adaptation, lower stress levels, and less anxiety and depression. While clinicians must be honest with their patients, they should also try to convey any "silver linings" in difficult situations. Doing so can help patients find hope and strengthen their relationship with their clinician.

Feelings of being alone in the situation, persistent pain, lack of sleep, and reduced self-esteem have a negative impact on hope. An empathetic dialogue with the patient – with a clear message from the clinician – leaves room for hope, which helps the patient heal more quickly and better connect with their clinician.

The primary sources of hope for patients include the following:

- their close relationship with their physician.
- better communication and connection with their clinician.
- a sense of self-worth.
- a positively assessed life.
- possibility of meaningful life goals.
- spiritual support.

A clinician's positive attitude toward their patients is contagious; miracles can happen with hope.

CONCLUSION

By following these four essential laws of connection – compassion, communication, shared decision-making, and hope – we can become connecting clinicians. It is crucial that we put extra effort into incorporating these laws in our daily practice to establish lifelong relationships with our patients.

REFERENCES

1. Bloom P. Empathy and its discontents. *Trends Cogn Sci.* 2017;21(1):24-31. doi: 10.1016/j.tics.2016.11.004

2. Kirby JN. Compassion interventions: The programmes, the evidence, and implications for research and practice. *Psychol Psychother.* 2017;90(3):432-455. doi:10.1111/papt.12104

3. Strauss C, Lever Taylor B, Gu J, et al. What is compassion and how can we measure it? A review of definitions and measures. *Clin Psychol Rev.* 2016;47:15-27. doi:10.1016/j.cpr.2016.05.004

4. Doohan I, Saveman BI. Need for compassion in prehospital and emergency care: a qualitative study on bus crash survivors' experiences. *Int Emerg Nurs.* 2015;23(2):115-119. doi:10.1016/j.ienj.2014.08.008

5. van der Cingel M. Compassion in care: a qualitative study of older people with a chronic disease and nurses. *Nurs Ethics.* 2011;18(5):672-685. doi:10.1177/0969733011403556

6. Lown BA, Muncer SJ, Chadwick R. Can compassionate healthcare be measured? The Schwartz Center Compassionate Care Scale. *Patient Educ Couns.* 2015;98(8):1005-1010. doi: 10.1016/j.pec.2015.03.019

7. Aziz F. The power of shared decision-making in medical settings. *WMJ.* 2023;122(1):5-6.

Post *Roe v Wade's* Overturn: Importance and Methods of Patient-Physician Confidentiality in Conversations Surrounding Isotretinoin and Contraception in Wisconsin

Sophia Neman, BA; Stephen R. Humphrey, MD

The overturning of the Supreme Court case *Roe v Wade* in the case of *Dobbs v Jackson Women's Health Organization* has far-reaching implications in medicine, even beyond the field of women's health. The ruling has obscured state abortion laws, leaving health care providers with questions regarding the legal parameters of reproductive health care.[1] Wisconsin, specifically, is now enforcing an 1849 statute, of which the original language prohibits all abortions except in cases that "preserve the life of [the] mother or shall have been advised by two physicians to be necessary for such purpose."[2] Wisconsin Governor Tony Evers voiced disapproval of the 1849 law and suggested that he would grant clemency to persecuted physicians, but this does not clarify the future of abortion access in Wisconsin.[3]

One specific area of ambiguity is whether pregnancies conceived while patients are prescribed teratogenic medications will fall within the legal exemptions of the abortion. When patients are under the age of 18, additional complexities are introduced. Minor consent laws, confidentiality, and the authority of patients' guardians must be considered when navigating next steps.

Dermatology is one specialty prescribing teratogenic medications, such as isotretinoin. Isotretinoin is the most effective treatment for patients with moderate-to-severe nodulocystic or recalcitrant acne vulgaris. Isotretinoin has a 20% to 35% risk of teratogenicity in fetuses, and its use is associated with neurologic malformations, thymic disorders, and cardiovascular and craniofacial defects.[4,5] The existing gravity of teratogens is now combined with the fact that there are no clear guidelines for abortion if patients become pregnant while prescribed isotretinoin.

> Providers outside the field of women's health may not be providing direct abortion counseling but, nonetheless, should be prepared to advocate for their patients' safety.

ISOTRETINOIN AND iPLEDGE

There were 6,740 reported pregnancies among patients taking isotretinoin from 1997 through 2017.[6] iPLEDGE is a risk evaluation and mitigation strategy program regulated by the US Food and Drug Administration that outlines strict regulations for contraception, abstinence, and pregnancy testing for patients prescribed isotretinoin. However, the intention of iPLEDGE may be different than its effect. A study found that while iPLEDGE regulations may emphasize treatment risks, this may not translate to reducing the number of pregnancies exposed to isotretinoin.[7] It is, therefore, vital to address gaps in patient care for the health of both patients and fetuses.

GAPS IN KNOWLEDGE ABOUT CONFIDENTIALITY

Patient-physician confidentiality is one such point of conversation. Although dermatologists are cognizant of the importance of discussing reproductive health, provider knowledge of confidentiality and consent laws for minors has been found to be limited.[8] Guardians also may have a limited understanding of confidentiality and mixed reactions to being excluded from health care conversations.[9] This is uniquely relevant to adolescents, as confidential conversations can be a key step towards developing their own perspective of their health.

Adolescents are more likely to disclose information, pursue treatment, and seek future care once physicians address confidentiality.[10]

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Only up to 43% of adolescents have had time alone with their physicians and may not even know that this is an option.[11] Physicians should address these concerns and clarify when guardians and partners will be included or asked to step outside to ensure transparency. One method is to normalize these conversations by assuring them that confidentiality is offered to all patients.

ADOLESCENT COGNITIVE DEVELOPMENT AND SEXUAL HEALTH

Knowledge of cognitive milestones and decisional capabilities can assist providers to tailor conversations about reproductive health accordingly. For example, early adolescents (12-14 years old) have difficulty thinking about the long-term consequences of their actions. Middle adolescents (15-17 years old) are better able to consider the consequences of their actions, but they are more likely to engage in risk-taking behavior, are more susceptible to peer influence, and often have more conflict with their parents. These behaviors tend to subside by late adolescence (18-21 years old).[12]

Data show that as of 2019, 3% of children engage in sexual intercourse before the age of 13, while 40% of high school students reported having had sex.[13] In order to be inclusive to adolescents in different stages of cognitive development and sexual activity, pediatric dermatologists should introduce the concept of confidential care as early as ages 11 years and older. In general, isotretinoin is typically not first-line acne treatment for patients younger than 12 years old. Outside of patients prescribed isotretinoin, the exact age may be tailored to whether the provider has existing rapport with the patient and the age the patient begins menstruating.

METHODS TO MAINTAIN PATIENT-PHYSICIAN CONFIDENTIALITY

Topics such as electronic health records (EHR), pharmacies, insurance documentation, after-visit summaries, and patient follow-up must be revisited to reinforce confidentiality. One method to protect confidentiality and sensitive information is to create a sensitive note. This note will be visible to the provider but not to the patient or their guardian. Another option is to make an adolescent privacy flag. The flag symbol will be visible, but guardians will not be able to see its content unless the patient consents. Physicians also have created systems of key phrases designed to remind themselves or other providers of confidential information.[14] Aside from monitoring sensitive information, some institutions even have been able to provide EHR portal access directly to patients under the age of 18.[15]

Within confidential conversations, dermatologists should ask patients their sexual preferences, gender identity, and preferred pronouns. Next, they should ask who is aware of this information to avoid sharing confidential information with guardians or partners. Isotretinoin treatment may interfere with gender-affirming hormonal treatment or raise questions among female-to-male transgender patients about their fertility. Due to the sensitivity of these conversations, sexual and gender minority patients may prefer a sexual and gender minority dermatologist.[16] Patient-physician confidentiality should be maintained once the appointment has ended as well.

Physicians can contact pharmacies to see if they send automatic messages about prescriptions or have medication sent to a pharmacy preferred by the patient.[17] Diagnoses and test results may be excluded from insurance documentation if a minor requests confidentiality.[18] Confidential information also can be excluded from the after-visit summary, or the after-visit summary can be given directly to minors. For follow-up purposes, physicians should ask patients under the age of 18 for an alternative phone number and address if communication absolutely cannot be sent to the minor's home, or, if the home phone number cannot be contacted, to speak in confidence to the patient.[19]

DISCUSSION

Keeping these confidentiality practices in mind, it is unclear whether the Wisconsin state legislature will change or clarify how teratogens will be considered in abortion access. In the meantime, there may be some change with how patients will engage with iPLEDGE and whether the percentage of patients choosing abstinence or other contraceptive options will shift. There also may be a change in adherence to selected methods now that there is an added risk of continuing with a pregnancy with birth defects and the added burden of traveling out of Wisconsin for an abortion.

Although the purpose of this commentary is to discuss isotretinoin counseling and confidentiality, this topic may be applied to any prescribed teratogenic medication. Providers outside the field of women's health may not be providing direct abortion counseling but, nonetheless, should be prepared to advocate for their patients' safety. Isotretinoin prescription among dermatologists must be acknowledged, specifically, to integrate the limitations of iPLEDGE, frequency of use among adolescents, and possible complications for sexual and gender minority patients.

This knowledge must be applied not only within appointments, but also extend to other methods of communication to ensure that confidentiality is maintained for the duration of isotretinoin treatment or for any other medication that has potential for teratogenicity. Navigating vulnerable conversations should always involve creating a safe space for patients; the court decision in *Dobbs v Jackson Women's Health Organization* is a reminder of the importance of confidentiality and its far-reaching implications.

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REFERENCES

1. *Dobbs v Jackson Women's Health Organization*, 597 US__(2022).

2. AB 116, 1849 Biennium, 1849 Reg. Sess. (Wis. 1849).

3. Edelman A. Wisconsin gov. vows to grant clemency to doctors charged under state abortion ban. *NBC News*. June 27, 2022. Accessed December 20, 2022. https://www.nbcnews.com/politics/wisconsin-gov-vows-grant-clemency-doctors-charged-state-abortion-ban-rcna35479

4. Altıntaş Aykan D, Ergün Y. Isotretinoin: still the cause of anxiety for teratogenicity. *Dermatol Ther.* 2020;33(1):e13192. doi:10.1111/dth.13192

5. Lammer EJ, Chen DT, Hoar RM, et al. Retinoic acid embryopathy. *N Engl J Med*. 1985;313(14):837-841. doi:10.1056/NEJM198510033131401

6. Tkachenko E, Singer S, Sharma P, Barbieri J, Mostaghimi A. US Food and Drug Administration reports of pregnancy and pregnancy-related adverse events associated with isotretinoin. *JAMA Dermatol.* 2019;155(10):1175-1179. doi:10.1001/jamadermatol.2019.1388

7. Akinbami LJ, Gandhi H, Cheng TL. Availability of adolescent health services and confidentiality in primary care practices. *Pediatrics*. 2003;111(2):394-401. doi:10.1542/peds.111.2.394

Incidence of Adverse Pregnancy Outcomes Based on the Degree of Short Interpregnancy Interval in Urban Milwaukee Population

Elizabeth Panther, BSN; Sarah Amherdt, MD; Margaret Macbeth, BSN; Brittany McNellis, BSN; Amy Pan, PhD; Anna Palatnik, MD

ABSTRACT

Introduction: Short interpregnancy interval is defined as conception occurring within 18 months of a previous live birth. Studies show increased risks of preterm birth, low birth weight, and small for gestational age with short interpregnancy intervals; however, it is unclear if these risks are higher for all short interpregnancy intervals or only for those less than 6 months. The objective of this study was to evaluate prevalence of adverse pregnancy outcomes among people with short interpregnancy intervals, stratified by degree: less than 6 months, 6 to 11 months, and 12 to 17 months.

Methods: We conducted a retrospective cohort study of people with 2 singleton pregnancies between 2015 and 2018 at a single academic center. The following outcomes were compared between patients with interpregnancy intervals of less than 6 months, 6 to 11 months, 12 to 17 months, and 18 months or more; hypertensive disorders of pregnancy (gestational hypertension and preeclampsia), preterm birth at less than 37 weeks, low birth weight (<2500 g), congenital anomalies, and gestational diabetes. Bivariate and multivariate analyses were done to examine the independent role of the degree of short interpregnancy interval and each outcome.

Results: A total of 1,462 patients were included in the analysis, with 80 pregnancies occurring at interpregnancy intervals less than 6 months, 181 at 6 to 11 months, 223 at 12 to 17 months, and 978 at 18 months or more. In unadjusted analysis, patients with interpregnancy intervals less than 6 months had the highest rate of preterm birth at 15.0%. In addition, patients with interpregnancy intervals less than 6 months and 12 to 17 months had higher rates of congenital anomalies versus those with interpregnancy intervals of 18 months or more. In multivariate analysis, controlling for sociodemographic and clinical confounding factors, interpregnancy intervals less than 6 months were associated with 2.3 higher odds of preterm birth (95% CI, 1.13-4.68), and those 12 to 17 months were associated with 2.52 higher odds of congenital anomalies (95% CI, 1.22-5.20). The odds of gestational diabetes were lower with interpregnancy intervals of 6 to 11 months compared to those 18 months or more (aOR 0.26; 95% CI, 0.08-0.85).

Conclusions: In this single-site cohort, people with interpregnancy intervals less than 6 months had higher odds of preterm birth, while those with interpregnancy intervals 12 to 17 months had higher odds of congenital anomalies, compared with the control group with interpregnancy intervals greater than or equal to 18 months. Future research should focus on identifying modifiable risk factors for short interpregnancy intervals and interventions to reduce them.

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INTRODUCTION

Short interpregnancy interval is defined as conception occuring within 18 months of a previous live birth.[1] Pregnancies occurring within short interpregnancy intervals increase the risk of adverse pregnancy outcomes, such as preterm birth.[2] About 1 in 3 pregnancies in the US are complicated by short interpregnancy intervals, with 12-17 months being the most common category.[3,4] The same statistics apply to Milwaukee,[5] Wisconsin – a city that has high infant mortality – with 49.2% of infant mortality being due to complications of prematurity.[6] Therefore, preventing short interpregnancy intervals, specifically in Wisconsin, could lead to substantial improvement in birth outcomes and reduction in infant mortality.

Current recommendations by the American College of Obstetricians and Gynecologists (ACOG) suggest avoiding interpregnancy intervals shorter than 6 months, and they urge clinicians to counsel patients about the risks of closely spaced pregnancies.[7] These risks include preterm birth, defined as birth before 37 weeks of gestation; low birth weight, defined as <2500 g; and small for gestational age, defined as birthweight at less than 10% for the gestational age.[2,7-13] The mechanistic link between short interpregnancy intervals and these adverse perinatal outcomes is not clearly understood; however, it could be related to nutritional store depletion.[14,15]

While association with neonatal outcomes is well documented, the association between short interpregnancy intervals and adverse maternal outcomes, such as hypertensive disorders of pregnancy or gestational diabetes, is less clear. More recent studies, including a systematic review of studies from high-resource settings, reported conflicting results regarding the association of short interpregnancy intervals and adverse maternal outcomes.[16-19] It is important to identify confounding factors for short interpregnancy intervals and adverse outcomes and determine the true independent role of short interpregnancy intervals in the association with adverse pregnancy outcomes, as short interpregnancy interval is one of a few modifiable risk factors for these complications. Therefore, the objective of this study was to examine the intersection of sociodemographic factors and the incidence of adverse maternal and neonatal outcomes based on the degree of short interpregnancy intervals in a cohort of an urban population in Milwaukee, Wisconsin, where short interpregnancy intervals complicate 30% of pregnancies.[5]

Table 1. Maternal Characteristics Stratified by Short Interpregnancy Intervals (IPI)

Maternal Characteristic	Control IPI ≥18 months (N = 978)	Short IPI <6 months (N = 80)	Short IPI 6-11 months (N = 181)	Short IPI 12-17 months (N = 223)	*P* value[b]
Maternal age at delivery (years)[a]	31.8 (27.8-34.7)	25.7 (22.6-30.8)	30.4 (25.2-33.5)	31.4 (28.3-34.1)	<0.001
Maternal race/ethnicity					<0.001
Non-Hispanic White	557 (57.0%)	27 (33.8%)	99 (54.7%)	165 (74.0%)	
Non-Hispanic Black	245 (25.1%)	42 (52.5%)	52 (28.7%)	35 (15.7%)	
Hispanic	93 (9.5%)	3 (3.8%)	11 (6.1%)	9 (4.0%)	
Other	83 (8.5%)	8 (10.0%)	19 (10.5%)	14 (6.3%)	
Prepregnancy body mass index (kg/m^2)[a]	26.9 (23.4-32.3)	29.7 (23.9-35.3)	26.0 (22.1-31.1)	24.3 (21.6-28.4)	<0.001
Marital status					<0.001
Married	593 (60.8%)	25 (31.3%)	107 (59.1%)	169 (75.8%)	
Single	354 (36.3%)	55 (68.8%)	70 (38.7%)	51 (22.9%)	
Divorced/widowed	29 (3.0%)	0 (0.0%)	4 (2.2%)	3 (1.4%)	
Insurance					<0.001
Private	567 (58.1%)	24 (30.0%)	98 (54.1%)	168 (75.3%)	
Public	405 (41.5%)	56 (70.0%)	82 (45.3%)	54 (24.2%)	
None	4 (0.4%)	0 (0.0%)	1 (0.6%)	1 (0.5%)	
Chronic hypertension	34 (3.5%)	2 (2.5%)	5 (2.8%)	4 (1.8%)	0.677
Smoking in pregnancy	88 (9.0%)	11 (13.8%)	12 (6.6%)	10 (4.5%)	0.033

[a]Data are presented as median and interquartile range.
[b]*P* value represents comparison of all 4 groups.

Table 2. Multivariable Adjusted Regression Model for Maternal Factors Associated With Short Interpregnancy Intervals (IPI)

	Short IPI <6 months Adjusted OR (95% CI)	Short IPI 6 – 11 months Adjusted OR (95% CI)	Short IPI 12 – 17 months Adjusted OR (95% CI)
Maternal age at delivery	**0.86 (0.81 – 0.91)**	**0.92 (0.88 – 0.95)**	**0.92 (0.89 – 0.96)**
Maternal race/ethnicity			
Non-Hispanic White	Referent	Referent	Referent
Non-Hispanic Black	1.34 (0.71 – 2.50)	0.90 (0.56 – 1.44)	0.63 (0.38 – 1.04)
Hispanic	0.37 (0.10 – 1.30)	0.57 (0.28 – 1.16)	0.37 (0.17 – 0.82)
Other	1.71 (0.72 – 4.07)	1.23 (0.70– 2.17)	0.62 (0.34 – 1.14)
Prepregnancy body mass index	1.03 (0.99 – 1.06)	0.96 (0.93 – 1.01)	0.96 (0.93 – 0.98)
Marital Status			
Married	Referent	Referent	Referent
Single	1.25 (0.63 – 2.47)	0.80 (0.50 – 1.30)	0.72 (0.44 – 1.18)
Divorced/widowed	—	0.84 (0.28 – 2.58)	0.63 (0.18 – 2.18)
Insurance			
Private	Referent	Referent	Referent
Public	1.26 (0.65 – 2.44)	1.08 (0.68 – 1.71)	0.62 (0.39 – 0.99)
None	—	2.22 (0.23 – 21.20)	1.65 (0.17 – 16.21)
Chronic hypertension	0.54 (0.12 – 2.58)	1.08 (0.40 – 2.91)	0.81 (0.27 – 2.39)
Smoking in pregnancy	0.99 (0.47 – 2.09)	0.67 (0.34 – 1.31)	0.62 (0.30 – 1.27)

METHODS

Study Population and Design

This was a retrospective cohort study of individuals with a singleton pregnancy between 2015 and 2018 receiving prenatal care at Froedtert and the Medical College of Wisconsin (MCW) in Milwaukee, Wisconsin. Institutional review board approval was obtained at MCW prior to any study procedures. Individuals were included in the study if they were 18 years or older and delivered at least 2 singleton pregnancies at a gestational age of 20 to 42 weeks. Individuals were excluded if they had a multifetal gestation, a previous preterm birth, had no delivery information, or did not have enough information about the index pregnancy and prior pregnancy in electronic health records (EHR). The interpregnancy interval was calculated using the last menstrual period of the index pregnancy subtracted from delivery date of previous pregnancy. It was considered short if less than 540 days. If the date of the last menstrual period was not known, first trimester ultrasound dating was used to calculate the date of conception.

Assessment of Exposure and Outcome Variables

The primary outcome was incidence of preterm birth, defined as giving birth prior to 37 weeks. Secondary outcomes included hypertensive disorders of pregnancy, defined as gestational hypertension or preeclampsia using ACOG criteria;[20] low birth weight (<2500 g); gestational diabetes; and presence of congenital anomaly. These outcomes were compared by 4 groups of interpregnancy intervals: less than 6 months, 6 to 11 months, 12 to 17 months,

Table 3. Pregnancy Outcomes Stratified by Short Interpregnancy Intervals (IPI)

≥18 months Pregnancy Outcome	Controls <6 months (N=978)	Short IPI 6–11 months (N=80)	Short IPI 12–17 months (N=181)	Short IPI *P* value (N=223)	
Cesarean delivery	43 (4.4%)	3(3.8%)	8 (4.4%)	13 (5.8%)	0.799
Hypertensive disorders of pregnancy	60 (6.1%)	6 (7.5%)	6 (3.3%)	8 (3.6%)	0.201
Preterm birth (37 weeks)	61 (6.2%)	12 (15.0%)	8 (4.4%)	13 (5.8%)	0.011
Low birth weight (<2500 g)	53 (5.4%)	6 (7.5%)	6 (3.3%)	7 (3.1%)	0.244
Congenital anomalies	22 (2.3%)	4 (5.0%)	8 (4.4%)	13 (5.8%)	0.024
Gestational diabetes	62 (6.3%)	3 (3.8%)	3 (1.7%)	9 (4.0%)	0.041

Table 3. Unadjusted and Adjusted Analyses for Pregnancy Outcomes Stratified by the Length of Interpregnancy Interval

Pregnancy Outcome	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)
Preterm birth (<37 weeks)		
Control (≥18 months)	Referent	Referent
Short interpregnancy interval <6 months	2.65 (1.36 – 5.16)	2.30 (1.13 – 4.68)
Short interpregnancy interval 6–11 months	0.70 (0.33 – 1.48)	0.72 (0.34 – 1.55)
Short interpregnancy interval 12–18 months	0.93 (0.50 – 1.73)	1.06 (0.56 – 1.20)
Congenital anomalies		
Control (≥ 18 months)	Referent	Referent
Short interpregnancy interval <6 months	2.28 (0.77 – 6.79)	2.39 (0.75 – 7.62)
Short interpregnancy interval 6–11 months	2.01 (0.88 – 4.58)	1.88 (0.80 – 4.38)
Short interpregnancy interval 12–18 months	2.69 (1.33 – 5.42)	2.52 (1.22 – 5.20)
Gestational diabetes		
Control (≥ 18 months)	Referent	Referent
Short interpregnancy interval <6 months	0.58 (0.18 – 1.88)	0.71 (0.21 – 2.41)
Short interpregnancy interval 6–11 months	0.25 (0.08 – 0.80)	0.26 (0.08 – 0.85)
Short interpregnancy interval 12–18 months	0.62 (0.30 – 1.27)	0.63 (0.30 – 1.30)

[a]Adjusted for maternal age, race and ethnicity, private insurance status, marital status, and smoking

and greater than or equal to 18 months. In addition, maternal demographic and clinical characteristics associated with short interpregnancy intervals were abstracted from the EHR and compared between the study groups. These included maternal age at delivery, maternal race and ethnicity, marital status, and insurance. Clinical factors abstracted included prepregnancy body mass index (BMI) (kg/m^2), history of chronic hypertension, and cigarette smoking during pregnancy.

Statistical Analysis

Data were presented as n (%) or median and interquartile range. Chi-square or Fisher exact test was used to compare categorical variables, while Mann-Whitney-Wilcoxon or Kruskal-Wallis test was used to compare continuous variables. Multinomial logistic regression analysis was performed to examine how maternal factors were associated with interpregnancy intervals. The effect of length of interpregnancy intervals on pregnancy outcomes was tested by logistic regression. Maternal age, race and ethnicity, insurance status, marital status, smoking, and history of preterm birth were included as potential confounding factors. Odds ratio (OR) or adjusted OR (aOR) with 95% confidence intervals were reported. All tests were 2-tailed and P value <0.05 was used to indicate statistical significance. All statistical analysis was done using SAS.

RESULTS

During the study period, a total of 1,462 patients met eligibility criteria and were included in the analysis. Of these, 484 (33.1%) had short interpregnancy intervals. Eighty pregnancies (5.5%) occurred at less than 6 months, 181 pregnancies (12.4%) at 6 to 11 months, 223 pregnancies (15.3%) at 12 to 17 months, and 978 pregnancies (66.9%) at 18 months or more.

Table 1 describes patient characteristics stratified by pregnancy interval. Individuals with interpregnancy intervals of less than 6 months were more likely to be non-Hispanic Black (P<0.001), have higher prepregnancy BMI (P<0.001), be single (P<0.001), have public insurance (P<0.001), and report smoking during pregnancy (P=0.033) compared to all other groups. Table 2 describes multivariate logistic regression, identifying sociodemographic characteristics independently associated with short interpregnancy intervals (IPI). Older maternal age (aOR 0.86, 95% CI, 0.81-0.91 for IPI <6 months; aOR 0.91, 95% CI, 0.88-0.95 for IPI 6-11 months; aOR 0.92, 95% CI, 0.89-0.96 for IPI 12-17 months), higher prepregnancy BMI (aOR 0.96; 95% CI, 0.93 – 0.98 for IPI 12-17 months), and Hispanic ethnicity (aOR 0.50; 95% CI, 0.31 – 0.79 for IPI 12-17 months) were associated with lower odds of short interpregnancy intervals.

Pregnancy outcomes stratified by short interpregnancy interval subgroups are depicted in Table 3. In univariate analysis, patients with interpregnancy intervals less than 6 months had the highest rate of preterm births at 15.0%, compared to a 6.2% preterm birth rate for the control group (IPI≥18 months). In addition, the rate of congenital anomalies was higher in the group with interpregnancy intervals less than 6 months and 12 to 17 months, compared to the control group (5.0% vs 5.8% vs 2.3%, respectively; P=0.024). In this cohort, there were 10 pregnancies with congenital anomalies: 6 with congenital cardiac anomalies, 2 with musculoskeletal anomalies, 1 with genitourinary anomaly, and 1 with neurologic anomaly. The rate of gestational diabetes was lower in the group with interpregnancy

intervals less than 6 months and 6 to 11 months compared to the control group (IPI ≥18 months) ($P = 0.041$).

Table 4 describes the multivariate analysis, controlling for sociodemographic and clinical confounding factors for the association between short interpregnancy intervals and adverse pregnancy outcomes. After controlling for potential confounding factors, interpregnancy intervals less than 6 months were associated with higher odds of preterm birth (aOR 2.30; 95% CI, 1.13 – 4.68). In addition, interpregnancy intervals of 12 to 17 months were associated with higher odds of congenital anomalies (aOR 2.52; 95% CI, 1.22 – 5.20). The 6- to 11-month group was associated with lower odds of gestational diabetes (aOR 0.26; 95% CI, 0.08 – 0.85).

DISCUSSION

Principal Findings

In this analysis, we found that older maternal age, Hispanic ethnicity, and higher prepregnancy BMI were associated with lower odds of short interpregnancy intervals. We also found that interpregnancy intervals less than 6 months were associated with higher odds of preterm birth, and interpregnancy intervals of 12 to 17 months were associated with higher odds of congenital anomalies. People with interpregnancy intervals of 6 to 11 months had lower risks of gestational diabetes.

Results in the Context of What is Known

As comparable to other studies, our study found the strongest association between preterm births and interpregnancy intervals less than 6 months.[21-22] Although our study did not confirm the higher risk of preterm birth with short interpregnancy intervals of 6 to 17 months, this may be due to smaller sample size and a weaker association with preterm birth in these specific subgroups.[10,23]

Based on our findings, we demonstrate a novel association between short interpregnancy intervals of 12 to 17 months and congenital anomalies. Several studies demonstrate increased odds of specific birth defects associated with an interval of less than 5 months and less than 6 months, and one study found an increased risk of certain defects (specifically cardiac defects and central nervous system anomalies) associated with interpregnancy intervals of 6 to 11 months, but none have directly correlated a statistically significant interval such as ours.[11,12,23,24,25] The lack of standardized categorization of short interpregnancy interval subgroups makes comparing our results to previous studies less clear. Nevertheless, our findings reinforce that an association is plausible, as it may be related to maternal depletion of important micronutrients to fetal health, such as folic acid. Since at least 30% of pregnancies are complicated by short interpregnancy intervals and approximately 50% of pregnancies in the US are unplanned, one strategy to reduce the risk of congenital anomalies could be to recommend the continuation of prenatal vitamins 1 to 2 years after pregnancy, especially in lactating patients.[1,4,26]

The association between interpregnancy intervals of 6 to 11 months and lower rates of gestational diabetes was an unexpected finding. A previous study by Hanley et al found an opposite association between short interpregnancy intervals less than 6 months and higher rates of gestational diabetes.[19] This association was supported by the hypothesis that there is less time to lose weight that was gained during the previous pregnancy, which ultimately leads to an increased risk of gestational diabetes. It would be important to investigate if a confounding factor was lack of time to complete screening for gestational diabetes, given association between inadequate prenatal care/late prenatal care and short interpregnancy intervals.[27]

Strengths and Limitations

A strength of the study is data verification through EHR abstraction, done by authors of this paper (EP, SA, MM, and BM). This allowed for high accuracy compared to most studies on this subject, which use administered data sets or birth certificate records.[3] Using verified medical record abstraction avoids the possibility of underreporting and/or data inaccuracy associated with administered and birth certificate records. Another strength is the characteristics of the study cohort. The cohort consisted of urban pregnant individuals of Milwaukee, Wisconsin – an area with high rates of preterm birth – where preventing short interpregnancy intervals could have a substantial impact on perinatal health. In addition, we excluded patients with prior preterm birth – the highest risk factor for preterm birth.

Despite these strengths, our study has a few limitations. First, the data collection regarding sociodemographic factors was based on EHR abstraction. Data on maternal education, housing instability, food insecurity, income, and many other important social risk factors, such as access to contraception, were missing. Second, we were unable to control for pregnancy intention. Knowing that unintended pregnancies previously have been linked to adverse obstetrical outcomes, this may have been a potential confounding factor.[28] Moreover, we did not have data on the degree of knowledge among reproductive-age individuals in our cohort regarding recommended pregnancy interval and risks associated with short interpregnancy intervals. One important future research direction could be assessing individual and community awareness of the definition of short interpregnancy intervals and associated pregnancy risks. Lastly, due to our desire to verify our data rather than use administered data, we had an overall small sample size.

CONCLUSIONS

We found that an interpregnancy interval of less than 6 months was the only group of short interpregnancy intervals associated with higher odds of preterm birth and that the interpregnancy interval of 12 to 17 months was associated with higher odds of congenital anomalies. Future research should focus on assessing

community awareness of short interpregnancy intervals and the associated risks, identifying modifiable risk factors, and designing interventions to reduce short interpregnancy intervals.

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REFERENCES

1. World Health Organization. Report of a WHO technical consultation on birth spacing: Geneva, Switzerland: June 13-15, 2005. Accessed April 19, 2022. https://www.who.int/publications/i/item/WHO-RHR-07.1

2. Xu T, Miao H, Chen Y, Luo L, Guo P, Zhu Y. Association of interpregnancy interval with adverse birth outcomes. *JAMA Netw Open*. 2022;5(6):e2216658. doi:10.1001/jamanetworkopen.2022.16658

3. Thoma ME, Copen CE, Kirmeyer SE. Short interpregnancy intervals in 2014: differences by maternal demographic characteristics. *NCHS Data Brief.* 2016;(240):1-8. Accessed June 20, 2022. https://www.cdc.gov/nchs/data/databriefs/db240.pdf

4. Copen CE, Thoma ME, Kirmeyer S. Interpregnancy intervals in the United States: data from the birth certificate and the national survey of family growth. *Natl Vital Stat Rep.* 2015;64(4):1-11. Accessed June 20, 2022. https://www.cdc.gov/nchs/data/nvsr/nvsr64/nvsr64_03.pdf

5. Wisconsin Department of Health Services, Division of Public Health, Office of Health Informatics. Annual Wisconsin birth and infant mortality report, 2017 (P-01161-19). June 2019. Accessed June 21, 2022.. https://www.dhs.wisconsin.gov/publications/p01161-19.pdf

6. Ngui E, Michalski K. Milwaukee fetal and infant mortality report: status report on 2016-2018 stillbirths and deaths. Milwaukee Health Department and Joseph J Zilber School of Public Health; December 2021. Accessed July 7, 2022.. https://city.milwaukee.gov/ImageLibrary/Groups/healthAuthors/ADMIN/PDFs/Reports/FIMRREPORT2021FINAL.pdf

7. Obstetric care consensus no. 8 summary: interpregnancy care. *Obstet Gynecol.* 2019;133(1):220-225. doi:10.1097/AOG.0000000000003026

8. Conde-Agudelo A, Rosas-Bermúdez A, Kafury-Goeta AC. Birth spacing and risk of adverse perinatal outcomes: a meta-analysis. *JAMA*. 2006;295(15):1809-1823. doi:10.1001/jama.295.15.1809

9. Appareddy S, Pryor J, Bailey B. Inter-pregnancy interval and adverse outcomes: evidence for an additional risk in health disparate populations. *J Matern Fetal Neonatal Med.* 2017;30(21):2640-2644. doi:10.1080/14767058.2016.1260115

10. Koullali B, Kamphuis EI, Hof MH, et al. The effect of interpregnancy interval on the recurrence rate of spontaneous preterm birth: a retrospective cohort study. *Am J Perinatol.* 2017;34(2):174-182. doi:10.1055/s-0036-1584896

11. Shachar BZ, Mayo JA, Lyell DJ, et al. Interpregnancy interval after live birth or pregnancy termination and estimated risk of preterm birth: a retrospective cohort study. *BJOG*. 2016;123(12):2009-2017. doi:10.1111/1471-0528.14165

12. Smits LJ, Elzenga HM, Gemke RJ, Hornstra G, van Eijsden M. The association between interpregnancy interval and birth weight: what is the role of maternal polyunsaturated fatty acid status?. *BMC Pregnancy Childbirth*. 2013;13:23. doi:10.1186/1471-2393-13-23

13. Lieberman E, Lang JM, Ryan KJ, Monson RR, Schoenbaum SC. The association of inter-pregnancy interval with small for gestational age births. *Obstet Gynecol.* 1989;74(1):1-5.

14. Chen I, Jhangri GS, Lacasse M, Kumar M, Chandra S. Relationship between interpregnancy interval and adverse perinatal and neonatal outcomes in Northern Alberta. *J Obstet Gynaecol Can*. 2015;37(7):598-605. doi:10.1016/S1701-2163(15)30197-3

15. Smits LJ, Essed GG. Short interpregnancy intervals and unfavourable pregnancy outcome: role of folate depletion. *Lancet*. 2001;358(9298):2074-2077. doi:10.1016/S0140-6736(01)07105-7

16. van Eijsden M, Smits LJ, van der Wal MF, Bonsel GJ. Association between short interpregnancy intervals and term birth weight: the role of folate depletion. *Am J Clin Nutr.* 2008;88(1):147-153. doi:10.1093/ajcn/88.1.147

17. Hutcheon JA, Nelson HD, Stidd R, Moskosky S, Ahrens KA. Short interpregnancy intervals and adverse maternal outcomes in high-resource settings: an updated systematic review. *Paediatr Perinat Epidemiol.* 2019;33(1):048-059. doi:10.1111/ppe.12518

18. Ball SJ, Pereira G, Jacoby P, de Klerk N, Stanley FJ. Re-evaluation of link between interpregnancy interval and adverse birth outcomes: retrospective cohort study matching two intervals per mother. *BMJ*. 2014;349:g4333. doi:10.1136/bmj.g4333

19. Hanley GE, Hutcheon JA, Kinniburgh BA, Lee L. Interpregnancy interval and adverse pregnancy outcomes: an analysis of successive pregnancies. *Obstet Gynecol.* 2017;129(3):408-415. doi:10.1097/AOG.0000000000001891

20. Gestational hypertension and preeclampsia: ACOG practice bulletin, number 222. *Obstet Gynecol.* 2020;135(6):e237-e260. doi:10.1097/AOG.0000000000003891

21. DeFranco EA, Stamilio DM, Boslaugh SE, Gross GA, Muglia LJ. A short interpregnancy interval is a risk factor for preterm birth and its recurrence. *Am J Obstet Gynecol.* 2007;197(3):264.e1-264.e2646. doi:10.1016/j.ajog.2007.06.042

22. Fuentes-Afflick E, Hessol NA. Interpregnancy interval and the risk of premature infants. *Obstet Gynecol.* 2000;95(3):383-390. doi:10.1016/s0029-7844(99)00583-9

23. Zhu BP. Effect of interpregnancy interval on birth outcomes: findings from three recent US studies. *Int J Gynaecol Obstet.* 2005;89 Suppl 1:S25-S33. doi:10.1016/j.ijgo.2004.08.002

24. Petersen JM, Yazdy MM, Getz KD, Anderka MT, Werler MM; National Birth Defects Prevention Study. Short interpregnancy intervals and risks for birth defects: support for the nutritional depletion hypothesis. *Am J Clin Nutr.* 2021;113(6):1688-1699. doi:10.1093/ajcn/nqaa436

25. Ekin A, Gezer C, Taner CE, Ozeren M, Mat E, Solmaz U. Impact of interpregnancy interval on the subsequent risk of adverse perinatal outcomes. *J Obstet Gynaecol Res.* 2015;41(11):1744-1751. doi:10.1111/jog.12783

26. Finer LB, Zolna MR. Declines in unintended pregnancy in the United States, 2008-2011. *N Engl J Med.* 2016;374(9):843-852. doi:10.1056/NEJMsa1506575

27. Teitler JO, Das D, Kruse L, Reichman NE. Prenatal care and subsequent birth intervals. *Perspect Sex Reprod Health.* 2012;44(1):13-21. doi:10.1363/4401312

28. Hall JA, Benton L, Copas A, Stephenson J. Pregnancy intention and pregnancy outcome: systematic review and meta-analysis. *Matern Child Health J*. 2017;21(3):670-704. doi:10.1007/s10995-016-2237-0

Cannabis Use Among Female Community College Students Who Use Alcohol in a State With and a State Without Nonmedical Cannabis Legalization in the US

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ABSTRACT

Introduction: Female community college students who use alcohol may be an at-risk group for cannabis use, especially in US states with nonmedical cannabis legalization. This study examined cannabis use among this population. We tested differences in current cannabis use across a state with versus a state without (Washington vs Wisconsin, respectively) nonmedical cannabis legalization.

Methods: This cross-sectional study included female students aged 18-29 who were current alcohol users attending a community college. An online survey assessed lifetime and current cannabis use (last 60 days) via the Customary Drinking and Drug Use Record. Logistic regression tested whether community college state and demographic characteristics were associated with current cannabis use.

Results: Among 148 participants, 75.0% (n = 111) reported lifetime cannabis use. The majority of participants from Washington (81.1%, n = 77) and Wisconsin (64.2%, n = 34) reported ever trying cannabis. Almost half of participants (45.3%, n = 67) indicated current cannabis use. Among Washington participants, 57.9% (n = 55) reported current use compared to 22.6% (n = 12) of Wisconsin participants. Washington school attendance was positively associated with current cannabis use (OR = 5.97; 95% CI, 2.50-14.28, $P < 0.001$), after controlling for age, race, ethnicity, grade point average, and income.

Conclusions: High cannabis use in this sample of female drinkers – particularly in a state with nonmedical cannabis legalization – underscores the need for prevention and intervention efforts targeted to community college students.

INTRODUCTION

College students are an at-risk population for cannabis use, with approximately 30% of 4-year college students reporting lifetime cannabis use.[1] As many as 20% of college students report past-30-day cannabis use, and almost 80% report that the substance is fairly or very easy to obtain.[2] Cannabis is associated with adverse health consequences, psychological impairment, and academic difficulties.[3] Increased frequency of cannabis use has been associated with an increase in alcohol use and more risky sexual behaviors.[4] These findings underscore the importance of research into risk factors associated with college students' cannabis use.

The legalization of nonmedical cannabis use could be an important influence on college students' cannabis use. Nonmedical cannabis use is legal in 18 states, and medicinal cannabis is legal in 36 states and Washington, D.C.[5] Such state-level cannabis legalization may increase perceptions of safety and normative approval among 4-year college students.[6-8] Further, growing evidence suggests a link between nonmedical cannabis legalization and frequency of use.[9,10] These findings highlight evidence of an association between nonmedical cannabis legalization and use and perceptions of the substance among college students. Thus, it is important to understand factors that may place college students at particular risk in states with legalization of nonmedical cannabis.

Demographic characteristics are associated with the use of illicit substances and marijuana.[11-16] In particular, the type of col-

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lege in which a student enrolls, alcohol use, and gender could be important indicators of risk for cannabis use. Community college students are more likely than 4-year college students to report frequent cannabis use.[17] However, they may have limited access to health resources, given that less than half of community colleges have campus health centers.[18] Additionally, when alcohol use is combined with cannabis use, risks of harm may be heightened. Among 4-year college students, those who use both cannabis and alcohol drink more alcohol and experience more related problems, including blackouts, injuries, and drunk driving.[19-22] Female college students may face unique risks. Early evidence suggests that females may be more sensitive to the effects of cannabis and develop problematic cannabis use more quickly.[23-25] For female college students, cannabis use is associated with greater alcohol-related harm, even when alcohol use is held constant.[26] Further, in states with nonmedical cannabis legalization, female 4-year college students show greater increases in use of the substance than their male counterparts at 4-year colleges.[27] Female community college students who use alcohol may face heightened risks with regard to cannabis and could be particularly susceptible to effects of nonmedical cannabis legalization.

Few studies have examined cannabis use among community college students.[17] Specific gaps remain in our understanding of cannabis use among community college students who use alcohol and identify as female; female community college students who use alcohol may represent an at-risk group for cannabis use. Further, most studies on associations between nonmedical cannabis legalization and use have focused on 4-year college students.[6-9,27] This study sought to understand cannabis use among female community college students who use alcohol, specifically lifetime, current, and frequency of cannabis use. We assessed differences between students in a state with and a state without nonmedical cannabis legalization, examining across demographic characteristics. As our study population is focused on alcohol users, we include an assessment of problematic alcohol use prevalence and any differences by state in problem alcohol use prevalence.

METHODS

This cross-sectional, secondary analysis used online survey data collected during a larger study of community college students' substance use and social media use. The study received approval from the University of Wisconsin Health Sciences Institutional Review Board and the 5 participating community colleges.

Setting

This study took place at 5 community colleges: 2 in Washington and 3 in Wisconsin. Similar to previous research, we defined a community college as a post-secondary school offering 2-year degrees.[28,29] Data were collected between March 2018 and December 2019.

Subjects

Individuals met eligibility criteria for the larger study if they were enrolled in a community college, 18-29 years old, English-speaking, a Facebook account owner (with at least monthly use), and a current alcohol user (within the last 28 days) with at least 1 episode of heavy episodic drinking (4+/5+ drinks female/males) in the past year. Students were excluded from the larger study if they were enrolled in community college courses prior to high school graduation. For this secondary analysis, only female-identifying students were included.

Recruitment and Survey Procedures

Recruitment strategies for this secondary analysis study were the same as those used in the larger study. These recruitment strategies were developed in partnership with each community college site in order to respect local rules and preferences, as well as to use approaches associated with successful past recruitment efforts. These strategies included combinations of 3 recruitment approaches. First, we shared information about the study on community colleges' websites. Second, established community college listservs were used to distribute a maximum of 3 emails with information about the study to current students. Finally, study flyers were displayed at public sites on the community college campuses. Interested students were directed to complete an online eligibility screening survey, and eligible, prospective participants were invited to complete an online consent process. Following the consent process, participants were invited to complete an online survey. The survey took 45 to 60 minutes, and participants received a $20 check incentive upon completion.

Measures

Cannabis Use. The validated Customary Drinking and Drug Use Record (CDDR) was utilized to assess participants' cannabis use.[30] To assess lifetime cannabis use, this instrument asked participants to indicate whether they had ever used the substance (yes or no) and to enter the approximate number of times (open-ended response options). For current cannabis use, participants were asked to indicate whether they used cannabis in the last 60 days and to enter the approximate number of times. Responses for number of times (open-ended response options) were recoded to yes (any use) or no (no use).

Alcohol Use. The Alcohol Use Disorders Identification Test (AUDIT) is a validated 10-item self-administered screening instrument for hazardous and harmful alcohol consumption.[31] The AUDIT indicates alcohol consumption, drinking behavior, and alcohol-related problems. Responses to each item are scored from 0 to 4, yielding a maximum possible score of 40. A score of less than 7 suggests low-risk consumption, while 8 to 14 suggests hazardous consumption, and 15+ indicates possible alcohol dependence. The validated AUDIT-C, or the AUDIT-Consumption, which focuses on general use of alcohol, also was

used. This instrument consists of 3 items of the full-scale AUDIT and assesses frequency of drinking, typical drinks consumed on a drinking day, and frequency of heavy drinking.[32] Responses to each of these 3 items are scored from 0 to 4, yielding a maximum possible score on the AUDIT-C of 12. A score of 4 for males or 3 for females suggests that drinking may be affecting one's health or safety. Both overall AUDIT scores and AUDIT-C scores were analyzed.

Demographic Information. Demographic information included age, race, ethnicity (Hispanic or not Hispanic), community college state (Wisconsin or Washington), most recent grade point average, and annual income. For most recent grade point average, participants were asked to choose from a list of grade point range options, from 0.0-0.5 to 3.6-4.0. For annual income, participants were asked to choose the appropriate range from a Likert scale spanning from less than $2,000 per year to more than $100,000 per year.

Analysis. Descriptive statistics were summarized as frequencies, percentages, and means. For analyses, given limited demographic diversity, we coded race into 2 categories: White and all other races. Multiple logistic regression was conducted to test whether community college state was associated with current cannabis use after controlling for demographic information. All analyses were conducted using SPSS 27. All *P* values were 2-sided, and $P < 0.05$ was used to indicate statistical significance.

RESULTS

Out of 726 students who completed the eligibility screening survey, 254 met eligibility criteria for the main study, and 187 enrolled. Out of 172 who completed the online survey, 148 identified as female and were included in analyses. Among these 148 participants, 76.4% identified as White/Caucasian, and 64.2% reported attending a community college in Washington. The average age was 22.89 years (SD = 3.31) with a range of 18 to 29. For full demographic information, see Table 1. The mean AUDIT score was 8.05 (SD = 5.66), and the mean AUDIT-C score was 4.16 (SD = 2.08). The mean AUDIT score for Wisconsin students was 7.54 (SD = 5.23), and for Washington students, the mean was 8.34 (SD = 5.90). Mean AUDIT-C scores were 4.55 (SD = 2.16) for Wisconsin students and 3.95 (SD = 2.02) for Washington students. Independent samples *t* test indicated there were no significant differences in overall AUDIT ($t(146) = -0.81$, $P = 0.41$) or AUDIT-C ($t(146) = 1.69$, $P = 0.094$) scores between participants from Washington and Wisconsin.

Three-quarters (75.0%, n = 111) of participants reported cannabis use at least once in their lifetime. These participants reported using cannabis an average of 136.11 times (SD = 210.49). Approximately 81.1% (n = 77) of participants attending a Washington community college reported lifetime cannabis use, and they reported ever using cannabis an average of 120.85 times (SD = 174.89). Among participants attending a Wisconsin community college, 64.2% (n = 34) reported use of cannabis at least once in their lifetime; these participants reported ever using cannabis an average of 83.66 times (SD = 163.96).

Table 1. Demographic Information for Female Community College Participants From Two States, N = 148

	Number (%)
Race	
White/Caucasian	113 (76.4%)
Other	9 (6.1%)
Asian or Asian American	6 (4.1%)
American Indian/ Alaska Native	3 (2.0%)
Black or African American	3 (2.0%)
Multiracial	3 (2.0%)
Native Hawaiian or Other Pacific Islander	1 (0.7%)
Did not report	10 (6.8%)
Ethnicity	
Non-Hispanic/Non-Latino	108 (73.0%)
Hispanic/Latino	38 (25.7%)
Missing	2 (1.4%)
Community college state	
Washington	95 (64.2%)
Wisconsin	53 (35.8%)
Most recent grade point average	
3.0 or greater	109 (73.6%)
2.0-2.9	33 (22.3%)
1.0-1.9	5 (3.4%)
0.0-0.9	1 (0.7%)
Annual income	
Less than $2,000	15 (10.1%)
Between $2001 and $5,000	17 (11.5%)
Between $5,001 and $10,000	21 (14.2%)
Between $10,001 and $15,000	25 (16.9%)
Between $15,001 and $25,000	30 (20.3%)
Between $25,001 and $50,000	34 (23.0%)
Between $50,001 and $75,000	3 (2.0%)
Between $75,001 and $100,00	1 (0.7%)
More than $100,000	1 (0.7%)
Did not report	1 (0.7%)

Current Cannabis Use

Across all participants, 45.3% (n = 67) reported current cannabis use, with an average of 6.54 times (SD = 9.44) in the last 60 days. Over half of participants attending a Washington community college (57.9%, n = 55) reported current cannabis use, and they indicated an average of 6.54 (SD = 9.44) times using the substance in the last 60 days. Among participants attending a Wisconsin community college, 22.6% (n = 12) reported current cannabis use; these participants reported using the substance an average of 1.81 (SD = 5.96) times in the last 60 days. Lifetime cannabis use was not significantly correlated with the AUDIT-C score ($r(148) = -0.02$, $P = 0.77$) or the full AUDIT score ($r(148) = 0.07$, $P = 0.41$).

The logistic regression analysis (Table 2) showed a significant association between community college state and cannabis use

in the last 60 days. Results showed that Washington students had a greater odds of reporting current use than Wisconsin students (OR = 5.97; 95% CI, 2.50-14.28, $P < 0.001$). Age, ethnicity, race, grade point average, and annual income were not found to be significantly associated with current cannabis use.

Table 2. Summary of Logistic Regression of Characteristics Associated With Past 60 Day Cannabis Use (N = 148)

Predictor	ß	SE	Odds Ratio	95% CI	*P* value
Age	-0.08	0.06	0.92	0.82 – 1.05	0.21
Ethnicity	0.41	0.51	1.51	0.55 – 4.10	0.42
Race	0.39	0.54	1.48	0.51 – 4.29	0.47
Grade point average	0.05	0.18	1.05	0.73 – 1.51	0.78
Annual income	0.16	0.11	1.17	0.94 – 1.46	0.16
Community college state	1.79	0.45	5.97	2.50 – 14.28	< 0.001

DISCUSSION

This study addressed gaps in the literature around the use of cannabis by community college students, namely those who use alcohol and identify as female. Differences in cannabis use between students in a state with and without legalized nonmedical cannabis use were examined. Findings suggest that current (past 60 days) use of cannabis is relatively common among female community college students who use alcohol, with more students reporting current use in a state with nonmedical cannabis legislation compared to a state without nonmedical cannabis legislation.

Lifetime cannabis use was common in the sample; approximately three-fourths of students had tried cannabis at least once. This is higher in comparison to past research reporting nearly half of 4-year college students with lifetime use but is consistent with previous research suggesting associations between college students' alcohol and cannabis use.[4,19] Further, we found that almost half of our sample of female community college students who reported alcohol use also reported current cannabis use. This finding is important given previous studies have found that more frequent cannabis use is more harmful, such as a study that found that daily users of cannabis exhibit more characteristics of dependency compared to lifetime or infrequent users.[33] A previous study of 4-year college students found that approximately 20% reported current use, comparatively lower than observed in the current study.[2] However, this study was of a broad population of college students across the US. This study's findings of comparatively high lifetime and current cannabis use suggest that female community college students who use alcohol are an at-risk group for cannabis use.

The study's main finding was that the most salient predictor of current cannabis use was community college state, with Washington students more likely to report current use compared to Wisconsin students. Washington has legalized nonmedical cannabis use; this may be a contributor to the higher lifetime and current cannabis use among those female community college students. One possible explanation for our findings may be the shifting perceptions of safety and harm around cannabis use. Studies have shown that only about a third of young adults think cannabis use places the user at risk, compared to over half a decade ago.[2] These perceptions may be particularly strong in states that have legalized nonmedical cannabis use. One study found that for some college students, legalization of nonmedical use is associated with perceptions that cannabis use is safe or even endorsed "by the government."[7] Thus, the current study's findings suggest that nonmedical cannabis legalization could be associated with higher use of cannabis among female community college students who use alcohol. However, another possible explanation is differences in cannabis use between the two states before cannabis legalization.

Limitations

Limitations of this study include that our recruitment criteria were targeted to identify current Facebook users because of the focus of the larger study, and the current sample is relatively small. While it is possible that our findings do not generalize to non-Facebook users, previous work has found that, at the time of this study, over 80% of young adults used the platform.[34] Another limitation is that because of the recruitment strategy used by the larger study—via campus websites, flyers, and listserv emails—a response rate could not be calculated. Additionally, there was a lack of racial and ethnic diversity in the study sample. Future research should examine effects of cannabis legalization on community college students identifying with specific racial and ethnic groups. Further, the current study focused on community college students who identified as female, reported alcohol use, and were from one of two states. The risk associated with cannabis use for other groups of community college students remains unclear. Cannabis use behaviors, in particular, may differ for a general sample of community college students who do not drink alcohol.

Nevertheless, our study included participants from 5 campuses and adds to the scant literature on cannabis use among community college students, particularly the potentially at-risk group of female community college students who use alcohol. Additionally, given that Washington, but not Wisconsin, currently has a nonmedical cannabis law for adults 21 and older, self-report of cannabis use may be associated with greater stigma in Wisconsin than in Washington. It is possible that students from Wisconsin underreported cannabis use compared to those from Washington. It is also possible that underage participants underreported their cannabis or alcohol use. A further limitation is that involved community colleges were not systematically selected to represent urban and rural settings. Future studies should examine the generalizability

of findings across urban and rural campus settings. Finally, causal associations cannot be inferred from this cross-sectional study.

CONCLUSIONS

This study's finding that current cannabis use was more likely among community college students from a state with legal nonmedical cannabis than one without highlights important implications. Cannabis prevention, screening, and treatment may be of particular importance at community colleges in states with nonmedical cannabis legalization. Given that nonmedical cannabis legalization was associated with higher use among community college students, future studies should examine mechanisms underlying this relationship, such as shifting norms or perceptions of safety. Further, cannabis use in states that have legalized cannabis may be associated with use of other substances as well as being of legal age, and future studies should explore these relationships. Such studies could inform development of prevention messages around influential factors for cannabis use among community college students in states with nonmedical cannabis legalization.

Our findings highlight the need to provide prevention and intervention approaches for female community college students who use alcohol, given that cannabis use behaviors may be problematic for some students. Cannabis prevention, screening, and treatment approaches targeting community college students who use alcohol may be important to consider toward preventing harm associated with cannabis use and cannabis-alcohol co-use. These efforts may be of particular benefit to female community college students who use alcohol but could assist in mitigating cannabis-related harm for all community college students. As most community colleges do not have onsite campus health centers, novel approaches are clearly needed.[18] A previous study found that many community college campuses have an online or social media presence.[35] Thus, it is possible that prevention education or screening and referral could leverage those online resources. For example, prevention messages could be delivered through community colleges' social media profiles.

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REFERENCES

1. Suerken CK, Reboussin BA, Egan KL, et al. Marijuana use trajectories and academic outcomes among college students. *Drug Alcohol Depend.* 2016;162:137-145. doi:10.1016/j.drugalcdep.2016.02.041

2. Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE, Miech RA. Monitoring the Future National Survey Results on Drug Use, 1975–2014: Volume 2: College Students and Adults Ages 19-55. Institute for Social Research, The University of Michigan; July 2015. Accessed March 2, 2020. https://deepblue.lib.umich.edu/bitstream/handle/2027.42/137911/mtf-vol2_2014.pdf

3. Chadwick B, Miller ML, Hurd YL. Cannabis use during adolescent development: susceptibility to psychiatric illness. *Front Psychiatry.* 2013;4:129. doi:10.3389/fpsyt.2013.00129

4. Simons JS, Maisto SA, Wray TB. Sexual risk taking among young adult dual alcohol and marijuana users. *Addict Behav.* 2010;35(5):533-536. doi:10.1016/j.addbeh.2009.12.026

5. Map of marijuana legality by state. DISA Global Solutions. Accessed January 12, 2022. https://disa.com/maps/marijuana-legality-by-state

6. Elliott JC, Carey KB. Pros and cons: prospective predictors of marijuana use on a college campus. *Psychol Addict Behav.* 2013;27(1):230-235. doi:10.1037/a0029835

7. Moreno MA, Whitehill JM, Quach V, Midamba N, Manskopf I. Marijuana experiences, voting behaviors, and early perspectives regarding marijuana legalization among college students from 2 states. *J Am Coll Health*. 2016;64(1):9-18. doi:10.1080/07448481.2015.1062769

8. Wallace GT, Parnes JE, Prince MA, et al. Associations between marijuana use patterns and recreational legislation changes in a large Colorado college student sample. *Addict Res Theory*. 2020;28:211-221. doi:10.1080/16066359.2019.1622003

9. Barker AK, Moreno MA. Effects of recreational marijuana legalization on college students: a longitudinal study of attitudes, intentions, and use behaviors. *J Adolesc Health*. 2021;68(1):110-115. doi:10.1016/j.jadohealth.2020.03.039

10. Kan E, Beardslee J, Frick PJ, Steinberg L, Cauffman E. Marijuana use among justice-involved youths after California statewide legalization, 2015-2018. *Am J Public Health.* 2020;110(9):1386-1392. doi:10.2105/AJPH.2020.305797

11. Arria AM, Garnier-Dykstra LM, Caldeira KM, Vincent KB, Winick ER, O'Grady KE. Drug use patterns and continuous enrollment in college: results from a longitudinal study. *J Stud Alcohol Drugs.* 2013;74(1):71-83. doi:10.15288/jsad.2013.74.71

12. Forster M, Rogers CJ, Benjamin SM, Grigsby T, Lust K, Eisenberg ME. Adverse childhood experiences, ethnicity, and substance use among college students: findings from a two-state sample. *Subst Use Misuse.* 2019;54(14):2368-2379. doi:10.1080/10826084.2019.1650772

13. Graves JM, Whitehill JM, Miller ME, Brooks-Russell A, Richardson SM, Dilley JA. employment and marijuana use among Washington state adolescents before and after legalization of retail marijuana. *J Adolesc Health*. 2019;65(1):39-45. doi:10.1016/j.jadohealth.2018.12.027

14. Meda SA, Gueorguieva RV, Pittman B, et al. Longitudinal influence of alcohol and marijuana use on academic performance in college students. *PLoS One.* 2017;12(3):e0172213. doi:10.1371/journal.pone.0172213

15. Skidmore CR, Kaufman EA, Crowell SE. Substance use among college students. *Child Adolesc Psychiatr Clin N Am.* 2016;25(4):735-753. doi:10.1016/j.chc.2016.06.004

16. White HR, Kilmer JR, Fossos-Wong N, Hayes K, Sokolovsky AW, Jackson KM. Simultaneous alcohol and marijuana use among college students: patterns, correlates, norms, and consequences. *Alcohol Clin Exp Res*. 2019;43(7):1545-1555. doi:10.1111/acer.14072

17. Cadigan JM, Dworkin ER, Ramirez JJ, Lee CM. Patterns of alcohol use and marijuana use among students at 2- and 4-year institutions. *J Am Coll Health.* 2019;67(4):383-390. doi:10.1080/07448481.2018.1484362

18. Ottenritter N. National study on community college health. American Association of Community Colleges. 2002. Accessed August 28, 2020. https://files.eric.ed.gov/fulltext/ED503502.pdf

19. Gunn RL, Norris AL, Sokolovsky A, Micalizzi L, Merrill JE, Barnett NP. Marijuana use is associated with alcohol use and consequences across the first 2 years of college. *Psychol Addict Behav*. 2018;32(8):885-894. doi:10.1037/adb0000416

20. Haas AL, Wickham R, Macia K, Shields M, Macher R, Schulte T. Identifying classes of conjoint alcohol and marijuana use in entering freshmen. *Psychol Addict Behav.* 2015;29(3):620-626. doi:10.1037/adb0000089

21. Keith DR, Hart CL, McNeil MP, Silver R, Goodwin RD. Frequent marijuana use, binge drinking and mental health problems among undergraduates. *Am J Addict.* 2015;24(6):499-506. doi:10.1111/ajad.12201

22. Shillington AM, Clapp JD. Heavy alcohol use compared to alcohol and marijuana use: do college students experience a difference in substance use problems?. *J Drug Educ.* 2006;36(1):91-103. doi:10.2190/8PRJ-P8AJ-MXU3-H1MW

23. Nia AB, Mann C, Kaur H, Ranganathan M. Cannabis use: neurobiological, behavioral, and sex/gender considerations. *Curr Behav Neurosci Rep*. 2018;5(4):271-280.

24. Cooper ZD, Craft RM. Sex-Dependent effects of cannabis and cannabinoids: a

translational perspective. *Neuropsychopharmacology*. 2018;43(1):34-51. doi:10.1038/npp.2017.140

25. Greaves L, Hemsing N. Sex and gender interactions on the use and impact of recreational cannabis. *Int J Environ Res Public Health.* 2020;17(2):509. doi:10.3390/ijerph17020509

26. Weiss KG, Dilks LM. Marijuana, gender, and health-related harms: disentangling marijuana's contribution to risk in a college "party" context. *Sociol Spectr.* 2015;35:254-270. doi:10.1080/02732173.2015.1021064

27. Bae H, Kerr DCR. Marijuana use trends among college students in states with and without legalization of recreational use: initial and longer-term changes from 2008 to 2018. *Addiction*. 2020;115(6):1115-1124. doi:10.1111/add.14939

28. Sheffield FD, Darkes J, Del Boca FK, Goldman MS. Binge drinking and alcohol-related problems among community college students: implications for prevention policy. *J Am Coll Health*. 2005;54(3):137-141. doi:10.3200/JACH.54.3.137-142

29. Velazquez CE, Pasch KE, Laska MN, Lust K, Story M, Ehlinger EP. Differential prevalence of alcohol use among 2-year and 4-year college students. *Addict Behav.* 2011;36(12):1353-1356. doi:10.1016/j.addbeh.2011.07.037

30. Brown SA, Myers MG, Lippke L, Tapert SF, Stewart DG, Vik PW. Psychometric evaluation of the Customary Drinking and Drug Use Record (CDDR): a measure of adolescent alcohol and drug involvement. *J Stud Alcohol.* 1998;59(4):427-438. doi:10.15288/jsa.1998.59.427

31. Saunders JB, Aasland OG, Babor TF, de la Fuente JR, Grant M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption--II. *Addiction*. 1993;88(6):791-804. doi:10.1111/j.1360-0443.1993.tb02093.x

32. Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. *Arch Intern Med*. 1998;158(16):1789-1795. doi:10.1001/archinte.158.16.1789

33. Hammersley R, Leon V. Patterns of cannabis use and positive and negative experiences of use amongst university students. *Addict Res Theory*. 2006;14:189-205. doi:10.1080/16066350500453309

34. Perrin A, Anderson M. Share of U.S. adults using social media, including Facebook, is mostly unchanged since 2018. Pew Research Center. April 10, 2019. Accessed November 19, 2020. https://www.pewresearch.org/fact-tank/2019/04/10/share-of-u-s-adults-using-social-media-including-facebook-is-mostly-unchanged-since-2018/

35. Burkhart L, Moreno M. Evaluating health services and information on community college campuses. *Community Coll J Res Pract.* 2019;43:341-352. doi:10.1080/10668926.2018.1480980

Population-Level Disease Prevalence Rates Correlate With COVID-19 Mortality

George L. Morris, III, MD, MPH

ABSTRACT

Introduction: Initial reports identified preexisting conditions associated with COVID-19 mortality risk. The Centers for Disease Control and Prevention (CDC) 500 Cities Project provides prevalence rate estimates at the census tract level for these conditions. The frequency of these individual condition prevalence rates may associate with the census tracts with greater risk of COVID-19 deaths.

Objective/Research Question: Can the census tract-level outcome of Milwaukee County COVID-19 death rates correlate with the census tract-level COVID-19 individual mortality risk condition prevalence rates?

Methods: This study used the 296 Milwaukee County, Wisconsin census tracts' COVID-19 death rates per 100,000 lives to perform a linear regression with individual COVID-19 mortality risk condition prevalence rates, obtained from the CDC's 500 Cities Project, and a multiple regression with 7 condition prevalence rates. The Milwaukee County Medical Examiner provided census tract identified deaths from COVID-19 from March 2020 through May 2020. Crude death rates for these 3 months per 100,000 population were analyzed in a multiple linear regression versus prevalence rates for these conditions in each census tract.

Results: There were 295 assessable COVID-19-related deaths in Milwaukee County in early 2020. The model of crude death rates showed statistical significance with the condition prevalence rates in Milwaukee County. A regression analysis of each condition's prevalence rate showed no association with crude death rates.

Conclusions: This study supports a correlation between high COVID-19 mortality rate census tracts and prevalence rate estimates of conditions associated with high individual COVID-19 mortality rates. The study is limited by the small COVID-19 death sample and the use of a single location. The ability to focus COVID-19 health promotion may save future lives if mitigation strategies are applied extensively in these neighborhoods.

INTRODUCTION

The COVID-19 pandemic challenged public health and medical providers.[1] A fatal COVID-19 clinical course has been associated with preexisting factors, including age group, race, sex, obesity, hypertension, diabetes mellitus, cardiovascular disease, chronic pulmonary disease, and chronic kidney disease.[2] Milwaukee County neighborhoods in Wisconsin contain a wide prevalence rate range of these individual factors.[3] The disparities in COVID-19 death rates in urban settings, like Milwaukee County, are clustered among minorities and in neighborhoods known for higher prevalence rates of these conditions.[4]

Health interventions, such as social distancing, wearing face masks, and good hygiene, have been projected to significantly reduce COVID-19 transmission rates.[5] In addition, vaccine awareness and uptake has predicted a decline in COVID-19 cases in the United States.[6]

Critical health issue interventions, like health promotion for the COVID-19 pandemic, are provided in a decentralized fashion at local health departments in the US. Local data within a health department's responsible area are valuable to create tailored localized health communication.[7] The specificity of health data at a US city level (hundreds of thousands of people) or ZIP code level (tens of thousands of people) can have considerable variability, such as seen in New York City, New York.[8]

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Table 1. Mean Prevalence and Range for the Seven Relevant Disease

Factors Among Tracts	Mean Prevalence %	Range %
Chronic asthma	11.10	7.9–16.30
Coronary heart disease	6.05	2.00–12.30
Chronic obstructive pulmonary disease	6.67	2.30–12.80
Chronic renal disease	3.17	1.20–6.80
Diabetes mellitus	11.13	3.00–25.00
Hypertension	31.04	11.80–51.00
Obesity	37.24	3.00–53.70

Table 2. Model and Factor Association Values

Model	95% CI	*P* value
All conditions	-88.20 to 134.63	0.001
Chronic asthma	-12.13 to 11.72	0.973
Coronary heart disease	-40.61 to 20.98	0.531
Chronic obstructive pulmonary disease	-20.29 to 20.02	0.989
Chronic renal disease	-14.21 to 109.62	0.131
Diabetes mellitus	-13.97 to 10.30	0.766
Hypertension	-2.84 to 1.83	0.671
Obesity	-4.50 to 2.03	0.456

The US census is conducted every 10 years, and information is gathered in smaller geographic regions, known as census tracts. Data at census tract levels involve single neighborhoods (hundreds to several thousand people) and are more similar as a group than larger, ZIP code-level areas.[8] This similarity among smaller groups at the census tract level versus the larger ZIP code-level populations allows specific health issue interventions, like COVID-19 mitigation and vaccination education, for the relevant population need.[9]

Health data using small area estimates are needed but uncommon.[8] The CDC's 500 Cities Project, supported by the Robert Wood Johnson Foundation, provides prevalence rate estimates of 27 health-related issues at the census tract level based on responses to the Behavioral Risk Factor Surveillance Survey (BRFSS).[9] These issues include prevention, behaviors, and disease measures and are presented as prevalence by census tract across the United States. Health outcome measures in the 500 Cities estimates include cancer, stroke, arthritis, mental health, teeth loss, chronic asthma, coronary heart disease, diabetes, hypertension, chronic renal disease, and obesity.[9] These prevalence estimates have been confirmed with samples of national and local prevalence rates.[10,11] The measures were developed to assist with assessments of and planning for health interventions at the more granular, neighborhood level.[12] These measures have highlighted the significant disparities at the neighborhood level and the need to address disparities at that granular layer.[7] The 500 Cities prevalence data have not been confirmed as a source to predict outcomes, such as COVID-19 death rates.

The value of census tracts can be in their focused size. Kong and Zhang have documented the greater homogeneity in smaller area analysis.[7] The authors document ZIP codes as having more heterogenicity than neighborhood-level health data. For an example of the size issue, the city of Milwaukee ZIP code–53206–contains multiple census tracts and over 22,000 residents, while the largest census tract in Milwaukee County contains just over 6,000. The data provided by the 500 Cities Project have many applications. Bu et al and Perlman encourage seeing this data as a planning tool.[13,14] Copello et al have applied these prevalence data to planning for disease management.[15] This planning involves different hospitals and clinics and is aided by small census tract samples, and its use has been verified by other data sources, such as medical services billing.[7]

This study asks the research question: Can the census tract-level outcomes of Milwaukee County COVID-19 death rates correlate with the census tract-level COVID-19 individual mortality risk condition prevalence rates? The aim is to show that the neighborhoods with the highest COVID-19 death rates are associated with higher disease prevalence rates at the census tract level in Milwaukee County, Wisconsin.

METHODS

Data Sources

Health Prevalence Data: The CDC's 500 Cities Project "provided city- and census tract-level small area estimates for chronic disease risk factors, health outcomes, and clinical preventive services use for the largest 500 cities in the United States. These small area estimates allowed cities and local health departments to better understand the burden and geographic distribution of health-related variables in their jurisdictions and assisted them in planning public health interventions."[11]

Health outcomes prevalence rates include chronic asthma (CASM), coronary heart disease (CHD), chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), hypertension (HTN), chronic renal disease (CRD), and obesity (OBS). The dataset contains the relevant population of Milwaukee County residents at the census tract level (adults 17 and older) and all of the relevant disease prevalence rates associated with greater COVID-19 mortality.

COVID-19 Mortality Data: Deaths occurring in Milwaukee County from COVID-19 were tracked and provided on public request from the Milwaukee County Coroner's Office. These data contain age, sex, and census tract locations for the months March 2020 through May 2020. The coroner's office collects these data for reporting to the Wisconsin Department of Health for the National Bureau of Vital Statistics.

Analysis

Data from the 500 Cities dataset and COVID-19 mortality data were combined into a single Excel comma-separated values file

and imported for analysis into the open-source statistical package version 3.6.3 with base R statistical packages (R Foundation for Statistical Computing, Vienna, Austria).

The R code is: ModelCDRandCM<-lm(CDR~CASM+CHD+COPD+CRD+DM+HTN+OBS), where

1) Crude death rate (CDR) is defined as assessable deaths per 100,000 lives in each of 296 census tracts and
2) the 7 CPR (CASM, CHD, COPD, CRD, DM, HTN, and OBS) are the mean prevalence rates in percentages for each illness.

The assumptions of linearity, variance, independence, and normality were established by reviewing the data prior to their inclusion in the analysis. The data were reviewed in a scatter plot and in a review of the residuals for variance and distribution. The alpha value was set at 95%.

RESULTS

The Milwaukee County Medical Examiner reported 368 deaths from COVID-19 from March 2020 through May 2020. Analysis was performed on 295 deaths of Milwaukee County residents. The deaths excluded from the analysis included those not part of Milwaukee County Census Tracts (N=28) and those recorded as nursing home residents in the tract (N=45), as residents of these care facilities have unknown tract origins.

Table 1 demonstrates the mean 7 disease prevalence rates and the prevalence range across the 296 Milwaukee County census tracts. The CDR for the 296 Milwaukee County census tracts were 29.48/100,000 (range 0–224.92).

Table 2 shows the results of the model with COVID-19 crude death rates as the outcome and the disease prevalence rate percentages as multiple factors for the regression. The model with the diseases' prevalence rates showed statistical significance for the total deaths (95% CI, -88.20 to 134.63; $P < 0.001$).

The individual census tracts were not associated with death rates nor were they associated with individual disease prevalence rates ($P > 0.05$)

DISCUSSION

This study found that higher COVID-19 mortality rates were associated with the 500 Cities estimated prevalence of 7 COVID-19 mortality risk conditions at a census tract level in Milwaukee County. The model statistically significantly associated COVID-19 death rates with all these conditions together, despite the early and small COVID-19 death sample. Individual disease prevalence rates separately did not correlate with higher COVID-19 mortality. The specificity for the community COVID-19 deaths reinforces how the health data characteristics of the neighborhood can associate with the neighborhood health outcomes. This association could support using the data from the CDC 500 Cities Project to plan areas for higher priority health issue intervention.

The COVID-19 pandemic highlights health promotion planning issues. First, the 500 Cities Project data were used to project the COVID-19 impact at the city level, ZIP code level, and for individuals. Du et al used the 500 Cities estimates to identify Texas city-level medical resource needs.[16] Do and Frank used ZIP code-level data to identify how communities of color are disproportionately affected by COVID-19 mortality.[17] Their conclusions about "neighborhoods" using the ZIP codes are based on a predominance racial percentage. They identified those ZIP codes with the predominant race of White, Black, Hispanic, and Other with populations over 40,000 to 60,000 persons in group.

The demographic refinement of census tract-level information may have presented even stronger associations for the study. Jin et al created a web-based calculator for COVID-19 individual risk using some of the 500 Cities prevalence estimates.[18] Bu et al asserts that data should be linked to critical outcomes and for planning and effective intervention.[13] This study links COVID-19 death rates to a valuable outcome in identifying high COVID-19 mortality risk neighborhoods.

Additionally, the health data collected by BRFSS provided great value for a COVID-19 pandemic that was not foreseen. This study shows how the 500 Cities prevalence estimates could and may have allowed strategic interventions at a neighborhood level. Strategic planning was important, as many unexpected burdens fell on local health departments to do more with the same resources. Many health departments, including Milwaukee County, used these risk-producing diseases' maps to identify at-risk populations. This study's result suggests that disease risk association assumption with COVID-19 outcomes may have been appropriate.

Study Limitations

This study's small sample size provides statistically significant findings but with wide confidence intervals. A larger sample is currently under investigation for March 2020 through May 2021. The sample is valid only in Milwaukee County, but the 500 Cities project reaches many cities where additional confirmation could be found. Milwaukee County's significant health disparities made the county a desirable choice for study, despite the smaller sample.[3]

Second, the 500 Cities data are an estimate of disease prevalence rates based on BRFSS surveys. The validity of the projections has been confirmed in 2 studies, but warnings about using projections have been made.[10,11,19] This study does use 2 independent data sources—the 500 Cities Project and Milwaukee County Medical Examiner's report—that address these warnings.

Race, age, and socioeconomic status (SES) factors have been associated with higher COVID-19 mortality rates.[2,17] The study did find that the individual disease prevalence rates were not predictive. Race, age, and SES may not independently be correlated but collectively—as with the preexisting conditions—add to the strength of the correlation. The model strength may be enhanced

by including the census tract racial percentages, median ages, educational attainment, and income measures.

There are estimate limitations to the 500 Cities Project. Estimates are for adults 17 years and older and residents of urban areas. Childhood deaths did not appear in the first months of the pandemic, so no comparison would have been possible. Rural communities often are not collected in health data and have significant health access issues to make more health data collection valuable.

Finally, the disease prevalence percentages are a very simplistic approach to modelling a correlation. Demographic features, such as age, race, and poverty, were also part of individual risk factors for COVID-19 mortality. This report was originally intended to answer the question regarding whether conditions that posed increased mortality risk for individuals could predict population-level mortality events. More work and identified features likely will be necessary to find a well-fitted model.

CONCLUSIONS

Disease prevalence estimates that correlate death outcomes may help local health departments direct health promotion resources. Larger samples, inclusion of other parameters, and wider application to other communities would demonstrate a wider use for this approach. The COVID-19 pandemic illustrates that health data collection may have many unexpected health promotion planning benefits. Funding for health data survey expansion could improve public health resource use and health promotion effectiveness.

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REFERENCES

1. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. *JAMA*. 2020;324(8):782-793. doi:10.1001/jama.2020.12839

2. Wortham JM, Lee JT, Althomsons S, et al. Characteristics of persons who died with COVID-19 - United States, February 12-May 18, 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69(28):923-929. doi:10.15585/mmwr.mm6928e1

3. Greer DM, Baumgardner DJ, Bridgewater FD, et al. Milwaukee Health Report 2013: Health Disparities in Milwaukee by Socioeconomic Status. Center for Urban Population Health; 2014. Accessed August 25, 2021. https://institutionalrepository.aah.org/pop/1/

4. Dorn AV, Cooney RE, Sabin ML. COVID-19 exacerbating inequalities in the US. *Lancet*. 2020;395(10232):1243-1244. doi:10.1016/S0140-6736(20)30893-X

5. Ferguson NM, Laydon D, Nedjati-Gilani G, et al. *Impact of Non-Pharmaceutical Interventions (NPIs) to Reduce COVID-19 Mortality and Healthcare Demand*. Imperial College London; 2020. Report 9. Accessed April 25, 2023. https://www.imperial.ac.uk/media/imperial-college/medicine/sph/ide/gida-fellowships/Imperial-College-COVID19-NPI-modelling-16-03-2020.pdf

6. Makhoul M, Ayoub HH, Chemaitelly H, et al. Epidemiological impact of SARS-CoV-2 vaccination: mathematical modeling analyses. *Vaccines (Basel).* 2020;8(4):668. doi:10.3390/vaccines8040668

7. Kong AY, Zhang X. The use of small area estimates in place-based health research. *Am J Public Health*. 2020;110(6):829-832. doi:10.2105/AJPH.2020.305611

8. Bi Q, He F, Konty K, Gould LH, Immerwahr S, Levanon Seligson A. ZIP Code-level estimates from a local health survey: added value and limitations. *J Urban Health.* 2020;97(4):561-567. doi:10.1007/s11524-020-00423-z

9. Division of Population Health, National Center for Chronic Disease Prevention and Health Promotion. 500 Cities Project: 2016 to 2019. Updated December 8, 2020. Accessed April 25, 2023. https://www.cdc.gov/places/about/500-cities-2016-2019/index.html

10. Zhang X, Holt JB, Lu H, et al. Multilevel regression and poststratification for small-area estimation of population health outcomes: a case study of chronic obstructive pulmonary disease prevalence using the behavioral risk factor surveillance system. *Am J Epidemiol.* 2014;179(8):1025-1033. doi:10.1093/aje/kwu018

11. Klompas M, Cocoros NM, Menchaca JT, et al. State and local chronic disease surveillance using electronic health record systems. *Am J Public Health.* 2017;107(9):1406-1412. doi:10.2105/AJPH.2017.303874

12. Dorn AV, Cooney RE, Sabin ML. COVID-19 exacerbating inequalities in the US. *Lancet*. 2020;395(10232):1243-1244. doi:10.1016/S0140-6736(20)30893-X

13. Bu DD, Liu SH, Liu B, Li Y. Achieving value in population health big data. *J Gen Intern Med.* 2020;35(11):3342-3345. doi:10.1007/s11606-020-05869-0

14. Perlman SE. Use and visualization of electronic health record data to advance public health. *Am J Public Health*. 2021;111(2):180-182. doi:10.2105/AJPH.2020.306073

15. Copello E, Mease A, Umapathy K, et al. Developing a GIS dashboard tool to inform non-profit hospitals of community health needs at the neighborhood level. *J Inf Syst Appl Res.* 2020;13(2):33-53.

16. Du Z, Wang X, Pasco R, et al. COVID-19 Healthcare Demand Projections: 22 Texas Cities. UT COVID-19 Consortium; 2020. Accessed August 24, 2021. https://sites.cns.utexas.edu/sites/default/files/cid/files/covid-19_analysis_for_22_texas_cities_033020.pdf

17. Do DP, Frank R. Unequal burdens: assessing the determinants of elevated COVID-19 case and death rates in New York City's racial/ethnic minority neighbourhoods. *J Epidemiol Community Health.* 2020;jech-2020-215280. doi:10.1136/jech-2020-215280

18. Jin J, Agarwala N, Kundu P, et al. Individual and community-level risk for COVID-19 mortality in the United States. *Nat Med.* 2021;27(2):264-269. doi:10.1038/s41591-020-01191-8

19. Ogburn EL, Rudolph KE, Morello-Frosch R, Khan A, Casey JA. A warning about using predicted values from regression models for epidemiologic inquiry. *Am J Epidemiol.* 2021;190(6):1142-1147. doi:10.1093/aje/kwaa282

Skin and Soft Tissue Infections in Young Infants

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ABSTRACT

Introduction: The management of young infants with skin and soft tissue infection is not well-defined.

Methods: We performed a survey study of pediatric hospital medicine, emergency medicine, urgent care, and primary care physicians to assess the management of young infants with skin and soft tissue infection. The survey included 4 unique scenarios of a well-appearing infant with uncomplicated cellulitis of the calf with the combination of age ≤ 28 days vs 29–60 days and the presence vs absence of fever.

Results: Of 229 surveys distributed, 91 were completed (40%). Hospital admission was chosen more often for younger infants (≤ 28 days) versus older infants regardless of fever status (45% vs 10% afebrile, 97% vs 38% febrile, both $P < 0.001$). Younger infants were more likely to get blood, urine, and cerebrospinal fluid studies ($P < 0.01$). Clindamycin was chosen in 23% of admitted younger infants compared to 41% of older infants ($P < 0.05$).

Conclusions: Frontline pediatricians appear relatively comfortable with outpatient management of cellulitis in young infants and rarely pursued meningitis evaluation in any afebrile infants or older febrile infants.

INTRODUCTION

The management of young infants with skin and soft tissue infection (SSTI) has not been well-studied and, in the few available studies, appears to be highly variable in both diagnostic evaluation and therapy.[1-6] "Skin and soft tissue infection" can refer to a variety of clinical manifestations, including pustulosis, carbuncles, furuncles, cellulitis, and abscesses. In the literature addressing young infants with skin infections, the majority consider SSTI to include only pustulosis (pus-filled lesion < 1cm), cellulitis, and abscess, while more severe associated processes (osteomyelitis, septic arthritis, bacteremia, meningitis) are considered "invasive bacterial infections" (IBI) and are studied separately.

In the literature reporting on young infants (≤ 90 days) with SSTI, fever is present in 3% to 20%, and IBI rate ranged from 0.6% to 11.9%, although if the study with the highest rate by Fortunov et al is removed, the resulting range in the remaining 5 studies is much smaller at 0.6% to 2.5%.[1-6] The study by Vidwan and Geis demonstrated a correlation of IBI with fever. The risk of IBI in afebrile infants was small at 0.6%; however, the risk in febrile infants was more meaningful at 7.7%.[1] While fever often dictates management in infants ≤ 60 days, this small base of literature demonstrates that fever is not present in the majority of reported cases. The evidence-based diagnostic evaluation for febrile infants ≤ 60 days is, therefore, not applicable in many cases. The threat of IBI is a driving force in the management of infants with possible infection, but rates of IBI are low in infants with SSTI, suggesting that invasive evaluation (eg, lumbar puncture) may not always be needed. The aim of this study was to describe the preferred diagnostic and management approach to a young infant with uncomplicated cellulitis.

METHODS

This was a cross-sectional study using online surveys to assess respondent perspectives on the management of young infants

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Table 1. Description of Study Participants

	Respondent N/Total Requested N (%)
Overall Survey Response Rate	94/229 (41.0)
Overall Survey Completion Rate	91/229 (39.7)
Service Division Response Rate[a]	
Urgent Care	12/45 (26.7)
Primary Care	34/116 (29.3)
Hospital Medicine	26/30 (86.7)
Emergency Medicine	19/35 (54.3)
	Respondent N (% of Total)
Years in Practice of Respondents (N = 87)	
0-5 years	36 (41.4)
6-10 years	21 (24.1)
11-15 years	12 (13.8)
≥16 years	18 (20.7)

[a]As clinicians might work in multiple divisions, sum does not add to 100.

with SSTI. Surveys were distributed to physicians in the clinical areas of pediatric hospital medicine, pediatric primary care, pediatric emergency medicine, and pediatric urgent care within an urban Midwestern tertiary pediatric hospital system. The survey was available from June 2020 to September 2020. Participants were emailed an anonymous survey link with 3 reminders sent over the 12-week study period. The study was approved by the Institutional Review Board of the Medical College of Wisconsin, project #00037408.

The survey included 4 hypothetical scenarios of a well-appearing infant with uncomplicated cellulitis of the calf. The patient's skin exam was described as "mildly indurated area on the calf without fluctuance," and it was clearly stated in the scenario to be "consistent with a diagnosis of uncomplicated cellulitis." The combination of the infant's age (≤ 28 days vs 29–60 days) and the presence or absence of fever made each of the 4 scenarios unique (Appendix A). Participants were asked to select diagnostic tests, disposition, and antibiotics for each clinical scenario. Possible diagnostic evaluation included (multiple tests could be chosen) blood culture, urine studies, cerebrospinal fluid (CSF) studies, chest radiograph, complete blood cell count (CBC), herpes simplex virus (HSV) studies, skin swab, needle aspirate, skin ultrasound, or no further evaluation.

For disposition, participants could choose either inpatient or outpatient care. Antibiotic choice utilized skip logic based on the disposition response. If inpatient was chosen, intravenous antibiotic choices included clindamycin, nafcillin or oxacillin, ceftriaxone or cefotaxime, vancomycin, cefazolin, ampicillin, piperacillin-tazobactam, cefepime, acyclovir, and gentamicin. If outpatient was chosen, oral antibiotics options included clindamycin, cephalexin, amoxicillin, amoxicillin-clavulanate, cefdinir, cefuroxime, and cefixime. There was no limit to the number of antibiotics a participant could select. Participant demographics collected included the participants' specialty and number of years in practice. Participants were required to answer each question before responding to the next and were able to change their previous responses. The data were summarized using descriptive statistics. For management decisions, the McNemar's test was used to compare scenarios by age (17 days vs 52 days) and fever status (febrile vs afebrile). For antibiotic usage, since it was based on the disposition response, analyses were done separately for inpatient and outpatient antibiotics, and the generalized linear mixed models with binary distribution and logit link function were used. Statistical software SAS 9.4 was used for all the analyses. A P value of <0.05 was considered statistically significant.

RESULTS

A total of 229 surveys were administered and 91 were completed (40%). Most (37%) survey respondents practiced in primary care, and most (41%) were in practice less than 5 years (Table 1).

Participants were significantly more likely to choose inpatient admission for younger infants versus older infants regardless of fever status (45% vs 10% when afebrile, 97% vs 38% when febrile, both $P < 0.001$). The patient's age was a significant factor in diagnostic evaluation. In the afebrile scenarios, respondents were more likely to choose blood cultures (76% vs 52%, $P < 0.001$), CBC (76% vs 52%, $P < 0.001$), urine studies (39% vs 17%, $P < 0.001$), CSF studies (38% vs 6%, $P < 0.001$), and HSV studies (6% vs 1%, $P = 0.046$) for the 17-day-old infant vs the 52-day-old infant. Respondents were significantly less likely to choose "no further evaluation" for younger infants compared to older infants in the absence of a fever (22% vs 39%, $P < 0.001$) (Table 2).

Respondents were significantly more likely to choose inpatient admission for febrile infants of both ages compared to afebrile infants (97% vs 45% for 17 days, 38% vs 10% for 52 days, both $P < 0.001$). They were significantly more likely to choose no further evaluation for afebrile infants of both ages ($P < 0.001$). Conversely, respondents were more likely to select blood cultures, CBC, urine studies, CSF studies, and ultrasound for infants with fever compared to infants the same age without a fever (Table 2). Management decisions by age and fever status are summarized in the Figure. The relationships between years of practice and management choices were not statistically significant, with the exception that physicians with less than 10 years of practice were more likely to order urine studies on the 17-day-old infant with fever, and physicians with more than 16 years of practice were more likely to order a chest x-ray on the 17-day-old infant with fever ($P = 0.011$ and $P = 0.0098$, respectively).

Antibiotic selection varied. Ampicillin and cephalosporins were the most commonly selected inpatient intravenous (IV) antibiotic in 17-day-old infants (64% and 67%, respectively), whereas clindamycin was chosen in only 23% of admitted 17-day-old infants. In 52-day-old infants, cephalosporins and clindamycin were the most commonly selected antibiotics (45% and 41%, respectively). Sixteen respondents (10%) selected IV vancomy-

cin. Clindamycin was the most commonly selected outpatient antibiotic in 17-day-old infants (31%) compared to a 1st generation cephalosporin in 52-day-old infants (49%) (Table 3).

DISCUSSION

There have been several small, retrospective studies on the topic of young infants with SSTI that demonstrate variability in diagnostic evaluation and therapy choices.[1-6] By using a survey method, we tried to ascertain physician management decisions in the idealized circumstance of a well-appearing infant with no concern for a complication. There is an abundance of guidelines and evidence supporting admission and thorough diagnostic evaluation, including CSF sampling, in young infants with a fever.[7-10] The difficulty comes when clinicians encounter an infant with a clear source of infection, such as an SSTI. Rates of CSF sampling in studies looking at young infants with SSTI ranged from 25% to 67%.[1-6] Rates of blood cultures in the same population ranged from 13% to 96%.[1-4] In 37% to 47% of cases, no further diagnostic evaluation (either blood or CSF) was done.[1,2,6] Admission was longest and 10 times more expensive for those infants who had CSF studies done.[2] For the sake of comparison, 26% to 58% of infants 29-60 days old with a febrile urinary tract infection had CSF sampling.[11-13] Young afebrile infants ≤ 28 days with acute otitis media had CSF studies in 34% of cases and blood cultures in 53% of cases compared to 33% and 13%, respectively, in infants 29-56 days old.[14]

In our study, 92% of respondents recommended CSF studies be obtained on the 17-day-old febrile infant, in keeping with the standard of care for a febrile infant ≤28 days.[8-10] For the 17-day-old infant without fever, however, only 38% recommended CSF evaluation, which was lower than expected given the high-risk age of the infant. Less than one-quarter of respondents recommended CSF evaluation in the 52-day-old infants both with and without fever, reflecting the overall more liberal practices in this age group. As expected, the younger infant and the febrile infant had a more thorough evaluation and were significantly more likely to have a blood culture, CSF evaluation, and urine studies compared to the older and afebrile infant, respectively ($P < 0.01$ for all).

The decision to admit an infant with SSTI has been shown to vary. Even in studies with the youngest cohorts of infants ≤ 30

Table 2. Management Differences (Total N = 87, Abbreviated)[a]

Management by Age (Fever Controlled)

	Afebrile			Febrile		
	17 days	**52 days**	***P* value**	**17 days**	**52 days**	***P* value**
Recommended Evaluation (N, %)						
Blood culture	66 (75.9)	45 (51.7)	<0.001	87 (100)	80 (92.0)	0.008
Urine studies	34 (39.1)	15 (17.2)	<0.001	75 (86.2)	50 (57.5)	<0.001
Cerebrospinal fluid studies	33 (37.9)	5 (5.8)	<0.001	80 (92.0)	12 (13.8)	<0.001
Complete blood cell count	66 (75.9)	45 (51.7)	<0.001	85 (97.7)	80 (92.0)	0.025
Herpes simplex virus studies	5 (5.8)	1 (1.2)	0.046	15 (17.2)	1 (1.2)	<0.001
No further evaluation	19 (21.8)	34 (39.1)	<0.001	1 (1.2)	5 (5.8)	0.10
Disposition (N, %)						
Admission	39 (44.8)	9 (10.3)	<0.001	84 (96.6)	33 (37.9)	<0.001

Management by Fever Status (Age Controlled)

	17 days			52 days		
	Febrile	**Afebrile**	***P* value**	**Febrile**	**Afebrile**	***P* value**
Recommended Evaluation (N, %)						
Blood culture	87 (100)	66 (75.9)	<0.001	80 (92.0)	45 (51.7)	<0.001
Urine studies	75 (86.2)	34 (39.1)	<0.001	50 (57.5)	15 (17.2)	<0.001
Cerebrospinal fluid studies	80 (92.0)	33 (37.9)	<0.001	12 (13.8)	5 (5.8)	0.008
Complete blood cell count	85 (97.7)	66 (75.9)	<0.001	80 (92.0)	45 (51.7)	<0.001
Herpes simplex virus studies	15 (17.2)	5 (5.8)	0.002	1 (1.2)	1 (1.2)	>0.99
Ultrasound	26 (29.9)	16 (18.4)	0.002	21 (24.1)	13 (14.9)	0.011
No further evaluation	1 (1.2)	19 (21.8)	<0.001	5 (5.8)	34 (39.1)	<0.001
Disposition (N, %)						
Admission	84 (96.6)	39 (44.8)	<0.001	33 (37.9)	9 (10.3)	<0.001

[a]Associations with chest x-ray, skin swab, and needle aspirate were not statistically significant. Complete data are available in Appendix B.

Figure. Management by Age and Fever Status

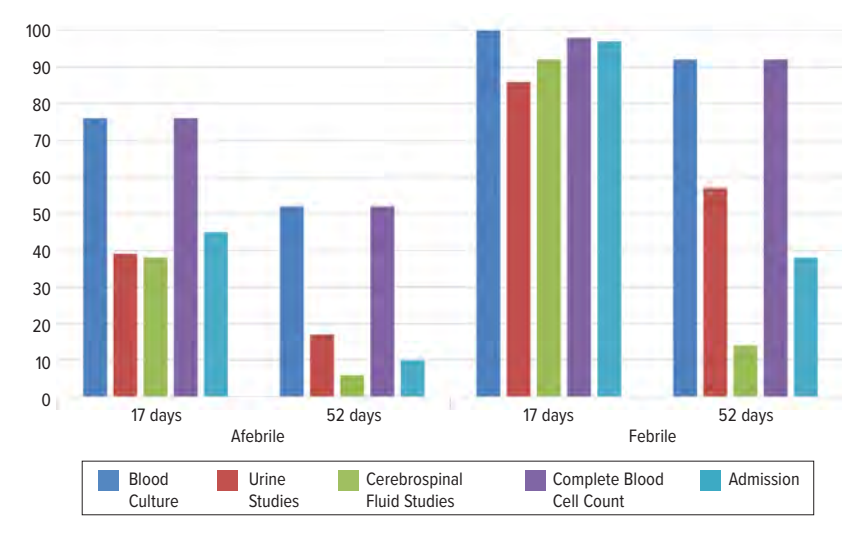

Table 3. Antibiotics by Age (Abbreviated)[a]

Inpatient Antibiotic Choice by Age			
	17 days (N=123, %)	**52 days (N=42, %)**	***P* value**
Nafcillin/oxacillin	5 (4.1)	1 (2.4)	0.41
Ampicillin	79 (64.2)	8 (19. 0)	<0.001
1st gen cephalosporin	7 (5.7)	2 (4.8)	0.96
3rd gen cephalosporin	40 (32.5)	12 (28.6)	0.64
4th gen cephalosporin	36 (29.3)	5 (11.9)	0.027
Clindamycin	28 (22.8)	17 (40.5)	0.048
Vancomycin	12 (9.8)	4 (9.5)	0.74
Outpatient Antibiotic Choice by Age			
	17 days (N=51, %)	**52 days (N=132, %)**	***P* value**
Amoxicillin	4 (7.8)	5 (3.8)	0.50
Amoxicillin-clavulanate	4 (7.8)	7 (5.3)	0.71
1st gen cephalosporin	22 (43.1)	65 (49.2)	0.40
Clindamycin	16 (31.4)	39 (29.6)	0.81

[a]Infrequently chosen antibiotics without significant associations were excluded from the Table. Complete data are available in Appendix C.

days, 12% to 36% were discharged home to complete outpatient antibiotic treatment.[3,5] In an older cohort of infants ≤90 days examined by Vidwan and Geis, 58% of afebrile infants and 59% of febrile infants were discharged home from the emergency department.[1] The large majority of respondents (97%) recommended admission of the febrile 17-day-old infants in our study, which is consistent with standard of care for a febrile infant in this age group. We were surprised to find that less than half (45%) of respondents recommended admission for the afebrile 17-day-old infant. Likewise, only 38% recommended admission for the febrile 52-day-old infant. Although this infant would not qualify as "low risk" in the febrile neonate algorithm for our institution due to the presence of a visible infection, our expectation was that more clinicians would consider the infant "high risk" and admit.

Choice of antibiotic for SSTI in young infants is not well agreed upon in the literature. Streptococci species and methicillin-sensitive *Staphylococcus aureus* (MSSA) are the most commonly implicated pathogens in nonpurulent cellulitis, and empiric therapy should be targeted toward these organisms.[15] There is good evidence that infants ≤60 days should be treated with a third-generation cephalosporin alone or in combination with ampicillin (if ≤28 days) as empiric therapy for possible sepsis.[9,16,17] Soft tissue infections are often treated with drugs targeting methicillin-resistant *Staphylococcus aureus* (MRSA), such as clindamycin or vancomycin.[18-20] Markham et al found that clindamycin was the most common (80%) antibiotic used in young infants with SSTI, and only 21% of infants received vancomycin. Combination therapy (ie, anti-staphylococcal drug with neonatal sepsis drugs) was used in 45% and was associated with a 30% longer length of stay and 40% higher costs.[4] We found a shift in the use of IV clindamycin in infants who were admitted: 52-day-old infants were significantly more likely to receive clindamycin (41% vs 23%, $P=0.048$) in addition to a 3rd or 4th generation cephalosporin. However, at our institution, 20% of all Staphylococcus aureus isolates are resistant to clindamycin, and there is evidence of rising clindamycin resistance among MSSA isolates over the last decade.[21] As empiric bacterial coverage for common SSTI organisms, clindamycin is not an ideal regimen, and these findings represent an opportunity for improved antibiotic stewardship.

Of note, at the time of our survey, we did not have any guideline for pediatric SSTI at our institution. Subsequently, a clinical practice guideline for the hospital medicine group was published in 2020 but excluded young infants. Therefore, clinical decisions were made at the discretion of the managing physician. Additionally, there is no national guideline published by the American Academy of Pediatrics or other group, to our knowledge, to drive management of SSTI in infants this age.

There were several limitations to this study. This was a survey study limited to respondents within a single tertiary care pediatrics system. We attempted to capture the physicians most likely to manage young infants by including primary care, hospital medicine, urgent care, and emergency medicine physicians; however, there are other pediatric and family practice physicians outside of our system who are also managing infants within our community. The response rate to our survey was only about 40%, and it is possible that there was bias related to the degree of comfort in managing infants with cellulitis and those physicians who chose to take the survey. The survey was administered during the pandemic, which may have affected response rates due to burnout from the large volume of emails related to pandemic concerns and other competing clinical obligations. The survey was developed by the authors of the study who practice pediatric hospital and emergency medicine, and response options were chosen based on prior literature and resources available within our health system. However, no previously validated survey on this topic exists. Inherent to all survey studies, participant answers may not reflect actual clinical practice.

CONCLUSIONS

Our findings suggest that physicians at our institution are quite comfortable with outpatient management of infants ≤28 days when afebrile and infants 29–60 days regardless of fever status. Likewise, diagnostic evaluation for meningitis with CSF studies was rarely recommended in afebrile infants regardless of age or febrile infants over 29 days. As expected, in accordance with febrile neonate guidelines, infants ≤28 days with fever were managed more aggressively, with the large majority being recommended for admission and CSF studies. With regard to antibiotic usage, we found a significant shift towards the use of clindamycin in older infants, which is not likely to be explained by any inherently higher risk of resistant bacteria and would potentially be a good target for future antimicrobial stewardship efforts.

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REFERENCES

1. Vidwan G, Geis GL. Evaluation, management, and outcome of focal bacterial infections (FBIs) in nontoxic infants under two months of age. *J Hosp Med.* 2010;5(2):76-82. doi:10.1002/jhm.583

2. Foradori DM, Lopez MA, Hall M, et al. Invasive bacterial infections in infants younger than 60 days with skin and soft tissue infections. *Pediatr Emerg Care.* 2021;37(6):e301-e306. doi:10.1097/PEC.0000000000001584

3. Kharazmi SA, Hirsh DA, Simon HK, Jain S. Management of afebrile neonates with skin and soft tissue infections in the pediatric emergency department. *Pediatr Emerg Care.* 2012;28(10):1013-1016. doi:10.1097/PEC.0b013e31826caaac

4. Markham JL, Hall M, Queen MA, et al. Variation in antibiotic selection and clinical outcomes in infants <60 days hospitalized with skin and soft tissue infections. *Hosp Pediatr.* 2019;9(1):30-38. doi:10.1542/hpeds.2017-0237

5. Fortunov RM, Hulten KG, Hammerman WA, Mason EO Jr, Kaplan SL. Evaluation and treatment of community-acquired *Staphylococcus aureus* infections in term and late-preterm previously healthy neonates. *Pediatrics*. 2007;120(5):937-945. doi:10.1542/peds.2007-0956

6. Hester G, Hersh AL, Mundorff M, et al. Outcomes after skin and soft tissue infection in infants 90 days old or younger. *Hosp Pediatr*. 2015;5(11):580-585. doi:10.1542/hpeds.2014-0232

7. Aronson PL, Wang ME, Shapiro ED, et al. Risk stratification of febrile infants ≤60 days old without routine lumbar puncture. *Pediatrics*. 2018;142(6):e20181879. doi:10.1542/peds.2018-1879

8. Huppler AR, Eickhoff JC, Wald ER. Performance of low-risk criteria in the evaluation of young infants with fever: review of the literature. *Pediatrics*. 2010;125(2):228-233. doi:10.1542/peds.2009-1070

9. Simonsen KA, Anderson-Berry AL, Delair SF, Davies HD. Early-onset neonatal sepsis. *Clin Microbiol Rev*. 2014;27(1):21-47. doi:10.1128/CMR.00031-13

10. Ferrera PC, Bartfield JM, Snyder HS. Neonatal fever: utility of the Rochester criteria in determining low risk for serious bacterial infections. *Am J Emerg Med*. 1997;15(3):299-302. doi:10.1016/s0735-6757(97)90020-6

11. Wang ME, Biondi EA, McCulloh RJ, et al. Testing for meningitis in febrile well-appearing young infants with a positive urinalysis. *Pediatrics*. 2019;144(3):e20183979. doi:10.1542/peds.2018-3979

12. Young BR, Nguyen THP, Alabaster A, Greenhow TL. The Prevalence of bacterial meningitis in febrile infants 29-60 days with positive urinalysis. *Hosp Pediatr.* 2018;8(8):450-457. doi:10.1542/hpeds.2017-0254

13. Nugent J, Childers M, Singh-Miller N, Howard R, Allard R, Eberly M. Risk of meningitis in infants aged 29 to 90 days with urinary tract infection: a systematic review and meta-analysis. *J Pediatr.* 2019;212:102-110.e5. doi:10.1016/j.jpeds.2019.04.053

14. McLaren SH, Cruz AT, Yen K, et al. Invasive bacterial infections in afebrile infants diagnosed with acute otitis media. *Pediatrics*. 2021;147(1):e20201571. doi:10.1542/peds.2020-1571

15. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;59(2):e10-e52. doi:10.1093/cid/ciu444

16. Stoll BJ, Puopolo KM, Hansen NI, et al. Early-onset neonatal sepsis 2015 to 2017, the rise of escherichia coli, and the need for novel prevention strategies. *JAMA Pediatr.* 2020;174(7):e200593. doi:10.1001/jamapediatrics.2020.0593

17. Polin RA; Committee on Fetus and Newborn. Management of neonates with suspected or proven early-onset bacterial sepsis. *Pediatrics*. 2012;129(5):1006-1015. doi:10.1542/peds.2012-0541

18. Khan A, Wilson B, Gould IM. Current and future treatment options for community-associated MRSA infection. *Expert Opin Pharmacother.* 2018;19(5):457-470. doi:10.1080/14656566.2018.1442826

19. Hatlen TJ, Miller LG. Staphylococcal skin and soft tissue infections. *Infect Dis Clin North Am.* 2021;35(1):81-105. doi:10.1016/j.idc.2020.10.003

20. Montravers P, Snauwaert A, Welsch C. Current guidelines and recommendations for the management of skin and soft tissue infections. *Curr Opin Infect Dis.* 2016;29(2):131-138. doi:10.1097/QCO.0000000000000242

De Quervain's Tenosynovitis in Primary Caregivers

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ABSTRACT

Introduction: The purpose of this study is to evaluate the incidence of de Quervain's tenosynovitis in newborn caregivers – both male and female – as well as potential associated factors, such as child's age or weight and lactation status.

Methods: Surveys were administered from August 2014 to April 2015 to parents with young children in the greater Buffalo, New York area. Parents were asked to report wrist pain symptoms and location, number of hours spent caregiving, child's age, and lactation status. Participants who reported wrist pain performed a self-guided Finkelstein test and completed a QuickDASH questionnaire.

Results: One-hundred twenty-one surveys were returned: 9 from males and 112 from females. Ninety respondents reported no wrist/hand pain (group A), 11 reported wrist/hand pain and a negative Finkelstein test (group B), and 20 reported wrist/hand pain and a positive Finkelstein test (group C). The mean QuickDASH score in group B was significantly smaller than that of group C. On average, child age was statistically significantly different across categories of pain with the oldest population in the positive Finkelstein group (group C) (272.8 ± 196.5 vs 481.9 ± 488.9, $P = 0.007$).

Conclusions: This study supports the hypothesis that mechanical components of newborn caregiving play a major role in the development of postpartum de Quervain's tenosynovitis. It also supports the concept that hormonal changes in the lactating female are not an important contributor to the development of postpartum de Quervain's tenosynovitis. Our results, as well as previous studies, suggest a high index of suspicion for the condition must be maintained when seeing primary caregivers with wrist pain.

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INTRODUCTION

Stenosing tenosynovitis of the first dorsal compartment, also known as de Quervain's tenosynovitis, is 6 times more common in women than men[1] and is particularly common in women of childbearing age.[2-6] Postpartum de Quervain's tenosynovitis is responsible for up to 40% of all cases.[5] Evidence is unclear regarding whether the condition is related to lactation and pregnancy or simply mechanical overuse.[2-4] There is also minimal evidence regarding the potential effect of baby size and time spent per day caregiving on the development of symptoms. Additionally, men have increasingly assumed the role of primary caregiver, and it is unclear whether this exposes them to increased risk for development of de Quervain's tenosynovitis.

Our primary questions are what is the incidence of postpartum de Quervain's tenosynovitis and if factors such as lactation, baby size, time spent caregiving, and caregiver sex are associated with the symptom development. To answer these questions, we surveyed postpartum caregivers regarding sex, lactation, baby size/age, number of hours spent caregiving, and the presence or absence of wrist pain. Additionally, respondents performed the self-guided Finkelstein test and reported the results.

We hypothesized that women – especially postpartum caregivers – will have a higher incidence of de Quervain's tenosynovitis symptoms, such as wrist pain, swelling, and activity-related pain, than the general population. Additionally, we hypothesized that

baby size will be positively associated with de Quervain's tenosynovitis symptoms; however, caregiver age and lactation will not be associated with these symptoms.

METHODS

Prior to the start of the study, approval was obtained from the institutional review board. Surveys were administered from August 2014 to April 2015 at local childcare centers and pediatric offices. Inclusion criteria included caregivers who had a child within the preceding 5 years and self-identified as the primary caregiver. All study participants provided written informed consent prior to being surveyed. Participants were queried regarding sex, age, lactation status, child age, average number of hours per day spent caring for the child, presence of any wrist pain, and the location and time of onset. Respondents who admitted wrist pain performed a self-guided Finkelstein test. A picture of full flexion of the thumb and forced ulnar deviation of the wrist was provided for direction. The figure was adapted from the American Academy of Orthopaedic Surgeons. Participants rated their pain as one of the following: none, mild, moderate, severe. Participants experiencing at least mild pain were considered to have a positive Finkelstein test.

Patients admitting to any form of hand or wrist pain since the birth of their child completed a QuickDASH questionnaire—an abbreviated version of the DASH questionnaire and a self-evaluation report asking questions regarding activities of daily living and other functional activities. Respondents rated these activities on a 5-point Likert scale, and the results were transformed to a score between 0 (no disability) and 100 (most severe disability).

Based on completed questionnaires results, respondents were stratified into 3 groups: group A, no wrist/hand pain since the birth of their child; group B, wrist/hand pain since the birth of their child and a negative Finkelstein test; and group C, wrist/hand pain since the birth of their child and a positive Finkelstein test.

Statistical Methods

Descriptive statistics were used to analyze respondents' demographic data. Additionally, we utilized 2-tailed *t* test and analysis of variance (ANOVA) to test for the difference between means of continuous variables across multiple categories of wrist pain and chi-square test to determine whether distribution of categorical variables varies across multiple categories of wrist pain. For analyses, *P* values < 0.05 were considered statistically significant.

RESULTS

Surveys of 121 caregivers were returned: 9 (7.4%) male and 112 (92.6%) female (Table 1). Of the 121 respondents, 90 (74.4%) reported no wrist/hand pain (group A) and 31 (25.6%) reported wrist/hand pain since the birth of their child. All who reported wrist/hand pain were female; 11 (9.1%) had a negative Finkelstein test (group B) and 20 (16.5%) had a positive Finkelstein test (group C). On average, respondents were 31.5 ± 4.8 years old (Table 1). We did not find a statistically significant difference in age between wrist/hand pain groups ($P = 0.884$). Respondents in group A spent, on average, more hours per day providing care to the child than the respondents in groups B and C (17 ± 7.0 vs 12.4 ± 7.7 vs. 16.9 ± 7.9 hours, respectively), but it was not statistically significant ($P = 0.154$). The 9 men caregivers with no reported pain spent, on average, 18.4 ± 7.4 hours per day providing care to the child. Table 1 and Figure 1 show the mean number of hours each group spent caregiving per day across categories of wrist/hand

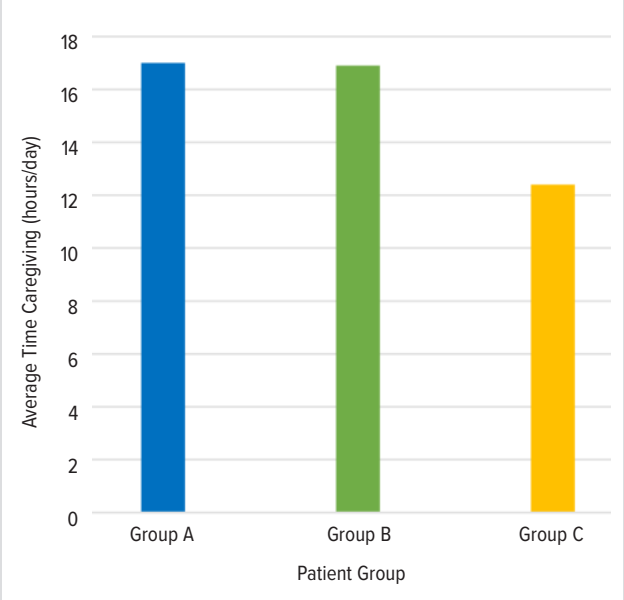
Table 1. Participants Categories Based on Wrist/Hand Pain Since Birth of Their Child and Finkelstein Test (N = 121)

	Group A[a] n = 90 (74.4%)	Group B[a] n = 11 (9.1%)	Group C[a] n = 20 (16.5%)	*P* value[b]
Age (years)	31.6 ± 5.0	30.8 ± 3.8	31.4 ± 4.3	0.884
Sex (% female)	81 (90)	11 (100)	20 (100)	0.187
Hours/day caregiving	17.0 ± 7.0	12.4 ± 7.7	16.9 ± 7.9	0.154
QuickDASH (0 – 100 scale)	N/A	11.9 ± 6.1	32.4 ± 18.6	0.004

[a]Group A: no wrist/hand pain; group B: wrist/hand pain, negative Finkelstein test; group C: wrist/hand pain, positive Finkelstein test.

[b]*t* test and analysis of variance (ANOVA) for difference between means of continuous variable across multiple categories of wrist pain and chi-square test to determine whether distribution of categorical variables varies across multiple categories of wrist pain. *P* values of < 0.05 were considered statistically significant.

Figure. Average Caregiving Time Among Groups



Group A: no wrist/hand pain; group B: wrist/hand pain, negative Finkelstein test; group C: wrist/hand pain, positive Finkelstein test.

Table 2. Participants Child Characteristics Based on Wrist Pain and Finkelstein Test (N = 121)

Variables	Group A[a] n = 90 (74.4%)	Group B[a] n = 11 (9.1%)	Group C[a] n = 20 (16.5%)	*P* value[b]
Child age (days)	272.8 ± 196.5	278.4 ± 136.2	481.9 ± 488.9	0.007
Child weight (pounds/ounces)	16.5 ± 6.2	19.7 ± 4.6	18.7 ± 4.9	0.152
Lactation (% yes)	37 (41.1)	5 (45.5)	8 (40)	0.725

[a]Group A: no wrist/hand pain; group B: wrist/hand pain, negative Finkelstein test; group C: wrist/hand pain, positive Finkelstein test.

[b]*t* test and analysis of variance (ANOVA) for difference between means of continuous variable across multiple categories of wrist pain and chi-square test to determine whether distribution of categorical variables varies across multiple categories of wrist pain. *P* values of < 0.05 were considered statistically significant.

pain. The mean QuickDASH score in group B was significantly smaller than group C (11.9 ± 6.1 vs 32.4 ± 18.6, $P = 0.004$) (Table 1). A statistically significant difference was observed for child age across different categories of pain, with the oldest population in the positive Finkelstein group (group C) (272.8 ± 196.5 vs 481.9 ± 488.9, $P = 0.007$) (Table 2).

DISCUSSION

In 1895, Fritz de Quervain published a report of 5 case studies on the stenosing tenosynovitis of the first dorsal compartment.[7] Since this time, the condition has been termed de Quervain's tenosynovitis, and 120 years later we still do not know its specific cause. Though there are limited pure epidemiology studies on de Quervain's tenosynovitis, current literature suggests an overall incidence of about 1% to 3%.[1,8,9] It has been well-established that the condition is more common in women than in men.[1-3] After evaluating a large military database, Wolf et al reported that women had a significantly higher rate of de Quervain's tenosynovitis at 2.8 cases per 1000 person-years compared to 0.6 cases per 1000 person-years for men.[4] Other studies have reported ratios as high as 6:1 female to male.[1]

Here we present the results of a survey aimed at female and male primary caregivers of newborns to determine the incidence of de Quervain's tenosynovitis and relationship between lactation, number of hours spent per day caregiving, and reported degree of disability. Of 121 surveys completed, 20 (16.5%) respondents were diagnosed with de Quervain's tenosynovitis based on their questionnaire and self-guided Finkelstein test, suggesting a much higher incidence among postpartum caregivers than previously reported in the general population.

Within the female population, the disease tends to be more common among women of child bearing age or women who are breastfeeding or pregnant.[8] While an extensive meta-analysis on work-related causes of de Quervain's tenosynovitis determined that there was no causal relationship between the condition and occupational risk factors, it has been suggested that a mechanical component may lead to the development of postpartum de Quervain's tenosynovitis.[1,10] In addition, the overall prevalence has not been shown to be increased in the dominant hand.[1,10] These observations led some to believe hormonal changes played a large role in the development of de Quervain's tenosynovitis in pregnant and lactating women.

Following these findings, studies were performed on hormonal involvement in de Quervain's tenosynovitis. Cellular-level changes in de Quervain's tenosynovitis have been well-documented as an increase in mucopolysaccharides within the tendon sheath representing myxoid degeneration.[11] It was thought that hormonal changes during pregnancy may alter the histologic changes seen in the condition. However, after examining synovial specimens from de Quervain's tenosynovitis both related and unrelated to pregnancy, Read et al found that the histopathological appearance of de Quervain's tenosynovitis in both groups had no significant differences.[8] Based on these results, it was postulated that postpartum de Quervain's tenosynovitis was likely secondary to the mechanical stresses related to caregiving and not hormonal changes. Our study found that half of the caregivers diagnosed with de Quervain's tenosynovitis were lactating and the other half were not, reinforcing the notion that hormonal changes in lactating females are not a major contributing factor in development of postpartum de Quervain's tenosynovitis.

Acknowledging that a mechanical component to newborn caregiving plays a major role in the development of postpartum de Quervain's tenosynovitis, we hypothesized there would be an increase incidence of the condtion in male caregivers. However, of the 9 males surveyed, none were found to have de Quervain's tenosynovitis. Certainly, the low sample size may have contributed to this finding.

When comparing the QuickDASH scores between group C (positive Finkelstein tet) and group B (negative Finkelstein test), group C had an average score over 3 times higher than group B ($P = 0.004$). This reiterates the amount of disability that may be associated with de Quervain's tenosynovitis and highlights the importance of patient education in the postpartum period. Bynum discussed different techniques, including the "scoop technique," when handling infants in the postpartum period to help reduce the likelihood of developing de Quervain's tenosynovitis.[12] Lactation consultants also have begun to stress the importance of reducing the mechanical factors related to holding newborns to help diminish pain and discomfort associated with de Quervain's tenosynovitis.[13]

Finally, we did not see any association between hours per day of caregiving and the diagnoses of de Quervain's tenosynovitis. One could presume that more hours caregiving would predispose one to the development of the disease. While we did find a statistically significant difference between all three groups—and groups A and C ($P = 0.007$)—related to age of the child, which could be a proxy

measure for overall duration of child care, respondents did not specifically comment on how long they were holding the newborn. If in fact it is a mechanical component that contributes to postpartum de Quervain's tenosynovitis, the focus of future studies will look specifically at hours spent holding the newborn.

Study Limitations

There are several limitations to this study. First, our findings could be influenced by the limited sample size, although we did find statistically significant differences in QuickDASH and babies age between wrist/hand pain groups, despite a small sample size. Second, as the study utilizes a questionnaire and self-guided Finkelstein test to diagnose postpartum de Quervain's tenosynovitis instead of an evaluation by a medical provider, self-reported and recall bias could be introduced. Third, one of the study aims was to investigate both male and female caregivers; however, a disproportionate number of females to males returned the survey. Moving forward, further studies analyzing an equal number of female to male newborn caregivers, in a larger sample size, would be beneficial.

CONCLUSIONS

This study supports the hypotheses that mechanical components of newborn caregiving play a major role in the development of postpartum de Quervain's tenosynovitis and hormonal changes in the lactating female are not an important contributor to postpartum development of the condition. These findings, as well as previous studies, suggest that a high index of suspicion for de Quervain's tenosynovitis must be maintained when seeing primary caregivers with wrist pain.

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REFERENCES

1. Ilyas AM, Ast M, Schaffer AA, Thoder J. De quervain tenosynovitis of the wrist. *J Am Acad Orthop Surg*. 2007;15(12):757-764. doi:10.5435/00124635-200712000-00009

2. Anderson SE, Steinbach LS, De Monaco D, Bonel HM, Hurtienne Y, Voegelin E. "Baby wrist": MRI of an overuse syndrome in mothers. *AJR Am J Roentgenol.* 2004;182(3):719-724. doi:10.2214/ajr.182.3.1820719

3. Schned ES. DeQuervain tenosynovitis in pregnant and postpartum women. *Obstet Gynecol.* 1986;68(3):411-414. doi:10.1097/00006250-198609000-00025

4. Wolf JM, Sturdivant RX, Owens BD. Incidence of de Quervain's tenosynovitis in a young, active population. *J Hand Surg Am*. 2009;34(1):112-115. doi:10.1016/j.jhsa.2008.08.020

5. Skoff HD. "Postpartum/newborn" de Quervain's tenosynovitis of the wrist. *Am J Orthop (Belle Mead NJ).* 2001;30(5):428-430.

6. Johnson CA. Occurrence of de Quervain's disease in postpartum women. *J Fam Pract*. 1991;32(3):325-327.

7. de Quervain F. On a form of chronic tendovaginitis by Dr. Fritz de Quervain in la Chaux-de-Fonds. 1895. *J Hand Surg Br*. 2005;30(4):388-391. doi:10.1016/J.JHSB.2005.01.004

8. Read HS, Hooper G, Davie R. Histological appearances in post-partum de Quervain's disease. *J Hand Surg Br.* 2000;25(1):70-72. doi:10.1054/jhsb.1999.0308

9. Adachi S, Yamamoto A, Kobayashi T, et al. Prevalence of de Quervain's disease in the general population and risk factors. *Kita Kanto Igaku.* 2011;61:479-482. doi:10.2974/kmj.61.479

10. Stahl S, Vida D, Meisner C, et al. Systematic review and meta-analysis on the work-related cause of de Quervain tenosynovitis: a critical appraisal of its recognition as an occupational disease. *Plast Reconstr Surg*. 2013;132(6):1479-1491. doi:10.1097/01.prs.0000434409.32594.1b

11. Clarke MT, Lyall HA, Grant JW, Matthewson MH. The histopathology of de Quervain's disease. *J Hand Surg Br.* 1998;23(6):732-734. doi:10.1016/s0266-7681(98)80085-5

12. Bynum DK. Postpartum de Quervain's tenosynovitis of the wrist. *Am J Orthop (Belle Mead NJ).* 2001;30(11):829.

13. Roberts D. Preventing musculoskeletal pain in mothers: ergonomic tips for lactation consultants. *Clin Lactat.* 2011;2(4):13-20. doi:10.1891/215805311807011539

Silicosis: Emerging Trends and How to Screen for Early Detection

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ABSTRACT

Background: National investigations are finding silicosis in young workers. We developed a silicosis case-finding process and conducted follow-up interviews to identify emerging exposure sources.

Methods: Probable cases were identified through Wisconsin hospital discharge and emergency department data and Wisconsin lung transplant programs. Interviews were attempted with case-patients under age 60.

Results: We identified 68 probable silicosis cases and interviewed 4 case-patients. Occupational exposures for cases under age 60 included sandblasting, quarry work, foundry work, coal mining, and stone fabrication. Two stone fabrication workers were diagnosed before age 40.

Discussion: Prevention is critically important to eliminate occupational silicosis. Clinicians should obtain the occupational and exposure history to identify cases of occupational lung disease and notify public health to identify and prevent workplace exposures.

BACKGROUND

Silicosis is an incurable occupational lung disease caused by inhaling respirable crystalline silica dust.[1] There are 3 forms of silicosis: chronic, accelerated, and acute.[2] Chronic silicosis is a slowly progressive disease and manifests as scarring of the lung tissue, which can be identified on chest imaging after 10 or more years of exposure. Accelerated silicosis can develop within 5 to 10 years after exposure to high concentrations of crystalline silica. Acute silicosis is a less common form of the disease, manifesting as an alveolar filling process that can become evident within weeks or months of very high silica exposure. Death from acute silicosis can occur within a few years of disease onset. Silica exposure also is associated with an increased risk of developing renal disease and autoimmune conditions, and the International Agency for Research on Cancer (IARC) has determined that silica is a lung carcinogen.[1]

Industries that place workers at high risk for silica exposure include construction, foundries, mining, and glass manufacturing. An emerging source of silica exposure in the United States is the cutting, grinding, and polishing of engineered stone products.[3] Engineered stone made from quartz has become a popular countertop for personal kitchens and bathrooms across the country. Engineered quartz imports have risen over 700% in the US during 2010 and 2019 (from $140 million to $1.2 billion).[4] There are an estimated 96,000 employees in the stone fabrication industry in the United States.[3] Because engineered quartz is more than 93% silica compared to granite (10%-45% silica), its fabrication can lead to higher airborne levels of silica dust.[5] Investigations conducted by 4 states during 2017–2019 identified 18 cases of silicosis—including 2 fatalities—among stone fabrication workers, all of whom were under 60 years of age. Prior to this study, only 1 case had been identified among engineered stone fabricators in the United States.[6]

To prevent silicosis, employers are required to comply with the Occupational Safety and Health Administration's (OSHA) comprehensive silica dust standard.[7] This includes using dust controls, such as wet methods that apply water at the point where dust is created (eg, cutting, grinding, sanding); using local exhaust ventilation that removes silica dust; using an enclosure to isolate the

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worker from the work process; providing effective respiratory protection; and conducting medical monitoring. Medical monitoring, per OSHA standards, involves offering medical exams every 3 years for workers who are exposed to silica dust above the action level or workers required to wear a respirator over 30 days per year. Exams include thorough medical and work history, physical exam, lung function testing, and chest radiography.

In January 2018, Wisconsin added silicosis to the state administrative code of reportable conditions.[8] The Wisconsin Department of Health Services (DHS) developed a silicosis case-finding process and conducted case follow-up interviews to identify emerging sources of exposure. We describe the methods and outcomes, present a case study of a stone fabrication worker, and provide an evaluation tool that physicians can use to facilitate early silicosis detection.

METHODS

DHS classifies silicosis cases according to the Council of State and Territorial Epidemiologists case definition.[1] A probable silicosis case is defined as a listing of silicosis or pneumoconiosis due to silica exposure in the death certificate, hospital discharge record, workers' compensation claim, or health care professional's report. Probable cases were identified by searching Wisconsin hospital discharge and emergency department visit data with principal or contributing diagnoses codes of J62 (International Classification of Diseases, Tenth Revision, Clinical Modification) and by requesting records from lung transplant programs in Wisconsin for any patients with diagnosed silicosis. We reviewed medical records for each case, including history and physical examination, emergency department documentation, and discharge summaries. Records were reviewed for mention of silicosis, exposure to silica, and occupations where exposure may have occurred. In order to identify cases caused by emerging sources of silica exposure, we attempted interviews with all case-patients under 60 years of age. Data collected during interviews included employment history, social history, occupational and exposure history, symptoms, diagnostic information, and history of other lung diseases.

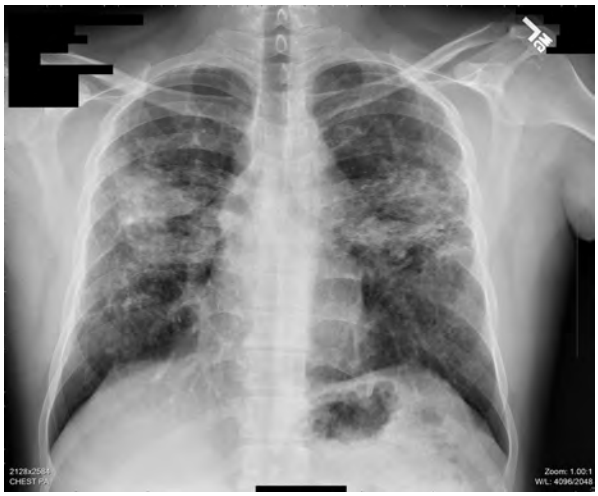
RESULTS

During January 2016 through March 2019, we identified 95 hospital or emergency department records with a diagnosis code of J62, representing 66 unique probable silicosis cases.[1] Two additional cases from a transplant program were identified (see Table). Of the 68 cases, 93% were male. Race and ethnicity were reported as 78% White, 10% Black, 10% Hispanic, and 2% American Indian. One case was under 40 years of age, 8 cases (12%) were 40–59 years, 39 cases (57%) were 60–79 years, and 20 cases (29%) were ≥80 years. We completed interviews with 4 of 9 individuals under age 60 (44%). Occupational exposures identified from case interviews included sandblasting, quarry work, coal mining, and stone fabrication. The medical records for 2 case-patients who could not be reached indicated a history of foundry work and stone fabrication.

Table. Characteristics of Persons With Silicosis in Wisconsin, January 2016-March 2019

	Number	%
Total N	68	100
Sex		
Male	63	93
Female	5	7
Race/Ethnicity		
Hispanic	7	10
American Indian	1	2
Black	7	10
White	53	78
Age		
<40	1	2
40-59	8	12
60-79	39	57
80+	20	29
Occupation for Persons Under 60 Found Through Interviews or Medical Record Searches (n=6)		
Coal mining	1	17
Foundry work	1	17
Sandblasting	1	17
Stone fabrication	2	33
Quarry work	1	17

Figure. Worker A: Chest Radiograph Demonstrating Bilateral Perihilar Airspace Opacities



Worker Case Study

Worker A is a nonsmoker under 40 years of age who began working in the stone fabrication industry at age 20 during the early 2000s. For the first 5 years of Worker A's career, the only respiratory protection provided was a dust mask, which was worn repeatedly during a work week then discarded. During this time period, the operation did not employ wet methods for cutting stone and engi-

Box. Clinical Evaluation Tool for Silicosis

1. Take an occupational history.
   - ☐ What is your job (what kind of work do you do)?
   - ☐ Tell me exactly what you do at work.
   - ☐ Is there usually visible dust in the air when you are working?
   - ☐ How many years have you done this type of work?
   - ☐ Name and address of current employer
   - ☐ What does your company make or do?
2. Observe for symptoms of silicosis and ask about symptom onset (eg, respiratory review of systems).
   - ☐ Cough
   - ☐ Dyspnea (shortness of breath)
   - ☐ Fatigue
   - ☐ Chest tightness
   - ☐ Myalgia or arthralgias (autoimmune diseases)
3. Use past medical history as indicators when considering silicosis. Such medical conditions include:
   - ☐ Rheumatoid arthritis or other autoimmune diseases
   - ☐ Recurrent pneumonia
   - ☐ Tuberculosis (TB)
   - ☐ Interstitial lung disease
   - ☐ Sarcoidosis (egg-shell lymphadenopathy also seen in silicosis)

If silicosis or significant occupational silica exposure is suspected based on history, consider additional clinical evaluation, as below.

4. Conduct a silica medical exam and screening.
   - ☐ Lung exam
   - ☐ Pulse oximetry
   - ☐ Chest x-ray with B-Read
   - ☐ Spirometry
   - ☐ TB test
5. Refer patient to a specialist (Occupation Medicine or Pulmonology) for any of the following indications:
   - ☐ B-Read is 1/0 or greater
   - ☐ Restrictive pattern on spirometry
   - ☐ Respiratory symptoms

6.Confirmatory testing is then needed to make a diagnosis. Specialist consultation recommended. Testing includes:
   - ☐ Full Pulmonary Function Tests (PFTs)
   - ☐ Chest CT scan
   - ☐ Bronchoscopy
   - ☐ Autoimmune testing (ANA and Rheumatoid Factor initially)
   - ☐ In some cases, biopsy by Video-Assisted Thorascopic Surgery may be required to obtain appropriate sampling of lung tissue.
7. Treatment of silicosis:
   - ☐ Remove the patient from continued silica exposure
   - ☐ Cough medication
   - ☐ Bronchodilators
   - ☐ Supplemental oxygen
   - ☐ Patients may eventually require a lung transplant.
8. Follow-up on patients with silicosis:
   - ☐ Conduct an annual chest x-ray and spirometry.
   - ☐ Inform the patient that they should file a workers' compensation claim.
   - ☐ File a case report with the Wisconsin Department of Health Services, required by Wisconsin Administrative Code Chapter DHS 145. You can do this four different ways.
     1. Report electronically through WEDSS.
     2. Fax a case report to the Bureau of Environmental and Occupational Health (BEOH): 608-267-4853
     3. Call BEOH: 608-266-1120
     4. Mail the report to: Wisconsin State Epidemiologist (BEOH)
1 West Wilson St, Room 150
Madison, WI 53703
9. Prevention for other workers:
   - ☐ Consider contacting OSHA if you suspect a workplace isn't providing respiratory protection and workplace controls to keep workers safe. Visit the Wisconsin OSHA contact page to find the office nearest you.

neered quartz, and the worker noted that there was dust contamination throughout the worksite, including the cafeteria.

After Worker A's first 5 years, the employer switched to wet cutting and provided workers with a respirator of unknown type. Worker A had only 1 respirator fit test during employment, despite OSHA requirements for annual fit testing (1910.134[f][2]).[9] Fit testing did not occur until the workers had been wearing respirators for an unknown period of time, and Worker A reported dust inhalation even after being fit tested. Worker A's employer did not conduct required medical clearance for respirator use (1910.134[e][1]).[9]

Worker A had 1 medical evaluation after 12 years of work. During this evaluation, breathing problems were identified and the worker was laid off. Worker A had wedge biopsies of the right middle and lower lobes at age 32. Prior to the surgical biopsy, Worker A had evidence of moderate expiratory flow limitation and hyperreactivity on pulmonary function testing (total lung capacity 5.99 L [94% predicted], diffusing capacity of the lungs for carbon monoxide [DLCO] 28.6 [99% predicted], forced vital capacity [FVC] 3.52 L [71% predicted], forced expiratory volume in the first second of expiration [FEV1] 2.63 L [64% predicted], and FEV1/FVC 75%). Preoperative computed tomography of the chest showed extensive consolidative changes in both lungs, with diffuse micronodular pulmonary infiltrates and multiple large blebs. Lung tissue pathology showed mixed dust pneumoconiosis (siderosilicosis) with massive fibrosis and emphysematous changes. Postoperative chest radiograph demonstrated stable perihilar airspace opacities extending into the upper lobes consistent with progressive massive fibrosis (Figure).

Worker A filed a claim and received workers' compensation benefits for medical treatment and impairment. DHS identified an additional silicosis case from the same worksite as Worker A. This coworker was diagnosed with silicosis in his 30s and had a lung transplant at age 38.

DISCUSSION

Silicosis among stone fabrication workers is occurring in persons under 40 years of age and is highly preventable with appropriate control measures. Enhanced public health surveillance of silicosis cases, including detailed interviews of workers, can identify industries and occupations that expose workers to hazardous levels of crystalline silica.

Prevention and early intervention is critically important to eradicate occupational silicosis. OSHA requires that industries with hazardous silica exposures provide effective engineering controls and, where necessary to further limit exposure below permissible levels, respiratory protection for their workers. New uses of silica continue to emerge, including countertop manufacturing, finishing, and installation and hydraulic fracturing in the oil and gas industry. Taking occupational histories on all patients is critical to identifying cases of occupational lung disease and creates opportunities to identify and prevent workplace exposures through collaboration with public health agencies.

We believe silicosis is more prevalent than current data suggest, but greater clinician awareness could help close that gap. Diagnosis of silicosis relies on a combination of occupational history, chest imaging with compatible findings, and exclusion of other diagnoses such as tuberculosis, sarcoidosis, or idiopathic pulmonary fibrosis. A brief work history, with focus on emerging sources of silica exposure, can help identify workers who might be at risk. Based on that brief screening, the clinician can gather more detailed information through clinical evalution. See Box for a clinical evaluation tool for silicosis, adapted from OSHA.[10] DHS will continue to conduct occupational lung disease surveillance and will develop outreach programs for workers and employers on silica hazards and exposure prevention

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REFERENCES

1. Centers for Disease Control and Prevention. Silicosis: 2010 case definition. Updated April 16, 2021. Accessed October 20, 2020. https://wwwn.cdc.gov/nndss/conditions/silicosis/case-definition/2010/

2. National Institute for Occupational Safety and Health. *Preventing Silicosis and Deaths in Construction Workers*. DHHS (NIOSH) publication 96-112. 1996. Accessed October 20, 2020. https://www.cdc.gov/niosh/docs/96-112/default.html

3. Rose C, Heinzerling A, Patel K, et al. Severe silicosis in engineered stone fabrication workers - California, Colorado, Texas, and Washington, 2017-2019. *MMWR Morb Mortal Wkly Rep.* 2019;68(38):813-818. doi:10.15585/mmwr.mm6838a1

4. USITC Dataweb. U.S. International Trade Commission; July 11, 2019, version 4.5.4. Updated September 17, 2022. Accessed August 18, 2020. https://dataweb.usitc.gov/

5. Occupational Safety and Health Administration. Hazard alert: worker exposure to silica during countertop manufacturing, finishing, and installation. February 2015. Accessed October 20, 2020. https://www.osha.gov/Publications/OSHA3768.pdf

6. Friedman GK, Harrison R, Bojes H, Worthington K, Filios M; Centers for Disease Control and Prevention (CDC). Notes from the field: silicosis in a countertop fabricator - Texas, 2014. *MMWR Morb Mortal Wkly Rep*. 2015;64(5):129-130.7.

7. Occupational Safety and Health Administration. OSHA FactSheet: OSHA's respirable crystalline silica standard for general industry and maritime. February 2018. Accessed October 20, 2020. https://www.osha.gov/Publications/OSHA3682.pdf

8. Wis. Admin. Code § DHS 145 Appendix A: Communicable Diseases and Other Notifiable Conditions (2018). Accessed October 20, 2020. http://docs.legis.wisconsin.gov/code/admin_code/dhs/110/145_a

9. Occupational Safety and Health Administration. Respiratory Protection. 29 CFR § 1910.134. Revised September 26, 2019. Accessed October 20, 2020. https://www.osha.gov/laws-regs/regulations/standardnumber/1910/1910.134

10. Occupational Safety and Health Administration. Appendix B to Respirable Crystalline Silica—Medical Surveillance Guidelines. 29 CFR § 1926.1153. Revised March 25, 2016. Accessed October 20, 2020. https://www.osha.gov/silica/AppendixBtosect1926.1153.pdf

What If We Don't? A Retrospective Review of Standard Precautions for MRSA

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ABSTRACT

Background: There are conflicting data in the literature about the need for contact isolation for active methicillin-resistant *Staphylococcus aureus* (MRSA) infections.

Methods: In this retrospective review, we compared the MRSA bloodstream standardized infection ratio for 1 year while contact precautions were in place for MRSA infections and for 1 year after routine contact precautions for MRSA were no longer in place.

Results: There was no change in the MRSA bloodstream standardized infection ratio between the two time periods.

Conclusions: With cessation of contact precautions for MRSA infections, there was no change in bloodstream MRSA standardized infection ratios across a large health system. While standardized infection ratios would not detect asymptomatic horizontal transmission of a pathogen, it is reassuring that bloodstream infections – a known complication of MRSA colonization status – did not rise with cessation of contact precautions.

BACKGROUND

Treating and preventing antimicrobial-resistant organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA) continues to pose a challenge for health care workers worldwide.[1,2] Historically, patients with MRSA infections have been placed in contact isolation although, due to a shortage in the supply of personal protective equipment (PPE), some institutions have reduced isolation protocols in the past few years.[2] While some reports suggest contact precautions for MRSA can help prevent nosocomial transmission,[1,2] other data suggest that cessation of isolation does not lead to higher rates of nosocomial infections.[3,4]

Catholic Health Initiatives, Midwest Division (CHI-MD), is a health system composed of 10 acute-care hospitals and 18 critical-access hospitals in Nebraska, Iowa, North Dakota, and Minnesota. In March 2020, CHI-MD stopped routine contact isolation for active MRSA infections in anticipation of a PPE shortage due to the SARS-CoV-2 pandemic. We later evaluated our standardized infection ratio (SIR) for MRSA bacteremia, comparing a 1-year time period in 2019 from prior to cessation of routine isolation to a 1-year time period in 2021-2022 after the change in isolation had been implemented for some time and the acute increase in hospitalizations due to the SARS-CoV-2 pandemic had diminished. In this retrospective analysis, we assessed the impact of discontinuation of routine contact precautions for active MRSA infections on the MRSA SIR.

METHODS

This was a retrospective evaluation using data from CHI-MD hospital facilities comparing 4 quarters of data from 2019 to 4 quarters of data from 2021-2022. Data were obtained by the infection prevention department from information reported to the National Healthcare Safety Network for hospital-associated MRSA blood stream infections. The baseline time period was the 4 quarters of calendar year 2019, prior to the change in isolation policy and prior to local issues of the SARS-CoV-2 pandemic. The time period of March 2021 to April 2022 was chosen as the postintervention evaluation period. This time period was chosen for a period of 1 year after the change in policy to make sure that it was well-established and to remove the significant impact that

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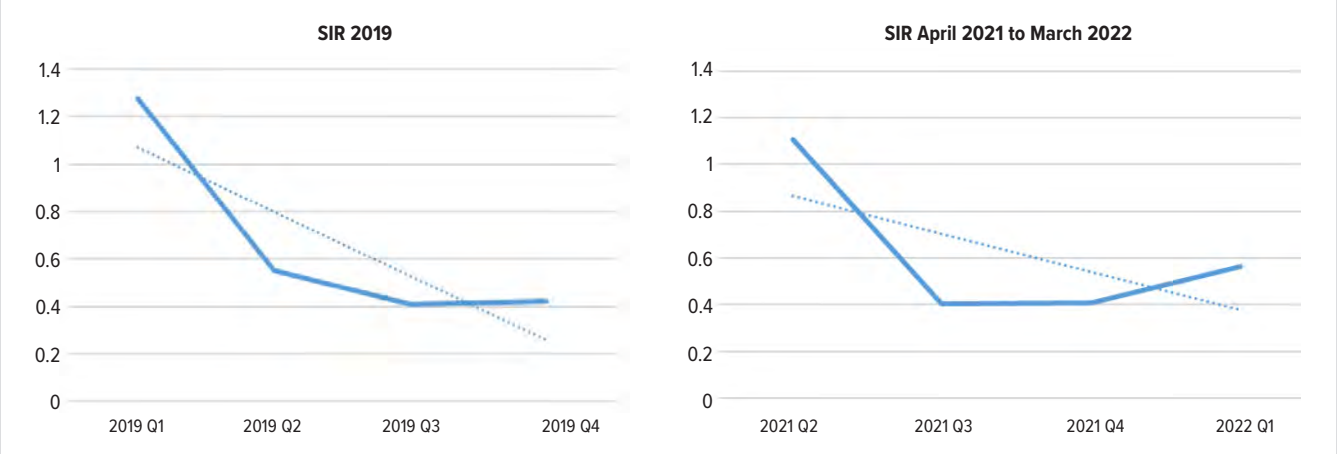
Figure. Methicillin-resistant *Staphylococcus aureus* (MRSA) Bloodstream Infection Standardized Infection Ratio (SIR) for Each Quarter



the increase in hospitalizations due to the SARS-CoV-2 pandemic may have on hospital-acquired infections.[5] The MRSA bloodstream SIR from the two time periods were compared to evaluate for any change that might be associated with the change in the isolation policy.

RESULTS

The MRSA SIR for the study time periods are outlined in the Table and Figure. Overall, the MRSA bloodstream infection SIR for the 2019 (baseline) time period was 0.698 (95% CI, 0.406-1.202). The overall MRSA bloodstream infection SIR for the 2021-2022 time period was 0.615 (95% CI, 0.357-1.060). Although there was a slight absolute reduction in SIR in the post-intervention time period (11.9%), this did not reach statistical significance (SIR difference as ratio 0.881, 95% CI, 0.409-1.900)

Table. Methicillin-Resistant *Staphylococcus Aureus* (MRSA) Bloodstream Infection Standardized Infection Ratio (SIR) for Each Quarter

Timeframe	SIR	SIR *P* value	SIR 95% CI
2019 Q1	1.278	0.5253	0.518 – 2.658
2019 Q2	0.553	0.3031	0.141 – 1.504
2019 Q3	0.408	0.1765	0.068 – 1.347
2019 Q4	0.424	0.2025	0.071 – 1.402
2021 Q2	1.107	0.7586	0.449 – 2.303
2021 Q3	0.405	0.1727	0.068 – 1.339
2021 Q4	0.407	0.1761	0.068 – 1.346
2022 Q1	0.565	0.3249	0.144 – 1.537

DISCUSSION

Contact isolation is not a benign intervention. It has been estimated that 71 pounds of waste is generated weekly by a patient on contact precautions for MRSA.[6] In addition to financial and environmental costs,[3] there can be decreased patient satisfaction scores,[7] reduced interaction between patients and health care providers,[8] and even increased patient adverse events.[9,10] Similar to other recent studies,[3] our data suggest that there was no increase in MRSA bacteremia SIR with discontinuation of contact isolation for this pathogen.

There are limitations to our evaluation. Our health system does not routinely screen for MRSA carriage on hospital admission; in-house MRSA acquisition may not be noticed unless an active infection develops during the hospital stay, leading to its inclusion in the overall MRSA bloodstream infection SIR. The presumptive goal of contact precautions is not to prevent bloodstream infections; it is to prevent the in-house horizontal transmission of potential pathogens. However, if there were a marked increase in MRSA colonization acquisition among patients due to cessation of contact precautions, this might be reflected in MRSA bloodstream SIRs since pathogens involved with bacteremia are typically part of the host flora. To truly determine whether contact precautions are effective in decreasing horizontal transmission of MRSA, it would be necessary to universally screen all patients on both admission and discharge during time periods when contact precautions are in place and when they are not. In addition, this data analysis does not include data on the facilities' compliance with contact isolation protocols; it is assumed that practice follows the established policies. Finally, analysis of data for other potential complications of in-house acquisition of MRSA (such as MRSA pneumonia or soft tissue infections) also could be examined to see if these rates change with the presence or absence of contact precautions.

One strength of our evaluation is the size of the health system involved. CHI-MD includes 10 acute care facilities, including a large tertiary level I trauma center, that contribute to this SIR data, as well as 18 critical access facilities. Collection of data from multiple facilities in several geographic regions increases the overall generalizability of the results.

CONCLUSIONS

Our results suggest that discontinuation of routine contact isolation for MRSA infection did not lead to an increase in nosocomial bloodstream MRSA infections. While a cost analysis was not performed for savings due to decreased PPE use, other analyses have shown that discontinuation of isolation is associated with significant cost savings.[3,4] While there may be some benefit for the use of contact isolation for active MRSA infections (eg, facilities with poor hand hygiene rates or a high baseline MRSA SIR), our results suggest that on a system-wide level, discontinuation of contact isolation for active MRSA infections does not lead to an increase in MRSA SIR.

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REFERENCES

1. Johnstone J, Shing E, Saedi A, et al. Discontinuing contact precautions for vancomycin-resistant enterococcus (VRE) is associated with rising VRE bloodstream infection rates in Ontario hospitals, 2009-2018: a quasi-experimental study. *Clin Infect Dis*.2020;71(7):1756-1759. doi:10.1093/cid/ciaa009

2. Khader K, Thomas A, Stevens V, et al. Association between contact precautions and transmission of methicillin-resistant *Staphylococcus aureus* in Veterans Affairs hospitals. *JAMA Netw Open*. 2021;4(3):e210971. doi:10.1001/jamanetworkopen.2021.0971

3. Martin EM, Colaianne B, Bridge C, et al. Discontinuing MRSA and VRE contact precautions: defining hospital characteristics and infection prevention practices predicting safe de-escalation. *Infect Control Hosp Epidemiol.* 2022;43(11):1595-1602. doi:10.1017/ice.2021.457

4. AlMohanna Z, Snavely AC, Viviano JP, Bischoff WE. Long-term impact of contact precautions cessation for methicillin-resistant *Staphylococcus aureus* (MRSA). *Am J Infect Control.* 2022;50(3):336-341. doi:10.1016/j.ajic.2021.10.044

5. Weiner-Lastinger LM, Pattabiraman V, Konnor RY, et al. The impact of coronavirus disease 2019 (COVID-19) on healthcare-associated infections in 2020: a summary of data reported to the National Healthcare Safety Network. *Infect Control Hosp Epidemiol.* 2022;43(1):12-25. doi:10.1017/ice.2021.362

6. Saber DA, Norris AE, Reinking J, Trompeter G, Sanford D. Analyzing the cost of hospital contact isolation practices: implications for nursing administrator practice, research, and policy. *J Nurs Adm.* 2022;52(6):352-358. doi:10.1097/NNA.0000000000001160

7. Mehrotra P, Croft L, Day HR, et al. Effects of contact precautions on patient perception of care and satisfaction: a prospective cohort study. *Infect Control Hosp Epidemiol.* 2013;34(10):1087-1093. doi:10.1086/673143

8. Dashiell-Earp CN, Bell DS, Ang AO, Uslan DZ. Do physicians spend less time with patients in contact isolation? A time-motion study of internal medicine interns. *JAMA Intern Med.* 2014;174(5):814-815. doi:10.1001/jamainternmed.2014.537

9. Stelfox HT, Bates DW, Redelmeier DA. Safety of patients isolated for infection control. *JAMA*. 2003;290(14):1899-1905. doi:10.1001/jama.290.14.1899

10. Karki S, Leder K, Cheng AC. Patients under contact precautions have an increased risk of injuries and medication errors: a retrospective cohort study. *Infect Control Hosp Epidemiol.* 2013;34(10):1118-1120. doi:10.1086/673153

Mountain Bike Injury Incidence and Risk Factors Among Members of a Wisconsin Mountain Bike Club

Lin Zhao, MD, MPH; Margaret Nolan, MD, MS; Patrick L. Remington, MD, MPH

ABSTRACT

Background: This study aimed to assess the incidence of and risk factors for mountain bike injuries among users of a local mountain bike trail system.

Methods: An email survey was sent to 1,800 member households, and 410 (23%) responded. Exact Poisson test was used to calculate rate ratios, and a generalized linear model was used for multivariate analysis.

Results: The injury incidence rate was 3.6 injuries per 1,000 person-hours of riding, with beginners at a significantly higher risk compared to advanced riders (rate ratio = 2.6, 95% CI, 1.4-4.4). However, only 0.4% of beginners required medical attention, compared to 3% of advanced riders.

Conclusions: More injuries occur among beginning riders, but the injuries are more severe with experienced riders, suggesting higher risk-taking or less attention to safety measures.

BACKGROUND

Mountain biking, or off-road biking, as a recreational sport rapidly gained popularity during the COVID-19 pandemic.[1] As an outdoor activity, mountain biking can improve physical fitness and has many mental health benefits.[2] However, it also can cause injuries, such as bone fractures or traumatic brain injuries.[3] Despite more people mountain biking, few studies focus on mountain bike injury prevention, surveillance, and management. Most existing mountain bike injury studies focus on professional races[4] or commercial mountain bike parks.[5] Lack of community-based mountain bike injury epidemiologic studies makes it challenging for physicians to advise patients on mountain biking safety.

Information from existing mountain bike injury studies is of limited utility for community injury prevention guidance, because different studies use different methods and focus on different study populations. For example, some studies use emergency department data to report mountain bike injuries,[6] while others use case report systems to monitor injury rates.[7] One study focuses on professional mountain bike racers,[4] while another focuses on mountain bike magazine subscribers.[8] Few studies focus on risk factors related to amateur mountain bikers that community physicians may encounter.

Moreover, injury rates are measured inconsistently in existing studies and, thus, difficult to compare. Riding time is a known exposure to injury – the longer people ride, the more they are exposed to injury risk. However, it is hard to record the precise time a person spends on a mountain bike. Some studies omit the riding time and report injury rate as a proportion.[9] Others estimate lifelong riding time, which is prone to severe information bias.[6,10]

Our study focuses on acute mountain bike injuries of community mountain bikers at different skill levels and takes riding time into consideration when calculating injury rate. We hope to provide a more accurate mountain bike injury rate and identify risk factors to help design injury prevention interventions and assist physicians to better advise patients on mountain biking safety.

METHODS

This was a cross-sectional study. An online Qualtrics survey that took approximately 10 minutes to complete was sent to mem bers

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Table. Descriptive Analysis of Risk Ractors for Mountain Bike Injury Rate

Factor	Total Participants	Rate of Injury (per 1,000 Person-Hours of Riding)	Rate Ratio (95% CI) (Unadjusted, Exact Poisson Test)
Age group			
2–12	85 (9.7%)	4.3	1.5 (0.79–2.9, *P* = 0.22)
13–20	104 (11.9%)	**6.3**	**2.2 (1.04–4.5, *P* = 0.04)**
21–40	185 (21.1%)	3.7	1.3 (0.66 to 2.5, *P* = 0.48)
41–60	379 (43.2%)	2.8	Ref.
60+	121 (13.8%)	3.5	1.2 (0.38–3.2, *P* = 0.79)
Years of experience			
0–2	290 (33.1%)	**6.4**	**2.4 (1.4–4.4, *P* = 0.002)**
3–10	334 (38.1%)	2.6	Ref.
10+	253 (28.8%)	3.2	1.2 (0.67–2.2, *P* = 0.57)
Gender			
Female	289 (33.0%)	2.5	Ref.
Male	571 (65.1%)	4.1	1.7 (0.93–3.2, *P* = 0.10)
Nonbinary/prefer not to say	17 (1.9%)	2.9	1.2 (0.03–7.7, *P* = 1.00)
History of mountain biking lessons			
Yes	331 (35.5%)	3.2	Ref.
No	565 (64.4%)	3.9	1.2 (0.73–2.0, *P* = 0.54)
Self-reported level			
Advanced	199 (22.7%)	2.6	Ref.
Intermediate	396 (45.2%)	3.2	1.2 (0.70–2.3, *P* = 0.53)
Beginner	281 (32.0%)	**7.7**	**3.0 (1.6–5.9, *P* = 0.001)**

of a local mountain bike club located in Middleton, Wisconsin. The club is a nonprofit 501c3 organization, and riding is limited to members only. It has about 10 miles of mountain bike trails that are maintained by volunteers. There were 1,800 registered households during the survey period from October 7 to November 13, 2021. The survey was distributed through member registered emails, club enewsletters, and a members-only Facebook page. Club members who biked between June 1 and September 30, 2021, on the club property were included.

All participants were asked general information, including age, gender (male, female, nonbinary/prefer not to say), years of mountain biking experience (0-2, 3-10, >10 years), history of taking mountain bike lessons (yes/no), and their self-estimated level of expertise (beginner, intermediate, advanced.) Riding time was calculated from self-reported average times per week and average hours/minutes per ride during the previous 4 months. Injury was defined as acute unexpected injury that caused pain or limitation of activity. Participants were asked to report number of injuries while riding a mountain bike on the club trails during the time of interest (June 1 - Sept 30, 2021), a detailed description of each injury, and if those injuries required medical attention (ie, seen by a health care provider).

Data analyses were completed using R studio (Rstudio Team, IDE 2022.02.4). Crude rate ratios of each risk factor and their 95% confidence intervals were calculated using an exact Poisson test. Intermediate riders and advanced riders were then combined into an experienced group; rate ratios compared to beginner riders were calculated and adjusted for age, gender, years of experience, and history of mountain bike lessons using a Poisson generalized linear model.

The study protocol was exempted from the University of Wisconsin Health Sciences Institutional Review Board since it was part of a quality improvement effort at the club. All participants were provided with survey information before they began the survey.

RESULTS

An estimated 1,800 households received the survey link. Of these, 410 households completed the survey (23% response rate), providing information for 877 individual bikers. The average age of the study population was 32.4 years (range, 2-73.) There were 571 (65%) riders who identified as male, 289 (33%) female, and 17 (2%) who identified as nonbinary or preferred not to say. The average years of mountain bike experience was 9.7 (range 0-58 years). The respondents reported having beginning (32%), intermediate (45%), and advanced (23%) skills, and 331 (36%) riders reported having taken a mountain bike lesson.

Among all respondents, 62 (7.0%) reported an injury and, of those, 19 (2.2%) reported an injury that required medical attention. The overall incidence rate was 3.6 injuries per 1,000 person-hours of riding. Higher rates were observed among male, younger (age 13-20), less experienced (<3 years riding), and beginning riders (Table). After multivariate analysis, beginners remained at significantly higher risk compared to more advanced riders (RR = 2.6, 95% CI, 1.4-4.4). However, beginners described their injuries as "abrasion, bruises, and scrapes" that did not require medical attention. In contrast, 12 advanced riders reported joint and bone injuries, and 13 reported the injuries were due to being "too fast, aggressive, or attempting a jump." Overall, only 0.4% of beginners required medical attention, compared to 3% of more advanced riders.

DISCUSSION

In this cross-sectional survey of recreational mountain bikers at a community biking club, mountain bike injuries were uncommon overall, with only 1 injury per 300 hours of riding, on average. The cross-sectional design and well-defined population and trail area allow future studies at the same club to provide time trend of injury rate and a platform to evaluate the effectiveness of injury prevention methods.

Overall, beginners reported a higher risk of injury. This find-

ing is different than the 2001 Gualrapp et al study,[8] which used similar methods (distributing a survey to mountain bike magazine subscribers) and found that there was no significant difference in the injury rate between beginners and athletes with more than 4 years of experience. Gualrapp et al[8] did not provide details on how riding time was collected. Based on the survey design, this time might be lifelong riding time for both beginners and advanced riders. All advanced riders started as beginners, and their injury rate changed as their skill level advanced. Thus, we think our cross-sectional design (focusing on one summer of riding) to investigate skill level as a risk factor yields more accurate results.

Despite a higher injury rate, most injuries reported by beginners were minor and did not require medical attention. In contrast, advanced riders had more joint and bone injuries than beginners, which also was reported in Gualrapp et al.[8] The most common causes of severe injuries were high speed, poor judgment of the trail condition, and attempting jumps. This suggests that the balance between experience and confidence plays a role in the cause of injury. Beginners have less experience and less confidence. They are more likely to hesitate and stop, causing more low-speed injury and/or injury on safer trails, which tend to be minor. Advanced riders have more experience and, for some, more confidence. Over-confidence can make a rider take greater risks or pay less attention to safety measures, causing more severe injuries. When it comes to injury prevention, more riding time to gain familiarity with the bike and the trail might help a beginner to reduce injuries. On the other hand, improved trail design and caution signage for advanced riders might prevent severe injuries.

Strengths of this study include the study population of community mountain bike riders, the short interval between study period and survey distribution time to improve recall, and the use of person-hours of riding. Limitations include the cross-sectional study design, which is prone to selection bias, the time lag from injury to the survey, and the low response rate. Ideally, research could be done using ongoing, active surveillance of injuries or video recording of the incident and on-the-spot rider interviews, as is done during professional mountain bike races. However, this would be costly and may be impractical in a community setting. Other limitations of our study include the lack of information on distance ridden, vertical distance ridden, and terrain ridden. The geographic information and more accurate time exposure can be recorded by global positioning system (GPS) devices. With more and more riders recording their activities on sports applications like Strava, those data can be available for future studies.

CONCLUSIONS

Mountain biking is an enjoyable sport and has significant health benefits for children and adults. However, injuries do occur and sometimes can be serious, requiring medical attention. Our study shows that the risk of injuries is low overall, and that beginner riders are at higher risk of minor injuries, while advanced riders are at high risk of serious injuries. This information should be used to design injury prevention efforts, such as more riding time for beginning riders and improved trail design and signage for more advanced riders

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REFERENCES

1. Newcomb T. Amid cycling surge, sport of mountain biking is seeing increased sales and trail usage. *Forbes*. July 13, 2020. Accessed July 28, 2022. https://www.forbes.com/sites/timnewcomb/2020/07/13/amidst-cycling-surge-sport-of-mountain-biking-seeing-increased-sales-trail-usage/?sh=4e7211a23ddf

2. Roberts L, Jones G, Brooks R. Why do you ride? A characterization of mountain bikers, their engagement methods, and perceived links to mental health and well-being. *Front Psychol.* 2018;9:1642. doi:10.3389/fpsyg.2018.01642

3. Nelson NG, McKenzie LB. Mountain biking-related injuries treated in emergency departments in the United States, 1994-2007. *Am J Sports Med*. 2011;39(2):404-409. doi:10.1177/0363546510383478

4. Kronisch RL, Pfeiffer RP, Chow TK, Hummel CB. Gender differences in acute mountain bike racing injuries. *Clin J Sport Med*. 2002;12(3):158-164. doi:10.1097/00042752-200205000-00003

5. Ashwell Z, McKay MP, Brubacher JR, Gareau A. The epidemiology of mountain bike park injuries at the Whistler Bike Park, British Columbia (BC), Canada. *Wilderness Environ Med*. 2012;23(2):140-145. doi:10.1016/j.wem.2012.02.002

6. Romanow NT, Hagel BE, Nguyen M, Embree T, Rowe BH. Mountain bike terrain park-related injuries: an emerging cause of morbidity. *Int J Inj Contr Saf Promot.* 2014;21(1):29-46. doi:10.1080/17457300.2012.749918

7. Willick SE, Cushman DM, Klatt J, Brobeck M, Spencer C, Teramoto M. The NICA injury surveillance system: design, methodology and preliminary data of a prospective, longitudinal study of injuries in youth cross country mountain bike racing. *J Sci Med Sport.* 2021;24(10):1032-1037. doi:10.1016/j.jsams.2020.05.021

8. Gaulrapp H, Weber A, Rosemeyer B. Injuries in mountain biking. *Knee Surg Sports Traumatol Arthrosc.* 2001;9(1):48-53. doi:10.1007/s001670000145

9. Kronisch RL, Pfeiffer RP. Mountain biking injuries: an update. *Sports Med.* 2002;32(8):523-537. doi:10.2165/00007256-200232080-00004

10. Carmont MR. Mountain biking injuries: a review. *Br Med Bull.* 2008;85:101-112. doi:10.1093/bmb/ldn009

Patient and Provider Factors Associated With Successfully Addressing Medical Needs Using Telehealth: A Cross-Sectional Survey

Obinnaya Wamuo, BA; Noorie Hyun, PhD; Jeana M. Holt, PhD, DNP, RN, FNP-BC; Melek M. Somai, MD, MPH; Bradley H. Crotty, MD, MPH

ABSTRACT

Few data exist that highlight areas where telemedicine shines or struggles from the patient perspective. We conducted a retrospective analysis of patient experience data from 19,465 visits using a logistic regression to model the odds a virtual visit addressed a patient's medical needs. Patient age (80 years: OR 0.58; 95% CI, 0.50-0.67 vs 40-64 years), race (Black: 0.68; 95% CI, 0.60-0.76 vs White), and connection (telephone conversion: OR 0.59; 95% CI, 0.53-0.66 vs video success) were associated with a lower likelihood of addressing medical needs; results varied modestly across specialties. These data suggest that while telehealth is generally well accepted by patients, differences are seen among patient factors and specialty.

BACKGROUND

During the initial phase of COVID-19, clinicians and patients rapidly adopted telehealth across specialties and use cases.[1] While telehealth provides access and convenience, challenges such as limited physical examination may restrict its utility.[2] Identifying where telehealth adequately addresses patient needs will help calibrate telehealth usage. As telehealth recedes from its pandemic peak, patients, clinicians, and systems are ascertaining where and how to use video and telephone-based services. Payors also are determining how they will cover telehealth after the public health emergency. Telehealth has proven itself as a viable option, with up to 76% of Americans wishing to continue using virtual services,[3] yet few data exist to highlight areas where telehealth shines or struggles from the patient perspective.

In this report, we provide data about how well telehealth services meet patients' needs, looking at patient demographics, modality (video or telephone), and clinical specialty.

METHODS

We retrospectively evaluated patients' experiences with telehealth from March 4, 2020, through December 31, 2020. All adult patients who completed a virtual visit at Froedtert & Medical College of Wisconsin, an academic-community health network, were invited to respond to a survey. All visits associated with the survey were completed through insurance. While Froedtert & Medical College of Wisconsin does offer cash pay, on-demand visits, clients using these services were asked to complete a different survey regarding their experience. In examining insurance-based visits, our focus was on ascertaining where virtual visits fit and what the outlook may be in the realm of more traditional scheduled care services. Because of their relatively small number within the health network and the heterogeneity of respondents (parents, adolescents), we excluded pediatric visits.

Our survey prompted patients to respond to the statement "The provider did a good job addressing my medical concerns" using a 5-point Likert scale (strongly agree to strongly disagree). Results were dichotomized to "top box" (strongly agree) or not. Visit information was extracted from the electronic medical record, including patient demographics, specialty, and modality (ie, failed video visits converted to telephone). We then used a

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Table 1. Descriptive Information About Participating Patients

Characteristic	N = 17,685
Age	
18 – 39	2,914 (16%)
40 – 64	8,085 (46%)
65 – 79	5,954 (34%)
80+	732 (4.1%)
Race	
White or Caucasian	15,733 (89%)
American Indian or Alaska Native	51 (0.3%)
Asian	253 (1.4%)
Black or African American	1,244 (7.0%)
Native Hawaiian or other Pacific Islander	9 (< 0.1%)
Other	395 (2.2%)
Insurance	
Managed care	8,935 (51%)
Commercial	185 (1.0%)
Global	24 (0.1%)
Medicaid	784 (4.4%)
Medicare	7,515 (42%)
Others	89 (0.5%)
Missing	153 (0.9%)
Household median income	
< $9,500	2,357 (13%)
$9,501 – $45,000	7,360 (42%)
$45,001 – $75,000	4,691 (27%)
$75,001 – $213,000+	3,277 (19%)

mixed-effects logistic regression to estimate the odds of having a "top box" assessment of meeting needs, while accounting for the compound symmetric correlation within the same provider. The final adjusted logistic regression model includes only statistically significant ($P < 0.05$) univariate factors, including patient race, patient age, video visit success, and specialty. STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines for cross-sectional studies were followed.[4] The Medical College of Wisconsin Institutional Review Board provided approval.

RESULTS

Out of a total of 143,419 virtual visits, 17,685 unique patients (response rate 12%) accounting for 19,465 visits (14% of total virtual visits) responded to the survey. Of the 19,465 visits, 17,969 (92%) were successful visits, while 1,496 (8%) were converted to telephone. Patient demographic information is summarized in Table 1. Overall, 82% of patients either agreed or strongly agreed that the virtual visit addressed their medical needs (67% top box). Older patients were less likely to perceive telehealth as sufficiently meeting their medical concern (80+ vs 40-65: OR 0.58; 95% CI, 0.50-0.67) (Table 2). Non-White patients had lower odds of top-box satisfaction of their medical concerns being addressed, compared with White patients (Black/African American vs White: OR 0.68; 95% CI, 0.60-0.76; Asian vs White: OR 0.62; 95% CI, 0.48-0.80; Other vs White: OR 0.78; 95% CI, 0.64-0.94). Compared with internal medicine, visits in neurology and surgery (OR 0.71; 95% CI, 0.60-0.83 and OR 0.82; 95% CI, 0.73-0.92, respectively) were less likely to be rated top box for addressing medical concerns, while obstetrics/gynecology was slightly higher (OR 1.31; 95% CI, 1.05-1.64). We also saw lower odds of a virtual visit adequately meeting patient needs during instances of virtual visit failure (telephone conversion) (OR 0.59; 95% CI, 0.53-0.66).

Table 2. Mixed-Effects Logistic Regression Modeling "Top Box" Satisfaction with the Visit Addressing Clinical Needs

Characteristic	OR	95% CI	*P* value
Age			
18 – 39	0.91	0.83 – 1.00	0.039
40 – 64	Ref	—	
65 – 79	0.87	0.81 – 0.93	< 0.001
80+	0.58	0.50 – 0.67	< 0.001
Race			
White or Caucasian	Ref	—	
Asian	0.62	0.48 – 0.80	< 0.001
Black or African American	0.68	0.60 – 0.76	< 0.001
Other	0.78	0.64 – 0.94	0.009
Video visit success			
Video success	Ref	—	
Telephone conversion	0.59	0.53 – 0.66	< 0.001
Specialty			
Primary care	Ref	—	
Behavioral heath	0.90	0.72 – 1.12	0.3
Dermatology	1.01	0.76 – 1.33	> 0.9
Gynecology	1.31	1.05 – 1.64	0.016
Internal medicine subspecialty	0.96	0.87 – 1.05	0.3
Neurology	0.71	0.60 – 0.83	< 0.001
Surgery	0.82	0.73 – 0.92	< 0.001

DISCUSSION

Overall, the majority of patients viewed virtual visits as a helpful avenue of health care delivery. An overwhelming majority of respondents reported that their visit sufficiently addressed their needs across a range of clinical domains. We did, however, identify differences across specialties, a finding that merits further research. Our data also show that telephone calls are not equivalent to video visits in terms of meeting patient needs – a finding with policy and health equity implications.

We identified several demographic factors – namely age and race – that were associated with perceiving telehealth as meeting patient needs. Comfort with technology and trust in both their clinician and in telehealth itself as an appropriate care modality may explain, in part, these findings. Research has shown that a gap exists in video visit adoption when comparing non-White patients to White patients, findings partially but incompletely explained by socioeconomic differences.[5,6] This digital divide is one reason that can explain the varying outlook on telemedicine's ability to sufficiently meet one's health care needs. Compounding this,

COVID-19 has caused both patients and clinicians to revisit the legacy of mistrust that exists between minorities and the US health care system. Additionally, despite the continued rise of technology adoption among older patients, many still report having low confidence in using electronic devices for online tasks.[7]

Beyond patient factors, we identified that modality (conversion to telephone) and specialty also affected likelihood of addressing patients' medical concerns. Regarding specialty, it is possible that physical examination may play a role, though confirmation and explanatory reasons require further investigation. Intriguingly, results showed that obstetrics/gynecology (OB/GYN)—a specialty where physical exams and procedures such as ultrasound are integral) experienced an increased likelihood of patient satisfaction. A possible explanation is that OB/GYN visits also serve as a primary care basis for women in the realm of topics that could be discussed virtually, such as contraception, changing birth control, and fertility consultation. Moreover, surveys show that, compared to men, women were more likely to take action in altering their routines to minimize chances of contracting COVID-19.[8]

Regarding modality, it is notable that patients were less likely to feel their medical concerns were addressed by telephone versus video visits. Further research is needed to identify explanatory factors, such as inability for examination, lack of nonverbal communication, or simply frustration of technology and internet connectivity issues. While telephone visits were less likely to meet patient needs than video, they may still be a lifeline for many patients.[9]

Limitations

The response rate of this single-institution patient survey, upon which the outcome was based, was modest, and response bias is possible. Based on demographics, younger patients (≤65) and non-White patients were less likely to respond and may be underrepresented; visit success or telephone conversion were not different between respondents and nonrespondents, nor were socioeconomic status or specialty. The duration of the visits was not recorded, and it is possible that troubleshooting video connections took time away from visits—an unmeasured factor that could affect how well the visit addressed medical needs. Further limitations include utilizing a top-box approach for our statistical analysis. Responses may be subject to personal biases, resulting in an avoidance of extreme responses to survey questions reported across some demographic groups.[10]

CONCLUSIONS

These data suggest that virtual video visits are generally well accepted by patients, but differences are seen due to patient factors and specialty. As telehealth moves into the mainstream as a care delivery modality, further exploration about where and when it works well compared with where and when it does not is warranted; building off these findings would help operational teams and payors move forward.

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REFERENCES

1. Fox B, Sizemore O. Telehealth: fad or the future. 2020. Epic Research. August 18, 2020. Accessed September 8, 2020. https://epicresearch.org/articles/telehealth-fad-or-the-future

2. Breton M, Sullivan EE, Deville-Stoetzel N, et al. Telehealth challenges during COVID-19 as reported by primary healthcare physicians in Quebec and Massachusetts. *BMC Fam Pract.* 2021;22(1):192. doi:10.1186/s12875-021-01543-4

3. Bestsennyy O, Gilbert G, Harris A, Rost J. Telehealth: a quarter-trillion-dollar post-COVID-19 reality? McKinsey & Company. Accessed October 18, 2021. https://www.mckinsey.com/industries/healthcare-systems-and-services/our-insights/telehealth-a-quarter-trillion-dollar-post-covid-19-reality

4. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med.* 2007;147(8):573-577. doi:10.7326/0003-4819-147-8-200710160-00010

5. Rodriguez JA, Betancourt JR, Sequist TD, Ganguli I. Differences in the use of telephone and video telemedicine visits during the COVID-19 pandemic. *Am J Manag Care*. 2021;27(1):21-26. doi:10.37765/ajmc.2021.88573

6. Luo J, Tong L, Crotty BH, et al. Telemedicine adoption during the COVID-19 pandemic: gaps and inequalities. *Appl Clin Inform*. 2021;12(4):836-844. doi:10.1055/s-0041-1733848

7. Anderson M, Perrin A. Tech adoption climbs among older adults. Pew Research Center. May 17, 2017. Accessed October 18, 2021. https://www.pewresearch.org/internet/2017/05/17/tech-adoption-climbs-among-older-adults/

8. Kahn C. U.S. men less likely to heed health warnings as coronavirus death toll mounts: Reuters poll. Reuters. March 27, 2020. Accessed June 1, 2020. https://www.reuters.com/article/us-health-coronavirus-gender-poll/u-s-men-less-likely-to-heed-health-warnings-as-coronavirus-death-toll-mounts-reuters-poll-idUSKBN21E1C9

9. Crotty BH, Hyun N, Polovneff A, et al. Analysis of clinician and patient factors and completion of telemedicine appointments using video. *JAMA Netw Open.* 2021;4(11):e2132917. doi:10.1001/jamanetworkopen.2021.32917

10. Chung S, Mujal G, Liang L, Palaniappan LP, Frosch DL. Racial/ethnic differences in reporting versus rating of healthcare experiences. *Medicine (Baltimore).* 2018;97(50):e13604. doi:10.1097/MD.0000000000013604

Diabetic Ketoacidosis Causing Transient Homonymous Hemianopia and Generalized Seizure: A Case Report and Literature Review

Felix E. Chukwudelunzu, MD, MBA; Leonardo Fugoso, MD

ABSTRACT

Introduction: Neurologic complications of hyperglycemia are common. Cases of seizures and hemianopia related to nonketotic hyperglycemia have been reported but are rare with diabetic ketoacidosis.

Case Presentation: We present clinical, laboratory, and radiologic findings in a patient with diabetic ketoacidosis associated with generalized seizure and homonymous hemianopia, with a literature review of reported cases.

Discussion: Neurologic complications of hyperglycemia are many, but seizure with hemianopia is most commonly associated with nonketotic hyperosmolar hyperglycemia rather than diabetic ketoacidosis.

Conclusions: Generalized seizure and retrochiasmal visual field defect are known neurological complications of diabetic ketoacidosis. Like nonketotic hyperosmolar hyperglycemia, these neurological symptoms are transient, and the structural changes in magnetic resonance imaging are usually reversible.

INTRODUCTION

Diabetic ketoacidosis (DKA) and nonketotic hyperosmolar hyperglycemia (NKHH) are major life-threatening complications of diabetes. DKA usually evolves over 24 hours. Common precipitating factors include inadequate administration of insulin, infections (including pneumonia, sepsis, or urinary tract infections), cerebral or coronary infarction, and pancreatitis. Patients present with multiple systemic symptoms, including nausea, vomiting, and abdominal pain. In DKA, glucose can range from 250-600 mg/dl, osmolality 300-320 mosm/kg, serum beta-hydroxybutyrate elevation (>2.5 mmol/L), decreased serum bicarbonate (<18 meq/L), and arterial pH (6.8–7.3) with elevated anion gap and urine ketones. In contrast, patients with NKHH present with several weeks of polyuria, weight loss, and varying degrees of altered level of consciousness. Precipitating factors are similar to DKA. They have marked hyperglycemia (600 – 1200 mg/dl), elevated osmolality (330-380 mosm/kg), decreased serum beta-hydroxybutyrate (<1.0 mmol/L), elevated serum bicarbonate (>18 meq/L), elevated arterial pH (>7.3) with normal anion gap and absent or trace urine ketones.

Both DKA and NKHH are characterized by intracellular dehydration and occur when the level of insulin is not sufficient to support transmembrane transport of adequate glucose into cells. In the case of DKA, the liver rapidly breaks down fat into ketones to employ as a fuel source. The overproduction of ketones ensues, causing them to accumulate in the blood and urine. For NKHH, the level of insulin is usually sufficient to inhibit free fatty acid mobilization, leading to little or no ketone accumulation in the blood or urine.

Neurologic complications of hyperglycemia are diverse, including choreoathetosis, hemiballism, dysphagia, seizures, and coma. Various types of seizures (occipital, focal, or complex partial) and hemianopia in the setting of NKHH have been reported.[1-12] We report the case of DKA complicated by homonymous hemianopia and generalized seizure, with a literature review.

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Table 1. Demographic, Clinical, Laboratory, Radiologic, and Electroencephalogram (EEG) Features of Cases

	Case Review	Present Case
Demographics		
Age at presentation, Mean (+/- SD); n = 24	53.0 (13.01)	38
Age at presentation, Median (Range); n = 24	53.5 (30.0-83.0)	
Sex, N = 24		
Male n (%)	16 (66.7)	Male
Female n (%)	8 (33.3)	
Known diabetic at presentation	11 (45.8)	Yes
Clinical Features		
Presenting symptoms		
[a]Occipital seizures n (%), N = 23	18 (78.3)	
Headache n (%), N = 24	5 (20.8)	
[b]Focal motor seizure n (%), N = 24	7 (29.2)	
[c]Generalized seizure n (%), N = 24	2 (8.3)	Yes
Neurologic examination findings		
Hemianopsia, n (%), N = 24	22 (91.7)	
Clinical seizure, n (%), N = 24 (focal, generalized, oroccipital)	24 (100)	
Laboratory findings at presentation		
Serum glucose mg/dl, mean (+/- SD), n = 24	472.1 (166.85)	487
Serum glucose mg/dl, median (range), n = 24	460.5 (261.0-999.0)	
Serum osmolality mOsmo/kg, mean (+/- SD), n = 20	297.1 (39.54)	321
Serum osmolality mosm/kg, median (range); n = 20	304.5 (136.0-333.0)	
Hemoglobin A1C %, mean (+/- SD), n = 10	13.1 (2.37)	16.5
Hemoglobin A1C %, median (range), n = 10	13.5 (9.4-17.8)	
Urine ketone present, n (%); N = 14	2 (14.3)	Yes
Beta-hydroxybutyrate mmol/l, mean (+/- SD), n = 24 (None reported in case review)	—	4.8
EEG findings, N = 23		
Interictal epileptiform discharge, n (%)	15 (65.2)	No
Nonspecific slowing, n (%)	4 (17.4)	Yes
Normal n (%)	4 (17.4)	No
MRI findings, N = 21		
T2/FLAIR hypointensity, n (%)	15 (71.4)	Yes
T2/FLAIR hyperintensity, n (%)	5 (23.8)	No
Restricted diffusion signal abnormality, n (%)	8 (38.1)	No
Enhancement on brain MRI n (%), N = 18	5 (27.8)	No
Normal, n (%), N = 22	3 (13.6)	No
Outcome at discharge/follow-up evaluation (2 days to 6 months), N = 24		
Clinical findings (seizure/hemianopia) resolved, n (%)	24 (100)	Yes
MRI findings resolved, n (%), N = 16	11 (68.8)	Yes
MRI findings incompletely resolved, n (%), N = 16	5 (31.2)	—
EEG findings completely resolved, n (%), N = 15	15 (100)	—

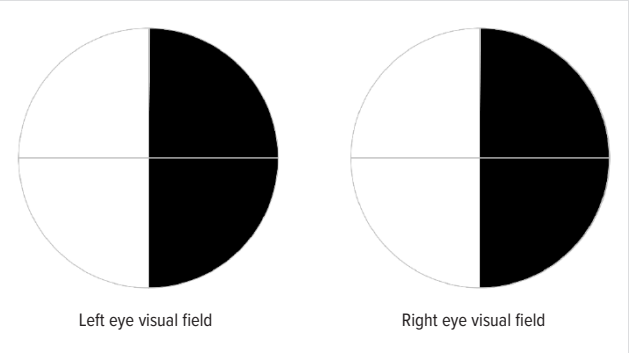
Abbreviations: MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery.

[a]Occipital seizure: Visual hallucinations characterized by flickering colored geometric designs or lights with or without blurry vision, generally lasting less than 1 minute for each occurrence.

[b]Focal seizure: Rhythmic jerking of 1 limb with preserved consciousness, lasting less than 5 minutes.

[c]Generalized seizure: Tonic-clonic limb movement of the upper and lower extremity with altered alertness, lasting 1-2 minutes, followed by postictal confusion and tiredness.

Figure 1. Visual Field Testing Showing a Right Homonymous Hemianopia



CASE PRESENTATION

A 38-year-old man had 2 weeks symptoms of progressive right visual loss and intermittent headache. He was bumping into objects in his right visual field. His past medical history included poorly controlled type 2 diabetes and hypertension.

On admission, he was afebrile, blood pressure was 144/95 mmHg, and neurologic examination showed dense right homonymous hemianopia. The hemianopia finding was confirmed by Ophthalmology and Neurology (Figure 1). Laboratory studies (Table 1) showed serum glucose of 487 mg/dl; bicarbonate of 14 mmol/l; serum osmolality of 321 mosm/kg; elevated anion gap, hemoglobin A_{1c}, and beta-hydroxybutyrate of 25, 16.5%, and 4.8 mmol/l, respectively. Spot urine analysis showed glycosuria (>1000 mg/dl) and ketonuria (>150 mg/dl). Significant improvement of all laboratory studies on hospital days 2 and 3 is demonstrated in Table 2. Brain magnetic resonance imaging (MRI) obtained on hospital day 2 showed T2/ fluid-attenuated inversion recovery (FLAIR) hypointense signal within the left parieto-occipital subcortical white matter (Figure 2A). There was no abnormality of the diffusion weighted imaging sequence (not shown). Computed tomography angiography of head and neck showed no flow-limiting stenosis.

The patient was started on intravenous (IV) hydration with normal saline and insulin. On hospital day 2, he had a witnessed stereotype generalized seizure of rhythmic tonic-clonic activity affecting both arms and legs with tonic upward eye deviation lasting 1 minute, followed by 45 minutes postictal drowsiness and confusion. He was treated with 2 mg of lorazepam intravenously once, followed by a loading dose of levetiracetam of 13.3 mg/kg and maintenance dose 500 mg orally twice daily. Electroencephalogram (EEG) obtained on the same day showed nonspecific slowing.

He was discharged on hospital day 4 with levetiracetam 500 mg twice daily and oral hypoglycemic agent. At neurologic follow-up evaluation 3 weeks later, he had complete resolution of his right homonymous hemianopia and abnormal brain MRI (Figure 2B), with no recurrent clinical seizure.

DISCUSSION

We present a unique case of ketotic hyperosmolar hyperglycemia complicated by generalized seizure and retrochiasmal visual field defect. None of the reported cases in our review had such a profound ketonuria (>150 mg/dl of urine ketone) or ketonemia (serum hydroxybutyrate 4.8 mmol/l). Our literature review identified 2 cases, one reporting trace ketonuria[1] and another high ketonuria.[13] The implication is that DKA can mimic NKHH neurologic complications.

Most of the patients with NKHH in our case review presented with occipital seizure (78.3%) and focal seizures (29.2%),[1-5, 7-12] while the minority presented with generalized seizure,[4,6] as was seen in our case. Brain imaging findings of reversible T2/FLAIR hypointensity, clinical symptom response to treatment with triple therapy (IV saline hydration, insulin, and antiepileptic drug), serum osmolality, and glucose levels above 300 mosm/kg and 400 mg/dl, respectively, seen in our case were similar to those in the literature review.

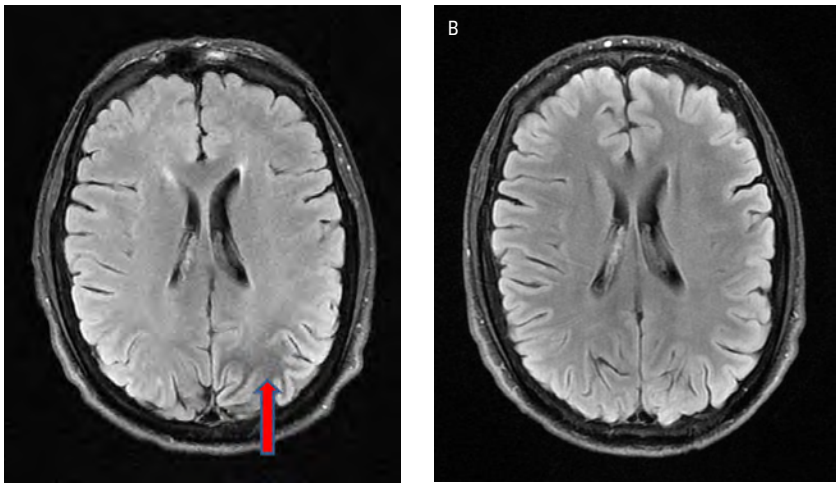
Interestingly, follow-up brain MRI findings of persistent abnormality involved restricted diffusion signal changes not seen in our patient. Restricted diffusion signal abnormality is in keeping with cytotoxic injury typically seen with ischemic infarct, while T2/FLAIR hypointense abnormality may be due transient deposition of free radicals and/or iron that resulted from excitatory axonal damage during hyperglycemia-induced seizures and intracellular dehydration in glial and supporting tissues.[14] EEGs were performed in 23 of the 24 cases in the literature, with 65.2% showing interictal epileptiform discharges. The minority (17.4%)—as in our case—showed nonspecific diffuse slowing.

The mechanism of cerebral injury from hyperglycemia is unclear. Many hypotheses have been proposed, including neuronal dysfunction due to intracellular dehydration and end-organ iron deposition;[14-15] autoregulation failure due to sympathetic dysautonomia, endothelial dysfunction, blood brain barrier breakdown, and free radical release;[16] and depletion of gamma aminobutyric acid due to alteration in Krebs cycle with resulting depressed glucose utilization during hyperglycemic conditions.[17]

CONCLUSIONS

Homonymous hemianopia and seizures are established complications of NKHH but rarely are reported in DKA. Both conditions, although different in many ways, have similar underlying hyperosmolar hyperglycemic states that may result in comparable neurological complications.

Figure 2. Magnetic Resonance Imaging (MRI) of the Brain



A. Brain MRI on hospital day 2, showed fluid attenuated inversion recovery (FLAIR) hypointensity in the left occipital lobe (red arrow).

B. Brain MRI 3 weeks after onset of symptoms showed complete resolution of the previous abnormality (Figure 2A) in the left occipital lobe.

Table 2. Comparison of Laboratory Data Hospital Days 1-3

Lab Parameters	Day 1[a]	Day 2	Day 3
Glucose (POC), mg/dl			
Mean	487	201.2 (n = 10)	185.8 (n = 13)
Median (Range)	—	179.0 (137-317)	163.0 (108-302)
Sodium, mmol/L	130	136	138
Chloride, mmol/L	91	105	104
Bicarbonate, mmol/L	14	20	24
Anion gap	25	11	10
Potassium, mmol/L	4.3	3.7	4.0
Osmolality mOsm/kg	321	ND	ND
HbA1c, %	16.5	ND	ND

Abbreviations: HbA1C, hemoglobin A1c; ND, not done.

[a]Admission day.

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REFERENCES

1. Xiang XH, Fang JJ, Yang M, Zhao GH. Hyperglycemic hemianopia: a case report. *World J Clin Cases*. 2021;9(7):1720-1727. doi:10.12998/wjcc.v9.i7.1720

2. Stayman A, Abou-Khalil BW, Lavin P, Azar NJ. Homonymous hemianopia in nonketotic hyperglycemia is an ictal phenomenon. *Neurol Clin Pract*. 2013;3(5):392-397. doi:10.1212/CPJ.0b013e3182a7bb76

3. Chen YS, Chen TS, Huang CW. Nonketotic hyperglycemia-related seizures of left parieto-occipital origin: a case report. *J Neurosci Nurs*. 2020;52(1):27-29. doi:10.1097/JNN.0000000000000481

4. Lavin PJ. Hyperglycemic hemianopia: a reversible complication of non-ketotic hyperglycemia. *Neurology*. 2005;65(4):616-619. doi:10.1212/01.wnl.0000173064.80826.b8

5. Gaballa S, Hlaing KM, Moursy S, Ahmed A, AlJaf A. Non-ketotic hyperglycemia causing a transient unilateral homonymous hemianopia: a manifestation of occipital lobe seizure. *Cureus*. 2020;12(6):e8527. doi:10.7759/cureus.8527

6. Nissa Z, Siddiqi SA, Abdool SA. Occipital seizures and persistent homonymous hemianopia with T2 hypointensity on MRI in nonketotic hyperglycemia. *Epilepsy Behav Case Rep.* 2016;6:3-5. doi:10.1016/j.ebcr.2016.04.008

7. Putta SL, Weisholtz D, Milligan TA. Occipital seizures and subcortical T2 hypointensity in the setting of hyperglycemia. *Epilepsy Behav Case Rep.* 2014;2:96-99. doi:10.1016/j.ebcr.2014.01.001

8. Hung WL, Hsieh PF, Lee YC, Chang MH. Occipital lobe seizures related to marked elevation of hemoglobin A1C: report of two cases. *Seizure*. 2010;19(6):359-362. doi:10.1016/j.seizure.2010.05.006

9. Del Felice A, Zanoni T, Avesani M, et al. EEG-fMRI coregistration in non-ketotic hyperglycemic occipital seizures. *Epilepsy Res.* 2009;85(2-3):321-324. doi:10.1016/j.eplepsyres.2009.03.025

10. Moien-Afshari F, Téllez-Zenteno JF. Occipital seizures induced by hyperglycemia: a case report and review of literature. *Seizure*. 2009;18(5):382-385. doi:10.1016/j.seizure.2008.12.001

11. Raghavendra S, Ashalatha R, Thomas SV, Kesavadas C. Focal neuronal loss, reversible subcortical focal T2 hypointensity in seizures with a nonketotic hyperglycemic hyperosmolar state. *Neuroradiology*. 2007;49(4):299-305. doi:10.1007/s00234-006-0189-6

12. Wang CP, Hsieh PF, Chen CC, et al. Hyperglycemia with occipital seizures: images and visual evoked potentials. *Epilepsia*. 2005;46(7):1140-1144. doi:10.1111/j.1528-1167.2005.56404.x

13. Strowd RE, Wabnitz A, Balakrishnan N, Craig J, Tegeler CH. Clinical reasoning: acute-onset homonymous hemianopia with hyperglycemia: seeing is believing. *Neurology*. 2014;82(15):e129-e133. doi:10.1212/WNL.0000000000000308

14. Hiremath SB, Gautam AA, George PJ, Thomas A, Thomas R, Benjamin G. Hyperglycemia-induced seizures - understanding the clinico- radiological association. *Indian J Radiol Imaging.* 2019;29(4):343-349. doi:10.4103/ijri.IJRI_344_19

15. Rowe PA, Kavanagh K, Zhang L, Harwood HJ Jr, Wagner JD. Short-term hyperglycemia increases arterial superoxide production and iron dysregulation in atherosclerotic monkeys. *Metabolism*. 2011;60(8):1070-1080. doi:10.1016/j.metabol.2010.11.003

16. Cotton F, Kamoun S, Rety-Jacob F, Tran-Minh VA, Nighoghossian N, Hermier M. Acute hypertensive encephalopathy with widespread small-vessel disease at MRI in a diabetic patient: pathogenetic hypotheses. *Neuroradiology*. 2005;47(8):599-603. doi:10.1007/s00234-005-1385-5

17. Guisado R, Arieff AI. Neurologic manifestations of diabetic comas: correlation with biochemical alterations in the brain. *Metabolism*. 1975;24(5):665-679. doi:10.1016/0026-0495(75)90146-8

Cannabis-Induced Catatonia in a 15-Year-Old Male: A Case Report

Trevor Gauthier, BS; Pradeep Bangalore Prakash, MD; Drew Keopple, NP; Ralph Vardis, MD

ABSTRACT

Introduction: Catatonia is a syndrome of primarily psychomotor disturbances most common in psychiatric mood disorders but that also rarely has been described in association with cannabis use.

Case Presentation: A 15-year-old White male presented with left leg weakness, altered mental status, and chest pain, which then progressed to global weakness, minimal speech, and a fixed gaze. After ruling out organic causes of his symptoms, cannabis-induced catatonia was suspected, and the patient responded immediately and completely to lorazepam administration.

Discussion: Cannabis-induced catatonia has been described in several case reports worldwide, with a wide range and duration of symptoms reported. There is little known about the risk factors, treatment, and prognosis of cannabis-induced catatonia.

Conclusions: This report emphasizes the importance of clinicians maintaining a high index of suspicion to accurately diagnose and treat cannabis-induced neuropsychiatric conditions, which is especially important as the use of high-potency cannabis products in young people increases.

INTRODUCTION

Catatonia is a syndrome of primarily psychomotor disturbances most common in psychiatric mood disorders but that also rarely has been described in association with cannabis use. We report the case of an adolescent male experiencing cannabis-induced catatonia.

CASE PRESENTATION

A 15-year-old White male presented to the emergency department with left leg weakness, altered mental status, and chest pain. He had experienced vague symptoms of fatigue and weakness for approximately 1 month. He had been diagnosed with COVID-19 a month prior and then with influenza A shortly after that, so his symptoms had been attributed to those illnesses. During his 4-day admission for further workup, he progressed to having global weakness, minimal speech, and a fixed gaze with little visual scanning of the environment. Past medical history was notable for cannabis use disorder, mild depression, and a remote history of seizures. The patient's medication list included vitamins, cetirizine for seasonal allergies, and albuterol infrequently for mild asthma symptoms.

Lab workup was largely unremarkable, with a normal complete blood cell count, comprehensive metabolic panel, C-reactive protein, erythrocyte sedimentation rate, troponin, and urine analysis. The only abnormal labs were an elevated D-dimer (926 ng/mL) and a urine drug screen positive for cannabinoids. Brain magnetic resonance imaging, extended electroencephalogram monitoring, and cerebrospinal fluid analysis all were unremarkable. In the absence of any evident organic cause of his condition, a psychiatric cause was suspected, and a diagnosis of catatonia was considered. The patient scored 3/69 on the Bush-Francis Catatonia Rating Scale, with symptoms of hypokinesia, minimal speech, and a partially fixed gaze. A lorazepam challenge test was administered to investigate a diagnosis of catatonia. Intravenous lorazepam 2 mg was administered and, within minutes, the patient's symptoms completely resolved.

Further history taken from the patient revealed that he had used marijuana approximately 3 to 4 times per week for the past 4 months and more recently had been vaping THC-O-acetate, a synthetic analog of tetrahydrocannabinol (THC) that is purport-

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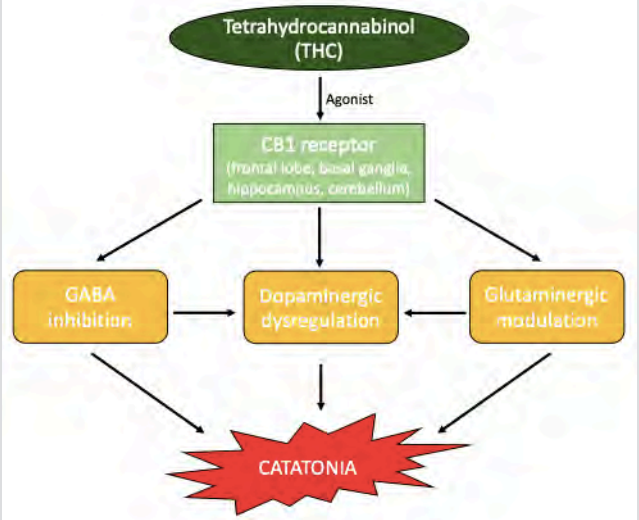
Figure. Neurotransmittter Systems Involved in Cannabis-Induced Catatonia



Adapted from Parenti et al[8] and Wegener et al.[10]

edly 2 to 3 times more potent than THC. He denied any affective or psychotic symptoms.

DISCUSSION

Catatonia is a syndrome of primarily psychomotor disturbances most common in psychiatric mood disorders, such as bipolar disorder, but also can occur from other psychiatric disorders, substance intoxication or withdrawal, or from medical or neurological causes.[1-3] Catatonia can manifest with a wide range of symptoms, regardless of the underlying cause.[1,3] The severity of catatonia can be quantified using symptom rating scales, with the Bush-Francis Catatonia Rating Scale being the method most used in clinical scenarios to assess the severity of catatonia and monitor treatment response.[4] To aid in diagnosis, a lorazepam challenge test can be performed, where 1 to 2 doses of 1 mg to 2 mg of lorazepam are administered; a positive response is a reduction in symptoms by 50% or more as measured by a symptom rating scale.[2,4] While other benzodiazepines likely have some efficacy in the treatment of catatonia, lorazepam is the most studied treatment and is first-line therapy for catatonia due to any cause, with remission rates greater than 70%.[1,2,4-6] The duration of lorazepam therapy in the treatment of catatonia is not clear, but it is important to ensure an adequate treatment time, as premature discontinuation of treatment can lead to catatonic symptoms reappearing.[4] For catatonia that fails to respond to lorazepam, electroconvulsive therapy is often effective.[1,3,6]

The neurobiology of catatonia has not yet been fully elucidated. The heterogeneity of the clinical manifestations of catatonia makes determination of its neural basis difficult, and because catatonia can cause both hypokinetic and hyperkinetic symptoms and can be triggered by many different causes, multiple neural pathways are likely involved.[5] Dysregulation of several neurotransmitter systems—particularly the dopaminergic, GABAergic, and glutaminergic systems—have been implicated in catatonia.[1,7]

Northoff[7] describes a model that refers to dysfunction of both "horizontal modulation" and "vertical modulation" in patients with catatonia. The horizontal (cortical-to-cortical) modulatory dysfunction refers to hyperactivity of the orbitofrontal cortex and other prefrontal cortex areas, with alterations in connections between these areas to motor and premotor areas of the cortex.[5,7] The vertical (cortical-to-subcortical) modulatory dysfunction refers to dysfunction of cortical areas, mostly in the frontal and parietal lobes, leading to alterations in connections to subcortical motor areas in the basal ganglia.[7] The cortical dysfunction seen in catatonia is related to decreased GABAergic tone, which explains the response to lorazepam.[1,5,7] The use of N-methyl-D-aspartate (NMDA) antagonists (eg, amantadine) also has some efficacy in the treatment of catatonia, likely related to the relative glutaminergic hyperactivity seen in the condition.[1,7] However, because the effect of NMDA antagonists in the treatment of catatonia is not as rapid and blatant as the effect of benzodiazepines, the relative excess of glutaminergic excitatory activity could be a result of impairment of the γ-aminobutyric acid (GABA) system, and not itself a direct cause of catatonia.[7] Parenti et al[8] describes these neurotransmitter disturbances in a neural excitatory/inhibitory imbalance model: an impairment in GABA inhibition and a relative excess of stimulatory glutaminergic action causes dysregulation of dopamine release, which could contribute to both the motor and psychotic symptoms of catatonia and explains the efficacy of benzodiazepines and NMDA antagonists in the treatment of catatonia.

GABAergic and glutaminergic system dysfunction are not only related to catatonia itself but are also related to cannabis use. Some evidence suggests that THC, the psychoactive compound in marijuana, causes alterations in the physiologic control that the endogenous cannabinoid system has on GABA and glutamate release.[9,10] THC is a partial agonist of CB1 and CB2 receptors, with CB1 being found mostly in the brain causing the psychoactive effects and CB2 located in the periphery.[10,11] CB1 receptor distribution in the brain is largely concentrated in areas of the cortex and basal ganglia that also are implicated in the neurobiology of catatonia, psychosis, and substance use disorder.[5,11,12] A framework for how THC agonism of CB1 receptors influences the neurotransmitter systems involved in catatonia is found in the Figure.

A recent review of catatonia related to cannabis and synthetic cannabinoids performed by Palma-Álvarez et al[12] analyzed the case reports and case series available on the topic. The review showcased the wide range of symptoms manifested in patients with cannabis-induced catatonia, as well as a wide range of the duration of symptoms—in some cases with symptoms continuing longer than would be expected given the half-life of THC. Half of the cases included in the review were patients with no previous psychiatric

history. Most of the cases involved cannabis-induced psychosis in addition to catatonic symptoms. In fact, the authors suggested that this could lead to an underreporting of cannabis-induced catatonia, with the motor symptoms of catatonia being overshadowed by more prominent positive psychotic symptoms. In cases analyzed that involved long-term use of marijuana, an increase in the frequency of use and/or the potency of the product preceded the onset of catatonia, as was the scenario in the case presented here. All cases were treated with lorazepam, with some also including the addition of antipsychotic medication, electroconvulsive therapy, or other psychiatric medications. However, the authors noted that most of the studies on catatonia are performed on people without a substance use disorder, so there is a poor knowledge base for the risk factors, treatment, and prognosis of substance-induced, or specifically cannabis-induced, catatonia.[12]

The landscape of cannabis consumption in the United States has changed greatly in recent years. States and localities have progressively made moves toward the legalization of marijuana for recreational use. The US has seen an increase in the number of people using cannabis, the frequency of use, and the amount consumed. The prevalence of daily or near-daily use has doubled in the US in the past decade.[13] The potency of cannabis products—as reflected by the concentration of THC—also has increased significantly in recent years,[14] with the availability today of high-potency resin oils having up to 90% THC.[15] Even as the potency of cannabis products continues to increase, there is an inverse relationship between the use of cannabis by American adolescents and the perception of cannabis as harmful—that is, as youth have perceived cannabis as being less harmful, the use of it among them has increased.[13]

The patient in this case was younger than any patient included in the review by Palma-Álvarez et al.[12] However, if this relatively newly described phenomenon is underdiagnosed and underreported, it is possible that the prevalence of this condition may be more common than currently understood in the pediatric population and in the larger population more generally. Because the prognosis, treatment duration, and long-term sequelae of this condition are poorly understood, it is important for these patients to maintain extended follow-up to monitor for recurrence and/or the development of additional neuropsychiatric symptoms.

CONCLUSIONS

This case report describes an adolescent male gradually developing catatonic symptoms of hypokinesia, minimal speech, and a partially fixed gaze after an extended period of frequent THC use with a recent switch to consumption of high-potency synthetic THC. This case adds to the limited but growing literature on cannabis-induced neuropsychiatric conditions in pediatric populations; to our knowledge, the patient described in this case is younger than any other previously described case of cannabis-induced catatonia.

This report highlights the need for further investigation into the neuropsychiatric effects of cannabis and synthetic cannabinoids that have been associated with the development of catatonia and other psychiatric conditions. It also emphasizes the importance of clinicians maintaining a high index of suspicion to correctly diagnose and treat cannabis-induced catatonia and other cannabis-induced psychiatric conditions and stresses the importance of pediatricians and primary care clinicians recognizing signs of cannabis abuse in patients and intervening before neuropsychiatric sequalae develop.

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REFERENCES

1. Daniels J. Catatonia: clinical aspects and neurobiological correlates. *J Neuropsychiatry Clin Neurosci.* 2009;21(4):371-380. doi:10.1176/jnp.2009.21.4.371

2. Sienaert P, Dhossche DM, Vancampfort D, De Hert M, Gazdag G. A clinical review of the treatment of catatonia. *Front Psychiatry.* 2014;5:181. doi:10.3389/fpsyt.2014.001813.

3. Bhati MT, Datto CJ, O'Reardon JP. Clinical manifestations, diagnosis, and empirical treatments for catatonia. *Psychiatry (Edgmont)*. 2007;4(3):46-52. Accessed March 2, 2022. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2922358/

4. Suchandra HH, Reddi VSK, Aandi Subramaniyam B, Muliyala KP. Revisiting lorazepam challenge test: clinical response with dose variations and utility for catatonia in a psychiatric emergency setting. *Aust N Z J Psychiatry*. 2021;55(10):993-1004. doi:10.1177/0004867420968915

5. Walther S, Stegmayer K, Wilson JE, Heckers S. Structure and neural mechanisms of catatonia. *Lancet Psychiatry.* 2019;6(7):610-619. doi:10.1016/S2215-0366(18)30474-7

6. Pelzer AC, van der Heijden FM, den Boer E. Systematic review of catatonia treatment. *Neuropsychiatr Dis Treat.* 2018;14:317-326. doi:10.2147/NDT.S147897

7. Northoff G. What catatonia can tell us about "top-down modulation": a neuropsychiatric hypothesis. *Behav Brain Sci.* 2002;25(5):555-604. doi:10.1017/s0140525x02000109

8. Parenti A, Jardri R, Geoffroy PA. How anti-NMDAR encephalitis sheds light on the mechanisms underlying catatonia: the neural excitatory/inhibitory imbalance model. *Psychosomatics.* 2016;57(3):336-338. doi:10.1016/J.PSYM.2016.01.007

9. Bossong MG, Niesink RJM. Adolescent brain maturation, the endogenous cannabinoid system and the neurobiology of cannabis-induced schizophrenia. *Prog Neurobiol.* 2010;92:370-385. doi:10.1016/j.pneurobio.2010.06.010

10. Wegener N, Kuhnert S, Thüns A, Roese R, Koch M. Effects of acute systemic and intra-cerebral stimulation of cannabinoid receptors on sensorimotor gating, locomotion and spatial memory in rats. *Psychopharmacology (Berl)*. 2008;198:375-385. doi:10.1007/s00213-008-1148-1

11. Deng H, Verrico CD, Kosten TR, Nielsen DA. Psychosis and synthetic cannabinoids. *Psychiatry Res.* 2018;268:400-412. doi:10.1016/j.psychres.2018.08.012

12. Palma-Álvarez RF, Soriano-Dia A, Ros-Cucurull E, et al. Catatonia related to cannabis and synthetic cannabinoids: a review. *J Dual Diagn*. 2021;17(2):159-171. doi:10.1080/15504263.2021.1904163

13. United Nations Office on Drugs and Crime. Booklet 3 – drug market trends: opioids, cannabis. *World Drug Report 2021.* United Nations; June 2021:1-121. Accessed March 2, 2022. https://www.unodc.org/res/wdr2021/field/WDR21_Booklet_3.pdf

14. Chandra S, Radwan MM, Majumdar CG, Church JC, Freeman TP, ElSohly MA. New trends in cannabis potency in USA and Europe during the last decade (2008-2017). *Eur Arch Psychiatry Clin Neurosci.* 2019;269(1):5-15. doi:10.1007/s00406-019-00983-5

15. Pierre JM. Risks of increasingly potent cannabis: the joint effects of potency and frequency. *Curr Psychiatr.* 2017;16(2):14-20. Accessed May 24, 2022. https://cdn.mdedge.com/files/s3fs-public/CP01602014.PDF

Teprotumumab-Induced Encephalopathy: A Rare Side Effect of a Novel Therapeutic

Megan D. Yee, BA; James McCarthy, MD; Brian Quinn, MD; Asif Surani, MD

ABSTRACT

Introduction: Teprotumumab is a novel monoclonal antibody used for treatment of thyroid eye disease (TED). To our knowledge, this is the second reported case of encephalopathy associated with teprotumumab therapy.

Case Presentation: A 62-year-old White woman with a history of hypertension, Graves' disease, and thyroid eye disease presented with 1 week of intermittent altered mental status following her third teprotumumab infusion. Neurocognitive symptoms resolved following plasma exchange therapy.

Discussion: By using plasma exchange as first-line therapy, our patient had a shorter time course from diagnosis to symptom resolution than was reported in the previously published case.

Conclusions: Clinicians should consider this diagnosis in patients with encephalopathy after teprotumumab infusion, and our experience suggests plasma exchange is an appropriate initial treatment. Proper counseling of this potential side effect is warranted for patients prior to starting teprotumumab to facilitate earlier detection and treatment.

INTRODUCTION

Thyroid eye disease (TED) or thyroid-associated ophthalmopathy is a rare, debilitating autoimmune condition with an annual incidence of 2.6 to 16.0 cases per 10,000 population per year.[1] It is postulated that the insulin-like growth factor-1 (IGF-1) receptor is involved in its pathogenesis. Teprotumumab, a novel therapeutic monoclonal antibody approved by the US Food and Drug Administration (FDA) in 2020, inhibits IGF-1 receptor signaling and blocks the autoimmune response that exacerbates TED.[2,3] Clinical trials of teprotumumab have shown substantial and rapid improvement in proptosis reduction in patients with TED.[4] Associated side effects are typically mild and transient, such as hyperglycemia, muscle cramps, auditory disturbances, and inflammatory bowel disease.[4,5] Severe adverse events leading to hospitalization also have been reported, including diarrhea, *Escherichia coli* sepsis, and urinary retention.[6] Encephalopathy related to teprotumumab was not seen in phase 3 trials but recently has been highlighted by Hoang et al.[7] We present a second case of teprotumumab-induced encephalopathy associated with a patient with TED.

CASE PRESENTATION

A 62-year-old White woman with past medical history of hypertension and Graves' disease associated with TED presented with 1 week of intermittent altered mental status. Her husband first noticed symptoms shortly after the patient's third teprotumumab infusion. She had difficulty performing basic tasks and following instructions, extreme mood swings, and episodes of amnesia, aphasia, insomnia, tremors, and anxiety. Neurologic evaluation demonstrated significant cognitive impairment. She was fully alert and oriented but struggled forming sentences and had occasional nonsensical speech. She was able to name 5 out of 5 objects, read sentences, and follow 1-step commands but was unable to follow commands with 2 or more steps. Her Montreal Cognitive Assessment (MoCA) score version 7.1 was 22, indicating mild cognitive impairment. A continuous electroencephalogram was normal without epileptiform discharges or seizures and

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brain magnetic resonance imaging (MRI) and computed tomography of the head were both negative for signs of hemorrhage, mass, or infarct. Lumbar puncture was notable for slightly elevated protein at 46 mg/dL but otherwise had normal cell counts with negative infectious, paraneoplastic, and autoimmune testing (Table). The patient's urine drug screen was negative, as were the screening tests for syphilis, HIV, nutritional deficiencies, and metabolic derangements. Her thyroid stimulating hormone was elevated at 7.42 uIU/mL; however, a free T4 and total T3 were within normal limits. In addition to teprotumumab at the onset of symptoms, her medications included atorvastatin 40 mg daily, brimonidine 0.2% ophthalmic drops 3 times daily, vitamin D3 supplements, coenzyme Q10 100 mg daily, lisinopril/hydrochlorothiazide 10 mg daily, methimazole 10 mg daily, and nabumetone 750 mg twice daily.

Based on a single case report of a patient on teprotumumab who exhibited similar symptoms that improved with plasma exchange after failing steroid and intravenous immunoglobulin (IVIG) therapy,[7] the decision was made to start plasma exchange treatment. The patient underwent 5 plasma exchanges on alternating days, with the first exchange occurring 13 days after her last teprotumumab infusion. The plasmapheresis parameters were 1 plasma volume exchange with 5% albumin as the replacement fluid. The patient and her husband were advised of the risks of plasma exchange, including hypocalcemia or hypomagnesemia secondary to citrate chelation, hypothermia, transfusion reactions, fluid and electrolyte abnormalities, increased bleeding risk, hypotension, flushing, and gastrointestinal symptoms such as nausea and vomiting. Her confusion and mentation improved to near baseline approximately 24 hours after her first exchange, but symptoms returned by the morning of her second plasma exchange. As her treatments progressed, she would have shorter periods of altered mental status and longer periods of baseline mental status. Serial assessments throughout the hospital course demonstrated improved mental status and cognition, with less pressured speech, decreased aphasia, and better visuospatial reasoning, as evidenced by improved clock and cube drawing (Figure). She tolerated the plasma exchange treatment well without any complications. She also had remission of her neurocognitive symptoms, although she reported persistent anxiety throughout the hospital course that did not fully resolve prior to her discharge. She reported resolution of her anxiety and continued remission of her symptoms at a follow-up appointment with her ophthalmologist 3 weeks after discharge.

DISCUSSION

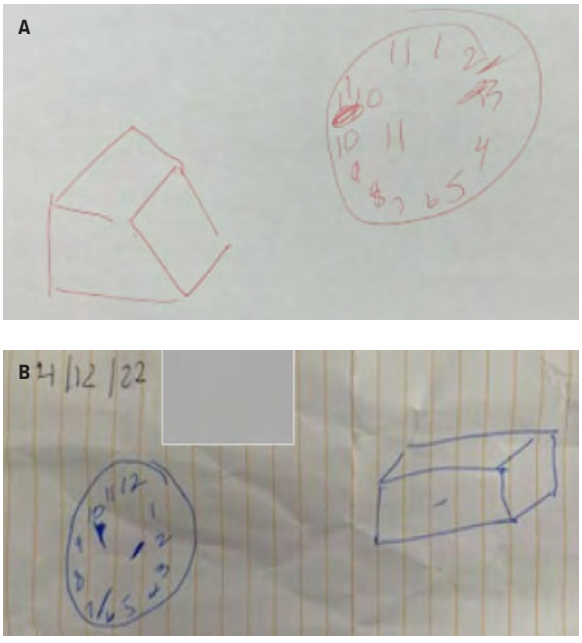
We present the case of a 62-year-old White woman with history of TED treated with teprotumumab who improved after plasma exchange therapy. To the best of our knowledge, this represents the second reported case of encephalopathy associated with teprotumumab.

Table. Serum Paraneoplastic and Autoimmune Encephalopathy Panel (Performed by Mayo Clinic Laboratories)

Result Name	Result	Reference Value
Antiglial nuclear antibody-1 (AGNA-1)	Negative	<1:2
AMPA receptor antibody CBA	Negative	Negative
Amphiphysin antibodies	Negative	<1:2
ANNA-1	Negative	<1:2
ANNA-2	Negative	<1:2
ANNA-3	Negative	<1:2
Contactin-associated protein-like 2 (CASPR2) IgG	Negative	Negative
Collapsin response-mediator protein 5 (CRMP-5) IgG	Negative	<1:2
DPPX antibody IFA	Negative	Negative
γ-aminobutyric acid ($GABA_B$) receptor antibodies	Negative	Negative
GAD65 antibody assay	0.00	≤0.02
Glial fibrillary acidic protein (GFAP) IFA	Negative	Negative
IgLON5 IFA	Negative	Negative
LGI1-IgG CBA	Negative	Negative
mGluR1 antibody IFA	Negative	Negative
VGKC antibodies	0.0	0.0 – 1.1
Neuronal intermediate filament (NIF) IFA	Negative	Negative
NMDA receptor antibody CBA	Negative	Negative
Purkinje cell cytoplasmic antibody type 1 (PCA-1)	Negative	<1:2
Purkinje cell cytoplasmic antibody type 2 (PCA-2)	Negative	<1:2
Purkinje cell cytoplasmic antibody, type Tr (PCA-TR)	Negative	<1:2

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CBA, cell-based assay; ANNA, antineuronal nuclear antibody; IgG, immunoglobulin G; DPPX, dipeptidyl-peptidase–like protein-6; IFA, immunofluorescence assay; GAD65, glutamic acid decarboxylase 65-kilodalton isoform; IgLON5, immunoglobulin-like cell adhesion molecule 5; LGI1, leucine-rich, glioma-inactivated 1 protein; mGluR1, metabotropic glutamate receptor 1; VGKC, voltage-gated potassium channel; NMDA, N-methyl-D-aspartate.

Figure. Patient's Clock and Cube Drawings



A. Initial drawing prior to plasma exchange.
B. Improved drawing after 3 rounds of plasma exchange.

Monoclonal antibodies like teprotumumab have been shown to advance treatment in several diseases; however, neurologic disorders associated with their use have been documented.[7-9] Literature shows that attenuation of IGF-1 signaling, as seen in teprotumumab use, has been related to increased risk of neurocognitive decline and psychological disorders.[7-9] In particular, teprotumumab has been shown to cause sensorineural hearing loss due to the effect IGF-1 plays in inner ear function,[10] as well as optic neuritis and Hashimoto's encephalopathy (HE).[7]

Encephalopathy related to teprotumumab therapy was first reported by Hoang et al,[7] and we approached the case under a similar hypothesis that the encephalopathy was induced by an autoimmune process related to teprotumumab. Clinical presentation and management in our case was slightly different when compared to the case reported by Hoang et al. The two patients were clinically similar in that they both exhibited behavioral changes, language deficits, inability to perform tasks requiring executive function, elevated protein in the cerebrospinal fluid, and an otherwise unremarkable workup. However, the clinical symptoms started after the fourth infusion of teprotumumab and lasted 6 weeks in the previously reported case compared to our case, where symptoms started after the third infusion and lasted 1 week before the patient sought treatment.

Our cases differ in how quickly plasmapheresis was started after the onset of symptoms. The patient in the Hoang et al case was treated with IV glucocorticoids and IVIG given their initial differential diagnosis, which included hepatic encephalopathy (HE), and literature supporting clinical improvement with these interventions.[11] However, the patient experienced progression of his neuropsychological symptoms to catatonia, mutism, and persistent memory deficits with this treatment. HE was later ruled out given that the patient had normal baseline serum thyroperoxidase antibodies (TPO) and thyroglobulin antibodies (TgAb), normal MRI/magnetic resonance angiography findings, and lack of clinical improvement with glucocorticoids and IVIG. They used plasma exchange based on the hypothesis that teprotumumab antibodies were responsible for his encephalopathy, and the patient started demonstrating clinical improvement after starting treatment. Based on the similarities between the cases and the previous patient's lack of response to IVIG and systemic steroids, our patient was treated with plasma exchange as a first line and was able to get her first round of plasma exchange within 2 weeks of her teprotumumab infusion.

Plasma exchange is the process in which a patient's blood is filtered through an apheresis machine that reinfuses red blood cells back into the patient with replacement fluid, such as plasma or albumin.[12] Given our hypothesis that the encephalopathy was an autoimmune response, plasmapheresis was deemed an appropriate intervention to remove teprotumumab antibodies from the patient in order to improve her neurological symptoms. Our transfusion medicine consulting team decided to start with 5 plasma exchanges based on the Hoang et al case report with a plan to perform more if clinical improvement was not achieved. An interesting aspect of the case was that the patient had resolution of symptoms to near baseline around 24 hours after the first plasma exchange, with symptoms returning the morning of her second plasma exchange. Although the exact physiology is unknown, perhaps residual antibodies remained in her system and required multiple plasma exchanges to be fully cleared out.

HE, a rare autoimmune vasculitis manifesting as acute or subacute encephalopathy with myoclonus and seizures, was an alternative diagnosis considered for our patient.[13] The literature shows that HE has been associated with teprotumumab, but only as a provisional diagnosis after a patient demonstrated episodic confusion with no other neurologic symptoms.[6] A limitation in our study is that we did not check antithyroid antibodies, which typically are elevated in this condition. However, we did not have a strong suspicion for HE given the absence of MRI abnormalities and seizures. In addition, an otherwise negative workup for other etiologies of encephalopathy, along with rapid improvement with plasma exchange in our previously neurologically normal patient, supports the diagnosis of teprotumumab-induced encephalopathy.

CONCLUSIONS

This case report elucidates a potentially detrimental side effect of teprotumumab and the importance of timely recognition and treatment. We provide a treatment framework with favorable results for patients who may experience encephalopathy after teprotumumab use. Proper counseling of this potential side effect is warranted for patients beginning this therapy, as it can help lead to earlier detection and treatment. This case is in the process of being reported to the FDA through MedWatch. Postmarketing surveillance efforts such as this are important to raise awareness of adverse effects that may not have been discovered during clinical trials.

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REFERENCES

1. Perros P, Neoh C, Dickinson J. Thyroid eye disease. *BMJ*. 2009;338:b560. doi:10.1136/bmj.b560

2. Douglas RS, Kahaly GJ, Patel A, et al. Teprotumumab for the treatment of active thyroid eye disease. *N Engl J Med*. 2020;382(4):341-352. doi:10.1056/NEJMoa1910434

3. Fernando R, Caldera O, Smith TJ. Therapeutic IGF-I receptor inhibition alters fibrocyte immune phenotype in thyroid-associated ophthalmopathy. *Proc Natl Acad Sci U S A*. 2021;118(52):e2114244118. doi:10.1073/pnas.2114244118

4. Slentz DH, Nelson CC, Smith TJ. Teprotumumab: a novel therapeutic monoclonal antibody for thyroid-associated ophthalmopathy. *Expert Opin Investig Drugs*. 2020;29(7):645-649. doi:10.1080/13543784.2020.1772752

5. Kang J, Lechuga M, Braun J, Kossler A, Douglas R, Cockerham K. Infusion center guidelines for teprotumumab infusions: informed consent, safety, and management of side effects. *J Infus Nurs*. 2021;44(6):331-338. doi:10.1097/NAN.0000000000000446

6. Smith TJ, Kahaly GJ, Ezra DG, et al. Teprotumumab for thyroid-associated ophthalmopathy. *N Engl J Med*. 2017;376(18):1748-1761. doi:10.1056/NEJMoa1614949

7. Hoang TD, Nguyen NT, Chou E, Shakir MK. Rapidly progressive cognitive decline associated with teprotumumab in thyroid eye disease. *BMJ Case Rep.* 2021;14(5):e242153. doi:10.1136/bcr-2021-242153

8. Bosch X, Saiz A, Ramos-Casals M; BIOGEAS Study Group. Monoclonal antibody therapy-associated neurological disorders. *Nat Rev Neurol.* 2011;7(3):165-172. doi:10.1038/nrneurol.2011.1

9. Gill C, Rouse S, Jacobson RD. Neurological complications of therapeutic monoclonal antibodies: trends from oncology to rheumatology. *Curr Neurol Neurosci Rep.* 2017;17(10):75. doi:10.1007/s11910-017-0785-3

10. Chow A, Silkiss RZ. Teprotumumab-associated chronic hearing loss screening and proposed treatments. *BMJ Case Rep.* 2022;15(4):e248335. doi:10.1136/bcr-2021-248335

11. Zvonarev V, Tregubenko P. Hashimoto encephalopathy: advanced review of clinical and scientific aspects. *J Neurol Neurobiol*. 2020;6(1):1-11. doi:10.16966/2379-7150.159

12. Bobati SS, Naik KR. Therapeutic plasma exchange - an emerging treatment modality in patients with neurologic and non-neurologic diseases. *J Clin Diagn Res.* 2017;11(8):EC35-EC37. doi:10.7860/JCDR/2017/27073.10480

13. Mocellin R, Walterfang M, Velakoulis D. Hashimoto's encephalopathy: epidemiology, pathogenesis and management. *CNS Drugs.* 2007;21(10):799-811. doi:10.2165/00023210-200721100-00002

A Case of Progressive Cholestatic Drug-Induced Liver Injury Due to Terbinafine

Dana Ley, MD; Jessica Musto, MD; Adnan Said, MD, MS

ABSTRACT

Introduction: Terbinafine is commonly prescribed for onychomycosis. It rarely leads to severe, prolonged cholestatic drug-induced liver injury. Clinicians should remain vigilant for this complication.

Case Presentation: A 62-year-old woman was started on terbinafine and developed mixed hepatocellular and cholestatic drug-induced liver injury, confirmed on liver biopsy. The injury became predominantly cholestatic. Unfortunately, she developed coagulopathy with elevated international normalized ratio and progressive drug-induced liver injury with severely elevated alkaline phosphatase and total bilirubin, requiring repeat liver biopsy. Fortunately, she did not develop acute liver failure.

Discussion: Prior case reports and series have documented severe cholestatic drug-induced liver injury (although with lesser degree of bilirubin elevation) due to terbinafine, which has very rarely been associated with acute liver failure, need for liver transplantation, and/or death.

Conclusions: Non-acetaminophen drug-induced liver injury is idiosyncratic. Complications including acute liver failure and vanishing bile duct syndrome can be slow to develop, so monitoring for them is important over longitudinal follow-up.

INTRODUCTION

Terbinafine is an allylamine antifungal medication administered both topically and orally. It is active against dermatophytes affecting the skin and nails and is thought to be effective due to selective inhibition of the fungal squalene epoxidase, which kills fungal cells. Oral terbinafine is used to treat onychomycosis, typically at a dose of 250 milligrams daily for 6 to 12 weeks.[1-2] Its most common side effects include headaches, change in taste, rash, and gastrointestinal disturbances.[3]

Terbinafine also has been associated with drug-induced liver injury (DILI). Oral terbinafine may lead to any degree of elevated serum aminotransferases in less than 1% of patients. These elevations are typically asymptomatic and resolve with discontinuation of the medication.[4] Clinically apparent liver injury is rare, usually arising within the first 6 weeks of therapy when it occurs.[5] Initially, the injury pattern may be hepatocellular or cholestatic, but it typically progresses into a cholestatic pattern, which may become prolonged.[6] The exact mechanism of liver injury is unknown but may be due to a hypersensitivity reaction.[7]

Most cases of DILI secondary to terbinafine resolve within 3 to 6 months of medication discontinuation. Rarely, the liver injury is severe and progressive, potentially leading to vanishing bile duct syndrome or acute liver failure, which may require liver transplantation or prove fatal.[8] This case highlights the importance of remaining attentive to development of these complications.

CASE REPORT

A 62-year-old woman with a history of thyroid cancer (status post-thyroidectomy and parathyroidectomy 40 years prior), hypothyroidism, type 2 diabetes mellitus, hypertension, depression, posttraumatic stress disorder, and pancytopenia of unknown etiology presented initially to an outside hospital with 1 week of weakness, a 20-pound weight loss, and 3 days of jaundice, dark urine, and pale stools. About 6 weeks prior, she started a 12-week

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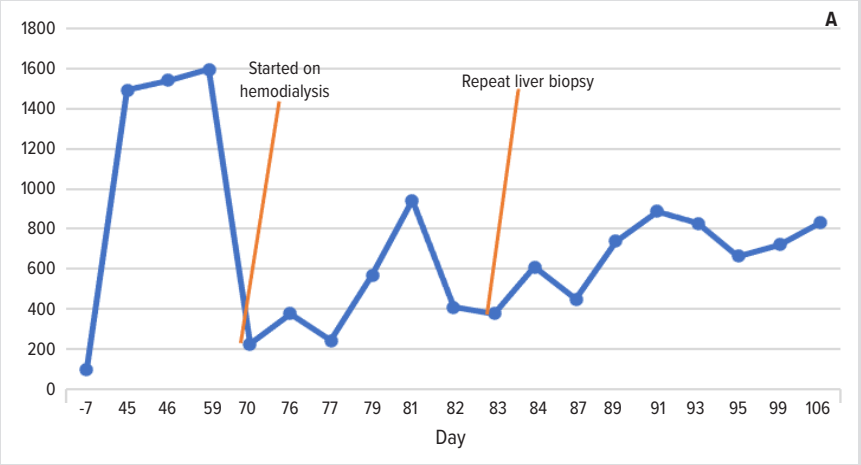
course of terbinafine 250 milligrams daily for onychomycosis of the toenails, which is the recommended length of treatment. Four days before presentation and 41 days after starting terbinafine, she discontinued its use due to malaise. She denied herbal, alcohol, or illicit drug use. Additional medications included bupropion, cromolyn nasal spray, diclofenac gel, levothyroxine, loratadine, metformin, risperidone, and sertraline. There were no other medication changes at the same time or after starting the terbinafine. She had no recent antibiotic use. She had no history of travel outside of her home state and no recent sexual activity. She had no prodromal viral symptoms.

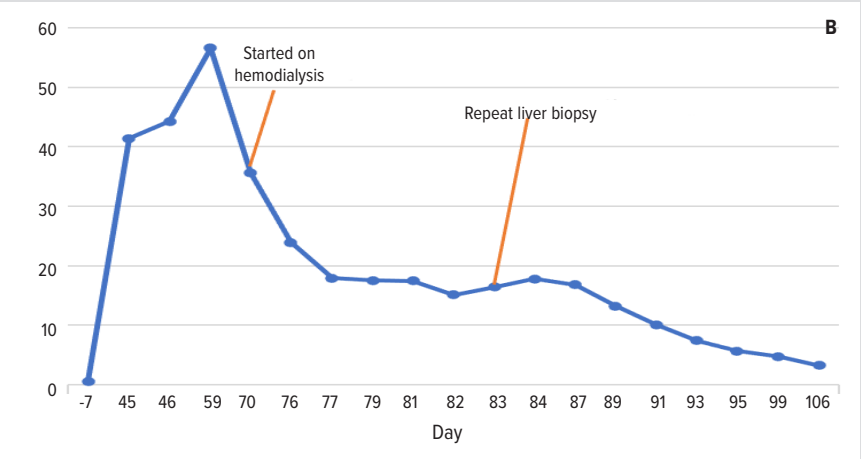
Initial labs were notable for persistent pancytopenia, characterized by a white blood cell count of 2.7, hemoglobin of 8.5, platelet count of 114, low absolute neutrophil count of 1.9, absolute lymphocyte count of 0.4, normal absolute eosinophil count of 0.1, and absolute monocyte count of 0.3. She also had an acute kidney injury with creatinine of 1.6 and liver injury with aspartate aminotransferase (AST) of 163, alanine aminotransferase (ALT) of 245, alkaline phosphatase of 1494, and total bilirubin of 41.4. The R factor—used to determine whether a liver injury is hepatocellular or cholestatic—was 0.59, suggestive of cholestatic injury. Albumin was 2.8, and international normalized ratio (INR) was 1.72. Baseline liver enzymes and creatinine were obtained 7 days prior to starting terbinafine and were normal. INR had not been obtained. Computed tomography of the abdomen and pelvis without contrast at presentation showed worsening splenomegaly and stable hepatomegaly (both present previously), nonspecific pericholecystic fluid, and a mild volume of perihepatic ascites. There was no evidence of skin rashes or fevers.

One day later, the patient was transferred to another hospital. Liver biopsy showed moderate to extensive hepatocanalicular cholestasis with mild lobular inflammation, which may consist of Kupffer cell aggregates (phagocytic cells

Figure 1. Patient's Alkaline Phosphatase Levels and Total Bilirubin

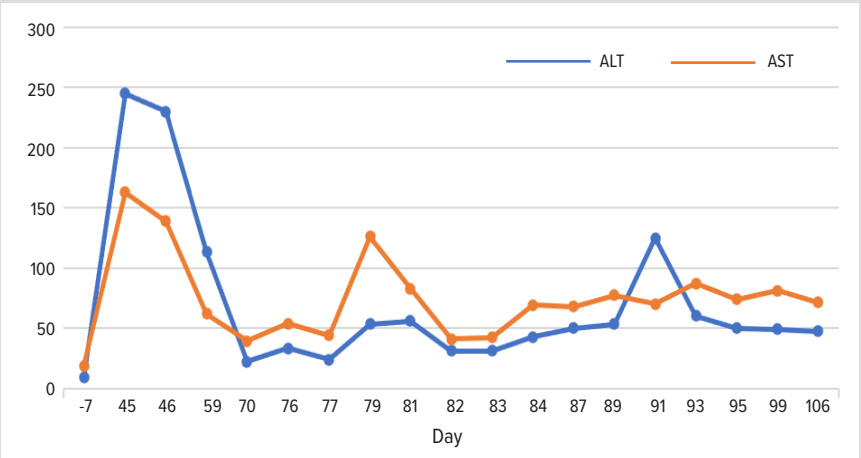


A. Trend in patient's alkaline phosphatase level over the course of her illness. X-axis shows day in relation to beginning terbinafine. Day -7 is the day where baseline labs were collected. Y-axis shows alkaline phosphatase levels measured in IU/mL.



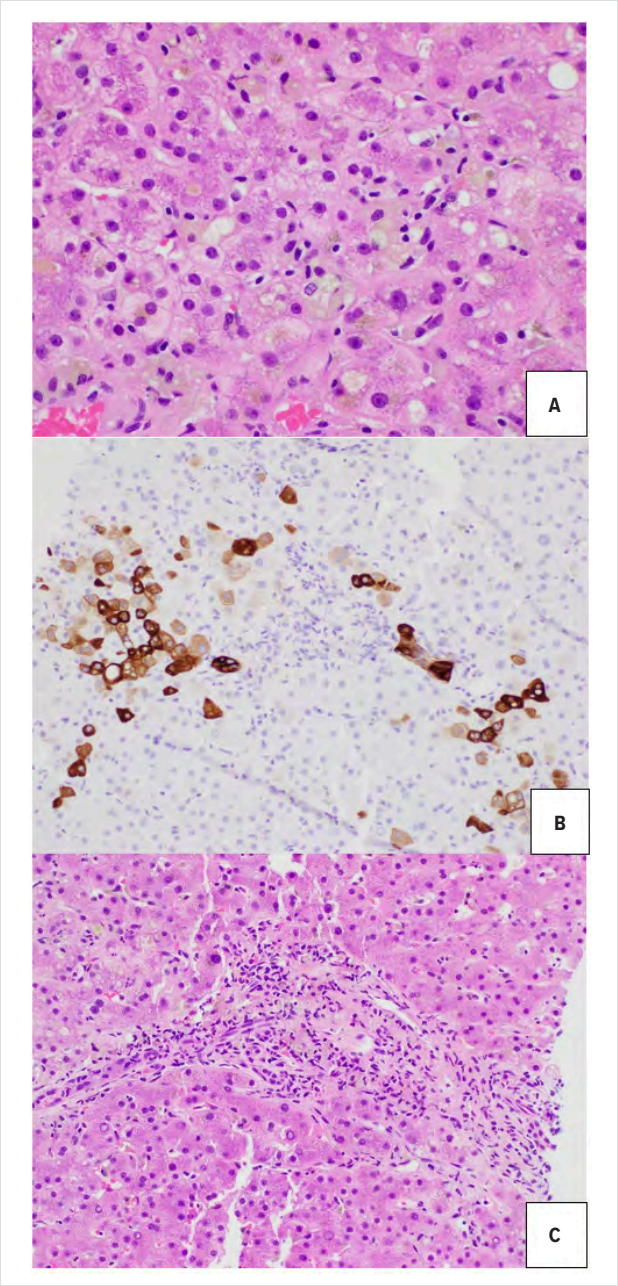
B. Trend in patient's total bilirubin level over the course of her illness. X-axis shows day in relation to beginning terbinafine. Y-axis shows total bilirubin levels measured in mg/dL.

Figure 2. Trend in Patient's Transaminases Over the Course of Her Illness



X-axis shows day in relation to beginning terbinafine. Day -7 is the day where baseline labs were collected. Y-axis shows patient's ALT and AST levels measured in IU/L.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Figure 3. Liver Biopsy Histologic Images



A. Image taken from liver biopsy done at our institution, demonstrating marked canalicular and hepatocytic cholestasis, accentuated near the efferent vein.
B. Liver biopsy image utilizing cytokeratin 7 (CK7) stain – indicating a bile ductular reaction.
C. Liver biopsy imaging demonstrating portal inflammation.

Pathology images courtesy of Yongjun Liu, MD, PhD, University of Wisconsin Department of Pathology and Laboratory Medicine.

that line the liver sinusoids) with or without fat globules, mononuclear cells, and occasional eosinophils and neutrophils, and no biliary injury or fibrosis, thought to be consistent with toxin or drug-induced liver injury. Magnetic resonance imaging showed significant gallbladder wall thickening and mural edema without gallstones, no intra- or extrahepatic biliary dilatation or choledocholithiasis, and an enlarged liver without lesions or parenchymal disease. It demonstrated features of portal hypertension, including a dilated main portal vein, marked splenomegaly, and a small volume of ascites, but the liver was not frankly cirrhotic, as there were no regenerative nodules or fibrosis. Additional laboratory evaluations included an antinuclear antibody of 1:80, normal complement levels, negative antidouble-stranded DNA, rheumatoid factor, antineutrophilic cytoplasmic antibody, antimitochondrial antibody, and antismooth muscle antibody, as well as negative serologies for viral hepatitides (Hepatitis C antibody and RNA, hepatitis B surface antigen, hepatitis A IgM, hepatitis E IgM, and cytomegalovirus and Epstein-Barr virus polymerase chain reactions). While there, she developed worsening acute kidney injury, unresponsive to crystalloid and colloid, and progressive cholestatic liver injury. She was transferred to our institution 13 days later for possible liver transplant evaluation.

At our institution, the patient developed oliguric kidney injury and rising liver enzymes (Figures 1 and 2) and was started on intermittent hemodialysis due to continued oliguria. Her acute kidney injury was thought to be secondary to acute tubular necrosis, with or without bile cast nephropathy. She never had evidence of acute liver failure, given lack of encephalopathy, but because of her rising alkaline phosphatase and relatively unchanged transaminases, total bilirubin (Figures 1 and 2), and INR—which followed a similar trend—she had a repeat liver biopsy nearly 1 month after transfer (Figure 3). At the time of her second liver biopsy, her INR was 1.2. Of note, she had received 3 days of intravenous vitamin K earlier in her admission to address the possibility that malnutrition and vitamin K malabsorption had contributed to the elevated INR.

The patient's liver biopsy demonstrated marked canalicular cholestasis, which refers to the presence of bile thrombi within the bile canaliculi, as well as hepatocytic cholestasis, which refers to the presence of bile throughout the cytoplasm of hepatocytes due to impaired secretion—especially near the efferent vein at the central zone. There was a mild inflammatory infiltrate involving most of the portal tracts and made up predominantly of lymphocytes. There was no significant steatosis, and a trichrome stain was negative for increased fibrosis. There were 10 portal tracts for evaluation, including three without native bile ducts—indicative of 30% native bile duct loss. The existing bile ducts were focally injured, characterized by unevenly distributed nuclei and nuclei irregularity without significant ductular reaction. An antihuman cytokeratin 7 (CK7) stain was used to accentuate the bile ducts and determine the degree of bile duct loss. Overall, this demonstrated a cholestatic pattern of injury, favored to be DILI. Biliary obstruction and infection were less favored. The pathology did not appear consistent with autoimmune hepatitis or chronic biliary disease.

The patient was then found to have a large pericardial effusion with early tamponade physiology, most likely secondary to uremia given her underlying renal dysfunction, for which she underwent pericardial drainage. She was also found to have *Klebsiella pneu-*

moniae bacteremia that was treated with meropenem. Her liver enzymes became stable to improved, and she was discharged to a long-term acute care hospital in her home state with recommendations for liver enzyme monitoring once to twice weekly. Nearly 6 months after discharge, her labs included an alkaline phosphatase of 480, ALT 105, AST 103, and total bilirubin 0.9. Her INR has remained normal since, and labs 16 months after discharge included a persistently elevated alkaline phosphatase of 520, ALT 30, AST 20, and total bilirubin 0.4.

Unfortunately, she was hospitalized locally 16 months after discharge for treatment of splenic marginal zone lymphoma and hemophagocytic lymphohistiocytosis, complicated by massive splenomegaly and Epstein-Barr viremia. At the time of this writing, she had received 6 cycles of rituximab, cyclophosphamide, and vincristine and continued to receive steroids and etoposide.

DISCUSSION

This patient developed severe, progressive, and prolonged cholestatic DILI secondary to terbinafine, which has been described in other case reports but not to the same degree of severity of our patient's injury.[9-11] DILI has been reported after oral but not topical terbinafine use. Our patient had evidence of portal hypertension at the time of her presentation, which may have been prehepatic due to her splenomegaly. It is possible that all along, her pancytopenia and splenomegaly could have been explained by an underlying hematologic process such as lymphoma, which may lead to splenomegaly and subsequent portal hypertension. Alternatively, an acute hepatic injury (which our patient had initially) may sometimes lead to intrahepatic portal hypertension.

Our patient would be considered to have chronic DILI, as chronic cholestasis (meaning the reduction or cessation of bile flow) typically refers to cholestatic liver injury persisting greater than 3 months.[12] In general, cholestatic DILI may occur when a drug leads to inhibition of the export of bile salts and drug metabolites from the hepatocytes into bile, leading to cholestasis in susceptible patients—especially those with mutations in genes that encode these transporters.[12] In most cases of DILI, the liver enzyme abnormalities resolve with drug cessation. However, for cholestatic DILI, including those secondary to antifungals such as terbinafine, the time course for improvement tends to be prolonged when compared to hepatocellular DILI. There is no medical therapy specifically for the treatment of cholestatic DILI. The mainstay of treatment is withdrawal of the drug, avoiding drug rechallenge, and treating the symptoms. Ursodeoxycholic acid can be used, but there are limited data to support this.[12] There is a role for management of pruritis with agents such as cholestyramine and antihistamines. That being said, in patients with non-acetaminophen–related DILI and acute liver failure, N-acetylcysteine has been found to significantly improve overall survival and transplant-free survival. In rare cases, acute liver failure due to cholestatic DILI may require liver transplantation.[12]

The development of cirrhosis and end-stage liver disease is another possible indication for liver transplantation. One of the rarest types of cholestatic DILI—vanishing bile duct syndrome, which is diagnosed when less than 50% of bile ducts are seen on liver biopsy—could potentially lead to cirrhosis by leading to prolonged, near complete absence of bile ducts. Cholestatic DILI—mostly secondary to chemotherapeutic agents—may lead to development of secondary sclerosing cholangitis and subsequent cirrhosis; and chronic cholestasis alone may lead to cirrhosis through the development of ductal sclerosis, periportal fibrosis, and bile duct loss.[12]

Our patient did not require liver transplant evaluation during her hospitalization, as she did not meet criteria for acute liver failure. Per the American Association for the Study of Liver Diseases, the criteria for acute liver failure includes evidence of coagulation abnormality (usually INR ≥1.5), any degree of encephalopathy in a patient without preexisting cirrhosis, and an illness of less than 26 weeks' duration.[13] Though our patient had an elevated INR, she did not develop encephalopathy.

Given her prolonged course and severely elevated alkaline phosphatase and total bilirubin, development of vanishing bile duct syndrome was a concern, and we obtained repeat liver biopsy. This syndrome is defined by loss of intralobular bile ducts with less than 50% of portal areas with a bile duct in a biopsy with at least 10 portal areas. Thus, our patient did not meet the criteria, although she had a lesser degree of bile duct loss, indicative of severe biliary injury or ductopenia.[14]

This case exemplifies key differences between DILI secondary to acetaminophen versus non-acetaminophen drugs, including terbinafine. DILI due to acetaminophen is dose-dependent and rarely occurs at therapeutic doses. There is a clear timeframe to development of DILI secondary to acetaminophen. At 24 to 72 hours post-ingestion, patients develop aminotransferase elevations. At 72 to 96 hours, they may develop jaundice, encephalopathy, coagulopathy, and acute liver failure. Recovery typically occurs 4 days to 2 weeks post-ingestion. Acetaminophen-induced DILI tends to have a better prognosis and more self-limited duration of injury due to faster hepatocyte regeneration. This differs from non-acetaminophen DILI, which is idiosyncratic, without a clear dose-response relationship. The timeframe for development of severe liver injury is unpredictable, often slower in onset and progression. Complications, including vanishing bile duct syndrome or liver failure, can be slow to develop, occurring as late as 6 months after initial onset of clinical liver injury. Thus, it is important to remain vigilant until complete recovery occurs.[14-15]

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REFERENCES

1. Bennett JE. Antimicrobial agents: antifungal agents. In: Brunton LL, Chabner BA, Knollman BC, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics.* 12th ed. McGraw-Hill; 2011:1571-1592.

2. Moseley RH. Antifungal agents. Antibacterial and antifungal agents. In: Kaplowitz N, DeLeve LD, eds. *Drug-Induced Liver Disease.* 3rd ed. Elsevier; 2013:470-473.

3. Hall M, Monka C, Krupp P, O'Sullivan D. Safety of oral terbinafine: results of a postmarketing surveillance study in 25,884 patients. *Arch Dermatol.* 1997;133(10):1213-1219. doi:10.1001/archderm.133.10.1213

4. Abdel-Rahman SM, Nahata MC. Oral terbinafine: a new antifungal agent. *Ann Pharmacother.* 1997;31(4):445-456. doi:10.1177/106002809703100412

5. Song JC, Deresinski S. Hepatotoxicity of antifungal agents. *Curr Opin Investig Drugs.* 2005;6(2):170-177.

6. Kyriakidis I, Tragiannidis A, Munchen S, Groll AH. Clinical hepatotoxicity associated with antifungal agents. *Expert Opin Drug Saf.* 2017;16(2):149-165. doi:10.1080/14740338.2017.1270264

7. Nicoletti P, Aithal GP, Bjornsson ES, et al. Association of liver injury from specific drugs, or groups of drugs, with polymorphisms in HLA and other genes in a genome-wide association study. *Gastroenterology.* 2017;152(5):1078-1089. doi:10.1053/j.gastro.2016.12.016

8. Kramer ON, Albrecht J. Clinical presentation of terbinafine-induced severe liver injury and the value of laboratory monitoring: a Critically Appraised Topic. *Br J Dermatol.* 2017;177(5):1279-1284. doi:10.1111/bjd.15854

9. Mallat A, Zafrani ES, Metreau JM, Dhumeaux D. Terbinafine-induced prolonged cholestasis with reduction of interlobular bile ducts. *Dig Dis Sci.* 1997;42(7):1486-1488. doi:10.1023/a:1018870828038

10. Fernandes NF, Geller SA, Fong TL. Terbinafine hepatotoxicity: case report and review of the literature. *Am J Gastroenterol.* 1998;93(3):459-460. doi:10.1111/j.1572-0241.1998.00459.x

11. Lazaros GA, Papatheodoridis GV, Delladetsima JK, Tassopoulos NC. Terbinafine-induced cholestatic liver disease. *J Hepatol.* 1996;24(6):753-756. doi:10.1016/s0168-8278(96)80273-x

12. Sundaram V, Björnsson ES. Drug-induced cholestasis. *Hepatol Commun.* 2017;1(8):726-735. Published 2017 Sep 11. doi:10.1002/hep4.1088

13. Polson J, Lee WM; American Association for the Study of Liver Disease. AASLD position paper: the management of acute liver failure. *Hepatology.* 2005;41(5):1179-1197. doi:10.1002/hep.20703

14. Zimmerman HJ. Antifungal agents. In: Zimmerman HJ. *Hepatotoxicity: The Adverse Effects of Drugs and Other Chemicals on the Liver.* 2nd ed. Lippincott; 1999:9-11.

15. Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. *Hepatology.* 2010;52(6):2065-2076. doi:10.1002/hep.23937

Withdrawal-Emergent Dyskinesia Related to Benztropine: A Case Report

Sharadhi Thalner, BS; Himanshu Agrawal, MBBS

ABSTRACT

Introduction: Benztropine is an anticholinergic drug used as a therapy for Parkinson's disease and treatment for extrapyramidal side effects. While tardive dyskinesia is an involuntary movement disorder that often occurs gradually after long-term use of medications, it does not commonly present acutely.

Case Presentation: A 31-year-old White woman experiencing psychosis presented with spontaneous, acute-onset dyskinesia induced with the withdrawal of benztropine. She had been followed in our academic outpatient clinic for medication management and intermittent psychotherapy.

Discussion: The pathophysiology of tardive dyskinesia is not fully understood, but several hypotheses exist, including the involvement of changes in basal ganglia neuronal systems. To our knowledge, this is the first case report to document acute-onset dyskinesia associated with the withdrawal of benztropine.

Conclusion: This case report, which describes an atypical response to discontinuing benztropine, might offer the scientific community potential clues to better understand the pathophysiology of tardive dyskinesia.

INTRODUCTION

Dyskinesia refers to involuntary muscle movements that can range from slight tremor to uncontrollable full body movements.[1] The tardive form of dyskinesia refers to the slow, or tardive, onset of involuntary movements of the face, lips, tongue, trunk, or extremities.[1] Tardive dyskinesia is defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as involuntary athetoid or choreiform movements of the tongue, lower part of the face, chin, arms, or legs secondary to the use of a neuroleptic medication for at least a few months.[2] It is often a side effect of antipsychotic medications thought to be related to blockage of dopamine D2 receptors. Although often developing gradually, a handful of cases have been noted wherein dyskinetic movements presented spontaneously with rapid onset. There are case reports of acute-onset dyskinesia from a single dose of metoclopramide, a dopamine blocking agent.[3]

Withdrawal dyskinesia[4] is a form of tardive dyskinesia in adults that occurs immediately after discontinuing or reducing the dose of a dopamine receptor-blocking agent; DSM-5 defines the dyskinesia presenting after changing, dose alteration, or stopping neuroleptic agents, as "withdrawal-emergent dyskinesia."[2] Research supports the occurrence of acute-onset dyskinesia related to withdrawal from second generation antipsychotics.[5-7] The term "masked TD" refers to tardive movements that resolve when a dopamine receptor-blocking agent is resumed or its dose is increased.

Benztropine is an anticholinergic drug approved by the US Food and Drug Administration for the adjunctive therapy for all forms of Parkinsonism. It is also used for medication-induced extrapyramidal side effects, as well as prevention and treatment of dystonic reactions.[8] There is literature that suggests that withdrawing anticholinergic agents may lead to the emergence of akathisia and to transient worsening of psychosis.[9] However, to the best of the authors' knowledge, there has been no doc-

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umented case of acute-onset withdrawal-emergent dyskinesia from benztropine.

CASE PRESENTATION

This case describes a 31-year-old divorced White woman who lived in a group home and had been followed in an academic outpatient clinic for medication management and intermittent psychotherapy. She had a diagnosis of schizoaffective disorder, bipolar type, most recent depressive episode, and generalized anxiety disorder. She was diagnosed with attention deficit hyperactivity disorder in childhood. Past diagnoses also include obsessive compulsive disorder, although she did not show any signs or symptoms during the time period described in this case report. Of note, at age 15, after being prescribed paroxetine, she was described as having a history of exophoria of both eyes (an abnormal muscle coordination likely central nervous system mediated). Selective serotonin reuptake inhibitors (SSRI) and mixed amphetamine salts reportedly worsened psychosis. Other past medications include methylphenidate, citalopram, escitalopram, sertraline, venlafaxine, bupropion, mirtazapine, trazodone, zolpidem, quetiapine, aripiprazole, divalproex, lithium carbonate, clonazepam, tiagabine, gabapentin, and buspirone. She has had a total of approximately 25 treatments of electroconvulsive therapy since her 20s. All labs were generally within normal range during the time period described in this case report.

Around the time the withdrawal-emergent dyskinesia occurred, the patient was taking risperidone 4 mg orally at bedtime, haloperidol 12 mg orally at bedtime, and benztropine 1 mg orally twice daily. On this regimen, she was relatively stable with respect to psychosis, mania, and depression; however, she reported concerns regarding cognitive issues. Since literature suggests cognitive problems can improve with discontinuing benztropine,[9] and since she was no longer on the original offending antipsychotic (aripiprazole), it was decided to try a slow taper off the benztropine—0.5 mg per week—with the plan to reinstate it if extrapyramidal side effects emerged. She was assessed every week and was displaying no signs of side effects when she was assessed at a dose of benztropine 0.5 mg orally per day. However, within 2 weeks of stopping the final 0.5 mg of benztropine, she developed slow, writhing movements affecting her tongue and head. On examination, she met criteria for dyskinesia. Benztropine was subsequently restarted and increased over the next 2 weeks all the way back to 1 mg orally twice daily; unfortunately, dyskinesia persisted. Newer medications that target tardive dyskinesia via the vesicular monoamine transporter 2[10,11] were considered; however, these were so costly to the patient that they were infeasible.[12] Therefore, over the next 2 weeks, she was cross tapered between benztropine and amantadine, which was increased to 200 mg orally twice daily.

Over the next 6 weeks, the patient showed steady improvement and gradual, complete resolution of dyskinesia. Thus, from the time of acute onset of this withdrawal-emergent dyskinesia, the involuntary movements persisted for a total of 10 weeks, at which point they subsided. Three months later, the amantadine was tapered off, with no signs of return of dyskinesia 1 year later. In retrospect, it is unclear whether amantadine helped resolve the dyskinesia or whether it gradually dissipated over 10 weeks spontaneously and would have done so even without amantadine.

DISCUSSION

The pathophysiology of tardive dyskinesia is not fully understood, and several hypotheses exist. Some theories propose the role of nicotinic cholinergic pathways.[13] However, the most commonly proposed mechanisms suggest that dopamine receptor hypersensitivity and/or an imbalance between dopamine type 1 (D1) and type 2 (D2) receptor-mediated effects in the basal ganglia are primarily responsible.[10,15] According to the dopamine hypothesis, antipsychotics preferentially block D2 receptors, resulting in excessive activity of D1-mediated striatopallidal output, altered firing patterns in medial globus pallidus, and eventual evolution of the clinical features of tardive dyskinesia. Its development also may involve changes in other basal ganglia neuronal systems. Tardive dyskinesia could result from loss of striatal interneurons that exert a feedback influence on nigrostriatal dopamine neurons and form part of an efferent output pathway from the basal ganglia. Such interneurons may utilize gamma-aminobutyric acid (GABA),[10,15] acetylcholine, or peptides as their neurotransmitter.[16]

Withdrawal-emergent dyskinesia has been observed as early as 1973 after sudden cessation of chronic antipsychotic treatment in children.[17] Its pathophysiology remains unclear, even though some theories have been put forth. For instance, Lo and Peng[18] hypothesize that hyperdopaminergic processes in basal ganglia secondary to the termination of the medications blocking dopaminergic receptors are believed to underlie the phenomenon. Teo et al[19] postulate that, similar to tardive dyskinesia, the development of D2 receptor hypersensitivity on the nigrostriatal dopaminergic pathway may be involved in withdrawal-emergent dyskinesia, and the indirect reversal of the inhibition on the globus pallidus internus and subthalamic nucleus by the D2 receptor hypersensitivity is believed to result in a hyperkinetic movement disorder. Yet another theory attributes withdrawal-emergent dyskinesia to the GABAergic hypofunction, as well as the increase in dopamine D3 receptors.[20]

The story of this clinical case includes several interesting features, which may or may not have contributed to the atypical withdrawal-emergent dyskinesia upon discontinuing benztropine.

- The patient has a history of exophoria coincident with the use of paroxetine. It is not entirely clear whether the exophoria was related to an oculogyric reaction; however, if it was, then this could increase the risk for future extrapyramidal side effects.[21]
- The patient has a history of "involuntarily swing[ing] her arms, back and forth, and muscle spasm" that was reported as an adverse reaction to paroxetine. Although abnormal movements

can occur from paroxetine, they are relatively uncommon (<1%, according to paroxetine drug information, Lexicomp).[22] Muscle spasm (dystonia) is even more rare, and when it has been described in case reports, it is hypothesized to be related to the decreased neuroplasticity of aging neurons and to previous exposure to neuroleptic medications, neither of which was true for this patient.[23] Nonetheless, if these symptoms represented some form of extrapyramidal side effects, this puts her at a higher risk for future side effects.[21]

- The patient has a history of being on several antipsychotics, and at the time of the withdrawal-emergent dyskinesia, she was on 2 potent antipsychotics (risperidone and haloperidol). If an atypical medication has been associated with extrapyramidal side effects in the past (in this case, paroxetine), it may be worth considering if there is increased risk that a different atypical medication (in this case, dense tropine) might lead to extrapyramidal side effects in the future.
- Finally, the patient also has a history of obsessive-compulsive disorder, which, like extrapyramidal side effects, has long been associated with basal ganglion dysfunction.[24] It might be worth considering whether some common underlying mechanism could be related to all three (obsessive-compulsive disorder, extrapyramidal side effects, and in a typical response to benztropine withdrawal).

One possibility considered by the authors is that this incident was not withdrawal-emergent dyskinesia, but "masked dyskinesia" from risperidone and haloperidol. In other words, the authors considered if the rapid-onset dyskinesia could be related to the fact that the patient was no longer on the antidote for tardive dyskinesia, and discontinuing the medication unmasked underlying, preexisting tardive dyskinesia. However, the fact that the patient continued to suffer from the dyskinesia long after the benztropine was reintroduced would speak against this theory. Additionally, although benztropine is known to improve extrapyramidal side effects, such as parkinsonism and dystonia, it is not known to improve dyskinesia generally.[25] Therefore, withdrawal from benztropine should not cause the emergence of dyskinesia.

The atypical response to discontinuing benztropine may offer potential clues to better understand the pathophysiology of dyskinesia. Additionally, given that the DSM-5 definition of tardive includes "persisting beyond 4 to 8 weeks," it may be worth considering if the term "tardive withdrawal" or "tardive withdrawal syndrome" should be utilized for instances like these, where involuntary movements, including dyskinesias, persist beyond 4 to 8 weeks after discontinuing certain medication—whether they be antipsychotics, benztropine, or some other medication.

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REFERENCES

1. Cornett EM, Novitch M, Kaye AD, Kata V, Kaye AM. Medication-induced tardive dyskinesia: a review and update. *Ochsner J*. 2017;17(2):162-174.

2. *Diagnostic and Statistical Manual of Mental Disorders.* 5th ed. American Psychiatric Association; 2013. January 24, 2022. https://doi.org/10.1176/appi.books.9780890425596

3. Wong CS, Perry KW, Rosenbaum A. Tardive dyskinesia in a postoperative gynecological patient after single dose administration of metoclopramide. *Cureus*. 2021;13(9):e18260. doi:10.7759/cureus.18260

4. Schooler NR, Kane JM. Research diagnoses for tardive dyskinesia. *Arch Gen Psychiatry.* 1982;39(4):486-487. doi:10.1001/archpsyc.1982.04290040080014

5. Alblowi MA, Alosaimi FD. Tardive dyskinesia occurring in a young woman after withdrawal of an atypical antipsychotic drug. *Neurosciences (Riyadh).* 2015;20(4):376-379. doi:10.17712/nsj.2015.4.20150078

6. Lore C. Risperidone and withdrawal dyskinesia. *J Am Acad Child Adolesc Psychiatry.* 2000;39(8):941. doi:10.1097/00004583-200008000-00001

7. Arat-Çelik HE, Kök-Kendirlioğlu B, Çetin B, Küçükgöncü S. Double-edged sword: a case with withdrawal-emergent dyskinesia. *Turk Psikiyatri Derg*. 2021;32(4):283-285. doi:10.5080/u25613

8. Ahuja A, Abdijadid S. Benztropine. In: StatPearls. StatPearls Publishing; 2022. January 24, 2022. https://www.ncbi.nlm.nih.gov/books/NBK560633/

9. Desmarais JE, Beauclair L, Annable L, Bélanger MC, Kolivakis TT, Margolese HC. Effects of discontinuing anticholinergic treatment on movement disorders, cognition and psychopathology in patients with schizophrenia. *Ther Adv Psychopharmacol*. 2014;4(6):257-267. doi:10.1177/2045125314553611

10. Niemann N, Jankovic J. Treatment of tardive dyskinesia: a general overview with focus on the vesicular monoamine transporter 2 inhibitors. *Drugs*. 2018;78(5):525-541. doi:10.1007/s40265-018-0874-x

11. Ricciardi L, Pringsheim T, Barnes TRE, et al. Treatment recommendations for tardive dyskinesia. *Can J Psychiatry.* 2019;64(6):388-399. doi:10.1177/0706743719828968

12. Morrow T. Two new drugs for tardive dyskinesia hit the market. *Manag Care.* 2018;27(1):35-36.

13. Quik M, Zhang D, Perez XA, Bordia T. Role for the nicotinic cholinergic system in movement disorders; therapeutic implications. *Pharmacol Ther*. 2014;144(1):50-59. doi:10.1016/j.pharmthera.2014.05.004

14. Gerlach J, Hansen L. Clozapine and D1/D2 antagonism in extrapyramidal functions. *Br J Psychiatry Suppl.* 1992;(17):34-37.

15. McEvoy JP. FDA-approved medications to treat tardive dyskinesia. *J Clin Psychiatry.* 2019;81(1):NU18041BR3C. doi:10.4088/JCP.NU18041BR3C

16. Gunne LM, Häggström JE, Sjöquist B. Association with persistent neuroleptic-induced dyskinesia of regional changes in brain GABA synthesis. *Nature*. 1984;309(5966):347-349. doi:10.1038/309347a0

17. Polizos P, Engelhardt DM, Hoffman SP, Waizer J. Neurological consequences of psychotropic drug withdrawal in schizophrenic children. *J Autism Child Schizophr.* 1973;3(3):247-253. doi:10.1007/BF01538282

18. Lo YC, Peng YC. Amisulpride withdrawal dyskinesia: a case report. *Ann Gen Psychiatry*. 2017;16:25. doi:10.1186/s12991-017-0148-0

19. Teo JT, Edwards MJ, Bhatia K. Tardive dyskinesia is caused by maladaptive synaptic plasticity: a hypothesis. *Mov Disord*. 2012;27(10):1205-1215. doi:10.1002/mds.25107

20. Kumar M, Mattison R, Baweja R. Withdrawal-emergent dyskinesia after acute discontinuation of risperidone in a child with autism spectrum disorder. *J Clin Psychopharmacol.* 2018;38(6):640-642. doi:10.1097/JCP.0000000000000958

21. Hedenmalm K, Güzey C, Dahl ML, Yue QY, Spigset O. Risk factors for extrapyramidal symptoms during treatment with selective serotonin reuptake inhibitors, including cytochrome P-450 enzyme, and serotonin and dopamine transporter and receptor polymorphisms. *J Clin Psychopharmacol.* 2006;26(2):192-197. doi:10.1097/01.jcp.0000203200.96205.34

22. Paroxetine: drug information. In: Post TW, ed. *UpToDate*. UpToDate Inc. Accessed January 24, 2022. http://www.uptodate.com

23. Arnone D, Hansen L, Kerr JS. Acute dystonic reaction in an elderly patient with mood disorder after titration of paroxetine: possible mechanisms and implications for clinical care. *J Psychopharmacol*. 2002;16(4):395-397. doi:10.1177/026988110201600418

24. Modell JG, Mountz JM, Curtis GC, Greden JF. Neurophysiologic dysfunction in basal ganglia/limbic striatal and thalamocortical circuits as a pathogenetic mechanism of obsessive-compulsive disorder. *J Neuropsychiatry Clin Neurosci*. 1989;1(1):27-36. doi:10.1176/jnp.1.1.27

25. Bergman H, Soares-Weiser K. Anticholinergic medication for antipsychotic-induced tardive dyskinesia. *Cochrane Database Syst Rev*. 2018;1(1):CD000204. doi:10.1002/14651858.CD000204.pub2

Delayed Injection Site Reaction to Fremanezumab for Chronic Migraine Treatment

Kevin V. Thomas, BA; Daniel D. Bennett, MD; Justin Endo, MD, MHPE

ABSTRACT

Introduction: Fremanezumab is a humanized monoclonal antibody administered through a subcutaneous injection. It is used for treatment of migraines, and occasional injection site reactions have developed after usage.

Case Presentation: This case report describes a nonimmediate injection site reaction on the right thigh of a 25-year-old female patient after starting treatment with fremanezumab. The injection site reaction presented as 2 warm, red annular plaques 8 days following a second injection of fremanezumab and about 5 weeks following the first injection. She was prescribed a 1-month course of prednisone that relieved her symptoms of redness, itching, and pain.

Discussion: Similar nonimmediate injection site reactions have been reported before, but this particular injection site reaction was significantly more delayed.

Conclusions: Our case illustrates that injection site reactions to fremanezumab can be delayed after the second dose and may require systemic therapy to alleviate symptoms.

INTRODUCTION

Fremanezumab is a subcutaneously injected monoclonal antibody used to treat migraines. Injection site reactions (ISR) have been described occasionally.[1-5] We report an ISR with 2 annular plaques adjacent to an injection site 8 days after the second dose of treatment.

CASE PRESENTATION

A 25-year-old woman presented to dermatology clinic with a warm, annular plaque on her right thigh with pruritus and sharp pain. She had severe, refractory migraines that failed to respond to several treatments, including galcanezumab-gnlm. She did not have any ISRs with other humanized monoclonal antibody treatment against calcitonin gene-related peptide (CGRP). Approximately 5 weeks prior to presentation, she received the first injection of fremanezumab in her right upper arm and did not report rash or complication. However, 8 days following the second injection in her right thigh, 2 round red plaques that quickly expanded appeared around the second injection site. They did not improve with clobetasol, diphenhydramine, cetirizine, acetaminophen, or cold packs. She denied mucosal lesions and otherwise felt well. There was no past or family history of rashes. She had no known allergies to the listed active and inactive ingredients in fremanezumab.

On examination, she had a bright, erythematous, warm, and slightly indurated annular plaque without secondary change (Figure 1). There was a similar but faint plaque inferior to this. A punch biopsy for routine histology was taken of the larger annular plaque (Figure 2). It showed a superficial and deep infiltrate with lymphocytes, eosinophils, and some neutrophils. Bacterial and fungal cultures were negative. The findings were consistent with an ISR.

She discontinued fremanezumab due to the ISR and was switched to incobotulinumtoxinA injections. A 1-month prednisone taper was prescribed, starting at 40 mg daily. Within a few days, the itching, pain, and redness improved.

DISCUSSION

Fremanezumab is a humanized monoclonal antibody that directly inhibits CGRP, which is part of a migraine signaling pathway.

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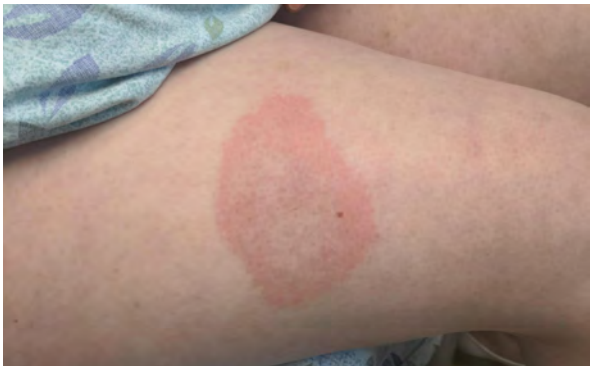
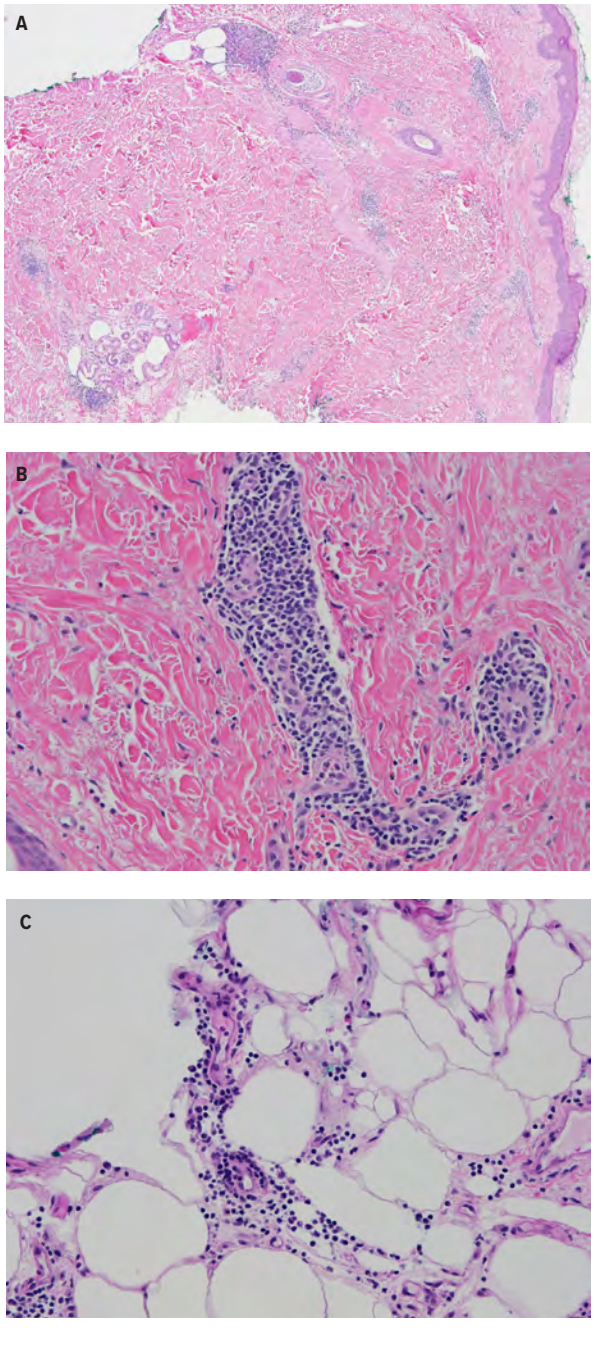
Figure 1. Delayed Injection Site Reaction to Fremanezumab



Clinical photograph of the patient's right thigh shows the bright, erythematous, and slightly indurated annular plaque and the second plaque inferior to it.

Figure 2. Delayed Injection Site Reaction to Fremanezumab



Punch biopsy with a superficial and deep perivascular and interstitial mixed infiltrate with lymphocytes, eosinophils, and rare neutrophils.
2A: 40x, 2B: 200x superficial; 2C: 200x deep.

The most common adverse reaction is ISR manifesting as localized induration, pain, hemorrhage, or erythema.[6] However, few detailed reports and images exist. The Table provides a summary of publications reporting skin eruptions associated with the use of fremanezumab for treatment of chronic migraines.

Thomaidou and Ramot classified biologic ISRs or their excipient into 3 types: type α, type β, and recall reactions.[7] Type α reactions are irritative and immediate due to an increase in proinflammatory cytokines from the injected substance. Type β reactions are immunogenic and can be either immediate or delayed responses due to antibody or T-cell induction, respectively. Recall reactions develop at sites where medication was administered previously. The ISR demonstrated in our case would most likely be a type β delayed reaction, which falls under the Type IV hypersensitivity reaction category based on the onset.

Moya et al[1] reported a case of delayed-type ISR to fremanezumab in a 52-year-old woman, which occurred within 48 hours after the second dose. The exanthem was described initially as an erythematous pruritic plaque on the right lower abdomen. Several herpetiform microvesicles then developed. A second plaque with micropustules formed inferiorly. The rash eventually responded to desloratadine and topical clobetasol propionate within a week.

Our case had some overlap but also differences from Moya et al.[1] The ISRs in both cases did not develop until after the second fremanezumab injection, but the onset in our case was even more delayed. Both ISRs had two separate plaques, but ours did not develop vesicles or pustules. It is plausible their case might have been acute localized exanthematous pustulosis or perhaps contact dermatitis, but a biopsy was not obtained.

Similar adverse injection site reactions have been reported with other anti-CGRP monoclonal antibodies. The majority of ISRs for galcanezumab-gnlm occurred on the day of the injection, with only 3 participants having it after 2 weeks.[8] The majority spontaneously resolved and did not lead to treatment discontinuation. Tepper et al reported injection site pain without rash in 4% of patients treated with erenumab (humanized monoclonal antibody targeting the CGRP receptor).[9]

CONCLUSIONS

Our case and review of the literature serve as a reminder that ISRs to fremanezumab can be significantly delayed after a second dose,

Table. Injection Site Reactions (ISR) Associated With Fremanezumab for Treatment of Chronic Migraines

Publication	Demographics	Fremanezumab Regimen	Rash Morphology	Time to Rash Onset	Patient Outcome
Moya et al[1] case report	52-year-old woman	225 mg every 4 weeks	Local, itchy erythematous plaque, 20 x 15 cm at injection site. Microvesicles then developed on plaque followed by pinhead-sized micropustules	48 hours after 2nd dose; delayed ISR	Skin lesion healed in 1 week with oral desloratadine 5 mg every 24 hours and topical clobetasol propionate 0.5 mg/g
Alex et al, retrospective study[2]	n = 16, age range 41.8 ± 16.2 years; female: n = 15 (93.8%)	Baseline 225 mg, followed by monthly doses of 120 mg for 6 months	Not presented	n = 1 (6.3%); acute ISR (within 1 hour)	Symptoms resolved
Sakai et al, clinical trial[3]	n = 25, age range 45.8 ± 7.0 years; female: n = 19 (76.0%)	Quarterly (675 mg at baseline and every 3 months)	Erythema Pruritus	n = 5 (20.0%); acute ISR (within 1 hour) n = 1 (4.0%); information not provided	Symptoms resolved; 1 patient discontinued treatment
	n = 25, age range 46.8 ± 7.9 years; female: n = 23 (92.0%)	Monthly (675 mg at baseline and 225 mg every month for a year)	Erythema Pruritus	n = 7 (28.0%); acute ISR (within 1 hour) n = 2 (8.0%); information not provided	Symptoms resolved; 1 patient discontinued treatment
Goadsby et al, clinical trial[4]	n = 551, age range 43.7 ± 12.0 years; female: n = 484 (88%)	Quarterly (single dose of 675 mg at baseline and placebo at weeks 4 and 8)	Erythema	n = 138 (25%); acute ISR (within 1 hour)	Symptoms resolved
	n = 559, age range 42.6 ± 11.8 years; female: n = 494 (88%)	Monthly (675 mg at baseline and 225 mg at weeks 4 and 8)	Erythema	n = 171 (31%); acute ISR (within 1 hour)	Symptoms resolved
Silberstein et al, clinical trial[5]	n = 376, age range 42.0 ± 12.4 years; female: n = 331 (88%)	Quarterly (single dose of 675 mg at baseline and placebo at weeks 4 and 8)	Erythema	n = 80 (21%); acute ISR (within 1 hour)	Symptoms resolved
	n = 379, age range 40.6 ± 12.0 years; female: n = 330 (87%)	Monthly (675 mg at baseline and 225 mg at weeks 4 and 8)	Erythema	n=75 (20%); acute ISR (within 1 hour)	Symptoms resolved

necessitating a careful history. The reaction might not occur at all injection sites or might be multiple and adjacent to the injection. Finally, systemic therapy might be required.

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REFERENCES

1. Moya B, Barranco R, García-Moguel I, Puerta-Peña M, Alonso L, Fernández-Crespo J. First confirmed case of nonimmediate hypersensitivity to fremanezumab during chronic migraine treatment. *Contact Dermatitis*. 2022;86(4):308-310. doi:10.1111/cod.14018

2. Alex A, Vaughn C, Rayhill M. Safety and tolerability of 3 CGRP monoclonal antibodies in practice: a retrospective cohort study. *Headache*. 2020;60(10):2454-2462. doi:10.1111/head.13956

3. Sakai F, Suzuki N, Ning X, et al. Long-term safety and tolerability of fremanezumab for migraine preventive treatment in Japanese outpatients: a multicenter, randomized, open-label study. *Drug Saf*. 2021;44(12):1355-1364. doi:10.1007/s40264-021-01119-2

4. Goadsby PJ, Silberstein SD, Yeung PP, et al. Long-term safety, tolerability, and efficacy of fremanezumab in migraine: a randomized study. *Neurology*. 2020;95(18):e2487-e2499. doi:10.1212/WNL.0000000000010600

5. Silberstein SD, Dodick DW, Bigal ME, et al. Fremanezumab for the preventive treatment of chronic migraine. *N Engl J Med.* 2017;377(22):2113-2122. doi:10.1056/NEJMoa1709038.

6. Dodick DW, Silberstein SD, Bigal ME, et al. Effect of fremanezumab compared with placebo for prevention of episodic migraine: a randomized clinical trial. *JAMA*. 2018;319(19):1999-2008. doi:10.1001/jama.2018.4853

7. Thomaidou E, Ramot Y. Injection site reactions with the use of biological agents. *Dermatol Ther.* 2019;32(2):e12817. doi:10.1111/dth.12817

8. Stauffer VL, Wang S, Bonner J, et al. Evaluation of injection-site-related adverse events with galcanezumab: a post hoc analysis of phase 3 studies in participants with migraine. *BMC Neurol.* 2020;20(1):194. doi:10.1186/s12883-020-01775-4

9. Tepper S, Ashina M, Reuter U, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet Neurol.* 2017;16(6):425-434. doi:10.1016/S1474-4422(17)30083-2

A Convoluted Picture of Diabetic Myonecrosis

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ABSTRACT

Introduction: A patient with well-controlled type 2 diabetes was found to have diabetic myonecrosis, a rare condition associated with poorly controlled type 2 diabetes. Diagnosis was masked by concern for lumbosacral plexopathy from a history of spinal cord infarct.

Case Presentation: A 49-year-old African American woman with type 2 diabetes and paraplegia secondary to spinal cord infarct presented to the emergency department with left leg swelling and weakness from her hip to toes. Hemoglobin A1c was 6.0%, and there was no leukocytosis or elevated inflammatory markers. Computed tomography showed evidence of infectious process or possible diabetic myonecrosis.

Discussion: Recent reviews show fewer than 200 reports of diabetic myonecrosis since first described in 1965. It typically is seen in poorly controlled types 1 and 2 diabetes, with average hemoglobin A1c of 9.34% at time of diagnosis.

Conclusions: Diabetic myonecrosis should be considered in diabetic patients with unexplained swelling and pain – particularly in the thigh – even with unremarkable lab values.

INTRODUCTION

Diabetic myonecrosis is a rare condition associated with poorly controlled type 1 and type 2 diabetes.[1] There have been few reported cases in the literature over the past several decades, despite the increasing worldwide prevalence of type 1 and type 2 diabetes.[1] Our case presents a patient with relatively well-controlled type 2 diabetes found to have diabetic myonecrosis, who presented with lower extremity weakness and edema that initially was confounded by concern for lumbosacral plexopathy due to her history of spinal cord infarct.

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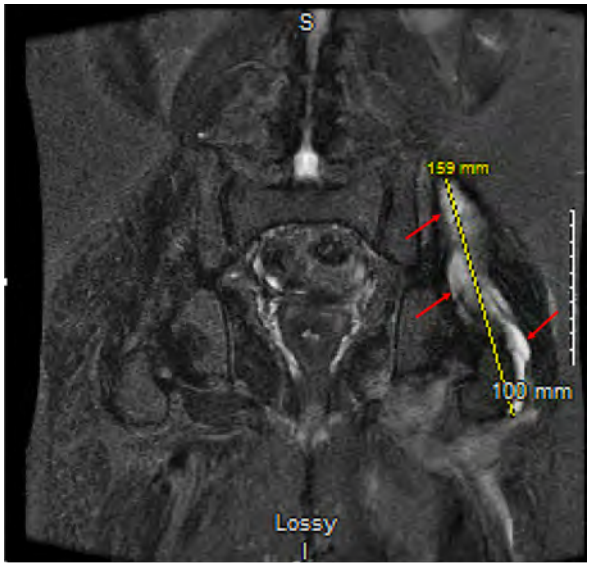
CASE PRESENTATION

A 49-year-old African American woman with a history of type 2 diabetes, hypertension, hyperlipidemia, and incomplete paraplegia secondary to spinal cord infarct complicated by neurogenic bowel and bladder presented to the emergency department with left leg swelling. Approximately 1 month prior to admission, she noted significant weakness in her left leg from her hip to her toes increased from baseline, without deficits in the right leg. There was swelling and a tingling sensation that did not improve with gabapentin or baclofen. She denied any systemic symptoms or new numbness in the leg. She has a history of a ventral spinal cord infarct in a T2-T8 distribution with decreased pinprick and temperature sensation at the T8 level, as well as weakness and absent patellar/ankle jerk reflexes in the bilateral lower extremities. She has spastic paraparesis for which she receives botulinum toxin injections, though there is no evidence of kidney disease secondary to her neurogenic bladder. Because of this history, there was concern for lumbosacral plexopathy; however magnetic resonance imaging (MRI), x-ray, and duplex ultrasound of the spine at this admission were unremarkable.

Admission lab work did not show leukocytosis or elevated inflammatory markers, reducing suspicion for an infectious or inflammatory cause. Ultrasound of the left lower extremity was negative for deep vein thrombosis (DVT), but computed tomography of the abdomen/pelvis showed low-attenuation areas in the left hip tissues concerning for an infectious process or diabetic myonecrosis. MRI demonstrated diffuse edema-like signal centered in the adductor compartment of the left thigh

Figure. Magnetic Resonance Imaging of the Pelvis With and Without Contrast



Red arrows pointing to areas of edema-like signal in adductor compartment, yellow line demonstrating length of likely muscle infarct.

with multiple areas of nonenhancement on postcontrast imaging, consistent with diabetic myonecrosis (Figure).

The patient was continued on aspirin therapy. With help from physical and occupational therapy, she endorsed improvement of weakness and symptoms during the hospital stay. She was discharged home on day 5 with outpatient physical therapy follow-up. Three months later, a follow-up electromyography study demonstrated lower motor neuron denervation changes in a diffuse yet patchy distribution consistent with probable diabetic myonecrosis in the left lower extremity. Together these results support diabetic myonecrosis as the cause of muscle infarct over other causes, such as the prior spinal cord infarct.

The patient was diagnosed initially with type 2 diabetes 7 years ago (2015), and her glycemic control is currently managed with metformin alone. Her hemoglobin A_{1c} (HbA_{1c}) value was 6.0% on this admission and 7.2% eight months ago. Her recent diabetic eye exam did not show evidence of retinopathy; her creatinine levels have remained stable and low for the past 4 years; and there was no evidence of diabetic neuropathy on exam. This suggests that her type 2 diabetes was well controlled at the time of diagnosis. She did mention that upon initial diagnosis of diabetes, she was started on insulin therapy and had a HbA_{1c} greater than 10%.

DISCUSSION

Diabetic myonecrosis is a rare condition associated with poorly controlled diabetes.[1] Recent reviews have shown fewer than 200 reports of this condition since it was first described in 1965.[1] It is typically seen in individuals with advanced diabetetes—both type 1 and type 2.[1] A recent case review demonstrated a mean reported HbA_{1c} of 9.34% at the time of diagnosis.[1] The pathophysiology is unclear, but proposed mechanisms include injury secondary to atherosclerosis, diabetic microangiopathy, vasculitis with thrombosis, or ischemia reperfusion injury.[2]

Suspicion for this rare condition should be increased in patients with poorly controlled diabetes presenting with acute muscle pain/swelling, particularly in the lower extremities. It is important to rule out acute conditions, such as DVT and trauma, in these patients as well, as they can sometimes present similarly or be related to underlying conditions such as sickle cell disease, which is more prevalent in African American populations.[3] In this patient without a history of sickle cell disease, the confounding factor was the previous spinal cord infarct that masked the picture, demonstrating once again how this condition is not routinely suspected. Routine laboratory values typically are not elevated, and blood and urine cultures typically do not yield any significant results.[1] However, inflammatory markers, such as erythrocyte sedimentation rate and C-reactive protein, appear to be somewhat useful and elevated in a large proportion of previous cases in which they were reported.[1] This patient's lab work, including inflammatory markers, was unremarkable and did not contribute to the diagnosis.

Typical locations of pain in these patients are in the lower extremities, particularly in the thighs.[1] This was seen in our case as well, with significant left thigh pain, swelling, and tingling sensations. Muscle biopsy can provide a definitive diagnosis; however, typically it is not done as it roughly doubles the time to symptom improvement.[1,4] MRI is sensitive and specific enough to diagnose diabetic myonecrosis without biopsy, showing edema with T2 hyperintensity or T1 iso-intensity or hypointensity.[1]

Therapies for diabetic myonecrosis should be targeted towards reduced recovery time and reduced rates of recurrence, as patients with diabetic myonecrosis are at high risk for recurrence of the condition.[1] The most effective evidence-based management for diabetic myonecrosis includes rest, analgesia using nonsteroidal anti-inflammatory drugs, and strict glycemic control.[1] Interestingly, the patient presented here had a recent HbA_{1c} of 6.0%, suggesting good glycemic control. Low-dose aspirin has been shown to reduce recovery time from 57 days to 39 days, on average, and reduce recurrence rates to 10% versus 32% for those on bed rest alone.[1] Surgical intervention has been shown to increase recovery time to 91 days and increase the recurrence rate to 50%.[1,5] While patients receiving physical therapy had a prolonged recovery time, the recurrence rate was reduced compared to those who were put on bed rest alone (18% vs 32% recurrence).[1] Because of this, physical therapy should be avoided in the acute phase of the illness but is recommended once patients are discharged from the hospital.

CONCLUSIONS

This case represents an even more rare case of diabetic myonecrosis in the setting of well-controlled type 2 diabetes, although the

patient's glycemic control was poor in the past. This finding suggests that diabetic myonecrosis should be considered in patients with diabetes presenting with extremity swelling, even in those with improved glycemic control. The presentation of this patient in the setting of recent spinal cord infarct, as well as normal lab markers and currently well-controlled type 2 diabetes, may serve to assist in making the diagnosis of diabetic myonecrosis in patients with an otherwise noncontributory workup and well-controlled type 2 diabetes.

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REFERENCES

1. Horton WB, Taylor JS, Ragland TJ, Subauste AR. Diabetic muscle infarction: a systematic review. *BMJ Open Diabetes Res Care*. 2015;3(1):e000082. doi:10.1136/bmjdrc-2015-000082

2. Habib GS, Nashashibi M, Saliba W, Haj S. Diabetic muscular infarction: emphasis on pathogenesis. *Clin Rheumatol*. 2003;22(6):450-451. doi:10.1007/s10067-003-0789-z

3. Ejindu VC, Hine AL, Mashayekhi M, Shorvon PJ, Misra RR. Musculoskeletal manifestations of sickle cell disease. *Radiographics*. 2007;27(4):1005-1021. doi:10.1148/rg.274065142

4. Trujillo-Santos AJ. Diabetic muscle infarction: an underdiagnosed complication of long-standing diabetes. *Diabetes Care*. 2003;26(1):211-215. doi:10.2337/diacare.26.1.211

5. Barohn RJ, Kissel JT. Case-of-the-month: painful thigh mass in a young woman: diabetic muscle infarction. *Muscle Nerve*. 1992;15(7):850-855. doi:10.1002/mus.880150715

Proceedings from the 2022 Medical College of Wisconsin Innovations in Healthcare Education Research Annual Conference

The following award-winning abstracts were presented during the 9th Annual Medical College of Wisconsin (MCW) Innovations in Healthcare Education Research (IHER) Annual Conference on September 20-22, 2022. Health care educators and researchers from MCW and other national institutions meet annually at IHER to present their research and innovative ideas and to learn from one another about the new and creative approaches to educating students and residents. The 3-day conference includes nationally recognized keynote speakers, panel sessions, workshops, roundtables, oral presentations, and posters which can be viewed at https://www.mcw.edu/IHER2022. Two-hundred ninety-five participants hailed from 31 states and 7 countries. The winning oral presentations and posters in the research and innovations categories are published below.

BEST ORAL PRESENTATION – INNOVATIONS

Using Personal Narrative as Foundation for Health Equity Education: Creating a Curriculum on Asian American, Native Hawaiian, and Pacific Islander Health

Ming Lin, MS; Joyce H. Lee, MS; Iaong Vang, Lana Minshew, PhD; Kajua Lor, PharmD

Problem Statement: Within health education (eg, medicine, pharmacy, nursing, dentistry, etc), there are currently limited opportunities for educating and training learners on Asian American/Native Hawaiian/Pacific Islander (AANHPI) health and health disparities. As more institutions continue to voice commitment towards greater diversity, inclusion, and cultural competency in curricula, spaces also must be created deliberately for AANHPI voices. Additionally, nationally there is currently no established curriculum or educational framework tailored to trainees at health professions schools on AANHPI health. Prejudices, biases, xenophobia, and microaggressions toward AANHPIs continue to persist. It is imperative to increase visibility, inclusion, and action for advocating for AANHPI health as part of antiracism efforts at health institutions, as well as in the greater fight towards true health equity.

Approach: In response to current gaps in health education on AANHPI health and health disparities, our team developed the "Health Advancement for Asian Pacific Islanders through Education" (HAAPIE) Initiative in 2021. Curriculum development proceeded through 3 main phases. First, our team established the values, objectives, and educational framework for learning and evaluation by exploring our experiences as AANHPIs and the narratives of the broader community. We determined the 2 main goals of increasing knowledge of AANHPI health issues and building cultural humility towards AANHPIs. Second, curriculum content utilized the cultural intelligence framework[1] to present information through the lens of history and intersectionality. Third, through purposeful collaboration with AANHPI communities and organizations, we continually refine and develop content that is relevant and practical.

Lessons Learned: Providing the historical context behind the social, political, and health issues faced by diverse AANHPIs served as an effective starting point for learners. Educational materials aimed to be varied, integrative, interactive, and purposefully equitable, which were appreciated by learners. We utilized case studies as a window to broader concepts, such as intersectionality, microaggressions, health literacy, and other social determinants of health. We highlighted AANHPI populations that faced inequities within the broader community. Learner evaluation consisted of self-reflection: "what do I currently know," "how do I put this to practice," and "what did I learn?" While Google Classroom was feasible, it had barriers for accessibility and presentation and organization of materials. Learners encouraged information be presented through more engaging ways than PowerPoints.

Significance: With only 0.17% of total National Institutes of Health funding dedicated to AANHPIs,[2] this population continues to be highly overlooked in health care. HAAPIE is the first compre hensive curriculum of its kind nationally

on AANHPI health, which may provide a useful framework for future work in health equity education.

References

1. Minshew LM, Lee D, White CY, McClurg M, McLaughlin JE. Cultural intelligence in pharmacy education: understanding student experiences. *Am J Pharm Ed*. 2021; 85(9):8580. doi:10.5688/ajpe8580

2. Đoàn LN, Takata Y, Sakuma KL, Irvin VL. Trends in clinical research Including Asian American, Native Hawaiian, and Pacific Islander participants funded by the US National Institutes of Health, 1992 to 2018. *JAMA Netw Open*. 2019;2(7):e197432. doi:10.1001/jamanetworkopen.2019.7432.

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BEST POSTER PRESENTATION – INNOVATIONS

Seeking Peer Outreach: An Integrated, Tiered Approach to Address Stigma and Isolation in Medical Education

Molly Thapar, BS; Omeed Partovi, BS; Andy Petroll, MD, MS; Himanshu Agrawal, MD; April Zehm, MD

Problem Statement: It is well established that early communication and clinical competency training is a crucial ingredient in creating an outstanding physician.[1,2] Despite this evidence, interpersonal skills training is still undervalued and underrepresented within undergraduate medical education, especially at the preclinical level.[2,3] While the Medical College of Wisconsin (MCW) offers much-needed communication training for difficult patient encounters in the form of a fourth-year elective course, there are currently no options available that train preclinical medical students to conduct difficult conversations. By the time medical students reach their clinical rotations in their third year, most have not witnessed, and therefore do not possess, the skills to properly address an uncomfortable or difficult situation. The lack of training also fosters anxiety and fails to build students' self-efficacy prior to clinical encounters.

Approach: In academic year 2021-2022, two cohorts of preclinical MCW medical students voluntarily participated in our semester-long extracurricular program, Operation Conversation (OC). Each OC participant attended 3 once-monthly virtual workshops. Students were assigned in pairs and grouped with a MCW faculty/resident facilitator who observed the student roleplays and provided immediate feedback. The roleplaying student physician, the roleplaying student patient, and the physician facilitator completed the same validated assessment tool to evaluate the student physician's performance. Following each workshop, students completed a self-reflection survey on their performance. After finishing the final workshop, participants completed a program evaluation survey. Data analysis is ongoing. We plan to discuss findings with the Kern Institute and develop a program manual for dissemination to other institutions.

Lessons Learned: Twenty-eight students and 14 facilitators attended the Fall 2021 program. Thirty-six students and 18 facilitators attended the Spring 2022 program, including some repeat participants. Attendance at workshops neared 100%.

After the final fall workshop, 22 out of 42 of participants (52%) submitted program evaluations. On preliminary analysis, 3 distinct findings were noted. First, nearly all participants (95.5%) said they would recommend the program to future students. Second, participants noted the best parts of the program to be skill development and sense of community within their groups. Finally, participants offered insightful critiques on all aspects of the program: scripts, learning materials, workshop format, and small-group cohesion. Further analysis of the communication assessment tool and student self-reflections from both semesters will determine OC's efficacy in building communication skills.

Significance: Despite known importance, interpersonal skills training is not prioritized in undergraduate preclinical curricula. Addressing this gap through the use of active roleplay, spaced learning, and reflection has applicability for MCW curriculum improvement, in addition to medical curricula elsewhere.

References

1. D'Souza PC, Rasquinha SL, D'souza TL, Jain A, Kulkarni V, Pai K. Effect of a single-session communication skills training on empathy in medical students. *Acad Psychiatry.* 2020;44(3):289-294. doi:10.1007/s40596-019-01158-z

2. Sahu PK, Chattu VK, Rewatkar A, Sakhamuri S. Best practices to impart clinical skills during preclinical years of medical curriculum. *J Educ Health Promot.* 2019;14(8):57. doi:10.4103/jehp.jehp_354_18

3. Meyer EC, Seller DE, Browning DM, McGuffie K, Solomon MZ, Truog RD. Difficult conversations: improving communication skills and relational abilities in health care. *Pediatr Crit Care Med*. 2009;10(3):352-359. doi:10.1097/PCC.0b013e3181a3183a

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BEST ORAL PRESENTATION – RESEARCH

Institutional Strategies to Combat Hospitalist Burnout and Improve Wellness

Komal Khoja, BA; Marie Luebke, MHS; Mohamed Abdelrahim, MA; Parsia Vazirnia, BS; Brian Quinn, MD; Muhammad Hammad, MD; Pinky Jha, MD

Introduction: Over 50% of practicing physicians in the United States report burnout, with internal medicine displaying some of the highest rates. There has been limited research on the impact of the COVID-19 pandemic on the psychological well-being of hospitalists. Our study seeks to assess wellness strategies and institutional recommendations to reduce burnout among frontline providers.

Methods: Academic hospitalists at Froedtert Hospital and the Medical College of Wisconsin were recruited to participate in qualitative focus groups conducted via Zoom during February 2022. We utilized a question guide developed by the research team, which covered contributors to burnout, the impact of COVID-19, and strategies to improve wellness. We conducted 4 focus groups with 21 hospitalists in total. These sessions were audio-recorded, transcribed, and coded for emergent themes by

a team of medical students using Taguette, an open-source qualitative data analysis software.

Results: A ubiquitous theme to combat burnout was increasing social interactions to allow providers to share experiences and seek guidance from one another. Specific suggestions included a workroom with windows, increased space, refreshments, and comfortable seating. It was also noted that space constraints have led to new hires being scattered, further increasing isolation. Suggestions for social interactions outside of work included a retreat, arranging activities for like-minded people, and holiday parties. Another emergent theme included providing avenues for 2-way communication between leadership and providers to share concerns and illicit feedback, allowing providers to feel more empowered.

Conclusions: Hospitalist burnout has been a prevalent issue prior to the onset of the COVID-19 pandemic. As the pandemic continues, the ongoing social isolation and lack of effective communication between providers and leadership contribute to further fatigue and frustration, which may worsen burnout. Enhancing community and fostering collaborative decision-making may positively impact the well-being of frontline hospitalists and reduce burnout.

Significance: Investigating changes in the mental health of hospitalists is crucial due to the ever-evolving COVID-19 burden. Our results may be useful in guiding institutional programs to mitigate burnout.

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BEST POSTER PRESENTATION – INNOVATION

Mentee Feedback from a Year in Review of F1-Doctors: A National Student-Led Platform for International Pre-Health Students

Gopika SenthilKumar; Kalina Tenorio L. Machado; Salvatore Capotosto; Deepali Bhalla; Rachel Jaber Chehayeb; Nicole Belliard Martuscelli; Abubakr El Sobky; Zezhou (Zach) Zhao; Salome Da Silva Duarte Lepez; Matheus M. S. Peraci

Introduction: International students interested in health sciences have limited availability to mentorship and trustworthy resources and face unique numerous challenges in the United States1. F1Doctors (https://www.f1doctor.com/) is the first national, student volunteer-led, online platform that connects undergraduate students with international medical students (M1-M4 students on a F1 visa), residents, and attending physicians in the US. The F1Doctors website also features reliable resources on universities that accept international students, funding/loan options, application requirements, etc. F1Doctors is maintained and overseen by a board of volunteer students, who not only keep the website updated and ensure effective communication between mentors and mentees, but also (1) host panel events with premed offices throughout the country; (2) collate stories for the F1Doctors podcast; (3) maintain an active social media presence featuring Q&As, Instagram Live events, and short infographics; (4) host virtual events to engage mentors and create a sense of community; and (5) disseminate surveys to assess the platform's benefits and areas of improvements. This study analyzes mentee feedback after a year of the platform's existence.

Methods: An open-response survey asking mentees about "the best part of their experience" and "areas to work on" was distributed through mailing lists and social media. Responses were deidentified. Two independent reviewers conducted a thematic analysis of responses. This methodology was selected to overcome response biases due to language concerns and/or differences in cultural interpretations of predrafted statements.

Results: Of the 115 students who responded, 73% sought out mentors for MD applications. The remaining were interested in MD-PhD, DO, residency, and dentistry. Forty-two percent of responses identified "positive attributes of their mentor's personality" as one of the best parts of their experience. Thirty-four percent mentioned "relating to mentors/mentors sharing their own experiences" 21% mentioned "getting helpful/useful premed advice," and 9% mentioned "feeling a sense of community." Fifty-seven percent of mentees said there were no areas for improvement. The remaining responses suggested topics for resources on the website and highlighted the need for ensuring timely response from mentors.

Conclusion: F1Doctors is well-received by mentees, and it is effective at proving relatable mentorship and creating a national community for international students interested in graduate health programs. The results of this survey will be used to guide future improvements and research directions for the platform..

Reference

1. Jaber Chehayeb R, SenthilKumar G, Saade Z, Gallo Marin B, Aghagoli G, Virji AZ. Examining the first peer-to-peer mentorship program (F1Doctors) for international medical students. *J Interdiscip Stud Educ.* 2022;16(1):102-125.

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Addressing Health Disparities Through Rural Training

Jillian Landeck, MD; Ryan J. Spencer, MD, MS; Robert N. Golden, MD

THE CHALLENGE

Approximately 1.5 million Wisconsinites, or 25% of our state's population, live in rural areas, yet only 11% of physicians practice in rural Wisconsin.[1] Rural communities comprise an important part of Wisconsin's culture, history, and economy. However, due to social inequities and decreased access to health care, individuals who live in rural Wisconsin disproportionately experience negative health outcomes, leading to higher overall rates of morbidity and mortality. According to analyses from the Wisconsin Office of Rural Health and the Wisconsin Department of Health Services (DHS), people who live in rural areas have higher rates of many chronic diseases, including coronary heart disease and strokes. Life expectancy is 0.8 years lower for men and 0.5 years lower for women in rural Wisconsin. Access to primary care physicians, dentists, and mental health providers is significantly lower, and rates of uninsured children and adults are higher.[1-3] Limited access to affordable housing, transportation, employment opportunities, telehealth, and broadband internet service disproportionately impacts individuals in rural Wisconsin and contributes to these negative health outcomes.

A lack of available clinicians is a significant driver of limited access to health care. The rural physician shortage is projected to grow as the need for a larger physician workforce expands due to the aging of the population and as current rural physicians retire. A recent study found that 12 (16%) of Wisconsin's 76 rural hospitals are vulnerable to closure.[4] Additionally, one-third of rural Wisconsin counties do not provide birthing services, and the number of rural hospitals that provide delivery services has declined 24% since 2009.[5] Maintaining a sustainable physician workforce in rural Wisconsin is a critical element in addressing the disparities of health care access in rural Wisconsin.

> We must continue to use our time, talents, human and financial resources, and shared knowledge to build and expand the entire pathway of rural physician development.

THE WISCONSIN SOLUTION

The Wisconsin Idea permeates all we do—including our efforts to address the rural health care crisis in our state. The University of Wisconsin School of Medicine and Public Health (SMPH) has a long tradition of supporting residency programs that train outstanding physicians to serve rural Wisconsin. Founded in 1996, the UW Baraboo Family Medicine Rural

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Training Track (RTT) supports two residents per year and was the first RTT in Wisconsin. It provides a longitudinal, integrated curriculum with strong procedural training and unique opportunities that include electives in addiction medicine and tribal health. The program has a strong record of placing family medicine physicians in rural practice.

Building on the Baraboo program's legacy, the SMPH has expanded rural training programs in recent years. In 2017, the Department of Family Medicine and Community Health (DFMCH) created the Family Medicine Rural Health Equity Track, which adds two residency slots per year and includes six months of rural rotations, along with unique experiences in leadership, community health, and advocacy for residents who intend to enter rural practice. In 2019, the school added a Rural Pathway option to its Family Medicine Residency Program. The DFMCH also provides support to statewide academic partner programs, including residencies in Eau Claire, La Crosse, and Wausau, as well as the Lakeland RTT in Barron County. Starting in July 2023, the DFMCH will provide Accreditation Council for Graduate Medical Education sponsorship and support to the Monroe Hospital RTT.

Many members of the SMPH community have recognized the critical need for a broad spectrum of physicians in rural areas. The school has become a recognized national leader in its support of rural training across multiple specialties. In 2016, the Department of Surgery launched its rural residency track, which places one general surgery resident each year into rural areas of Wisconsin for 12 months of training. In 2017, the Department of Obstetrics and Gynecology began the nation's first rural track in this field; trainees in this track gain six months of rural experience. Funding opportunities through the Wisconsin Rural Physician Residency Assistance Program allow for the creation and ongoing support of rural residency tracks across Wisconsin.

Data heavily support the creation of these programs and the allocation of the required resources. The amount of rural exposure during medical school and residency has a direct impact on rural physician placement. It has been estimated that at least 50% of family medicine residency program graduates may enter rural practice if they receive 12 to 24 weeks of training in rural settings.[6] Still, many factors impact rural placement and retention, including less-modifiable factors, such as a significant other's wishes.[7]

A personal rural background is one of the strongest predictors of future rural practice. It is critical to create and sustain effective pathways that expose students from rural backgrounds to career opportunities in medicine as early as middle school and high school. Wisconsin's strong network of regional Area Health Education Centers exposes more than 5,000 high school and undergraduate learners annually to health care career-mentoring opportunities. The SMPH's Wisconsin Academy for Rural Medicine (WARM) recruits medical students who intend to practice in rural Wisconsin, and participants are largely from rural Wisconsin backgrounds. Ninety-one percent of WARM graduates are practicing in Wisconsin, and 52% are practicing in primary care.

STATE AND NATIONAL PARTNERSHIPS

Success in this endeavor depends on a strong network of dedicated partners. Rural program leaders at the SMPH benefit from, and contribute to, statewide and national partnerships in these efforts. Within Wisconsin, we enjoy wonderful, crucial relationships with the Wisconsin Hospital Association, the Wisconsin Collaborative for Rural Graduate Medical Education, the Wisconsin Office of Rural Health, and the Wisconsin DHS. These partnerships provide a rich environment for professional development, funding, and curriculum development and share a mission-driven commitment to enhancing health care for people in rural Wisconsin. Faculty leaders of our rural programs have key relationships with national organizations, including the Rural Training Track Collaborative, and hold prominent positions within the Health Resources and Services Administration's Rural Residency Program Development Technical Assistance Center. Our SMPH program leaders are disseminating throughout the United States the lessons they have learned over decades of developing rural residency training in Wisconsin, with the goal of promoting rural residencies across all medical specialties. This is truly the Wisconsin Idea at work—promoting improved health of rural communities in Wisconsin and beyond.

THE FUTURE

The projected shortage of health care providers will continue to significantly affect rural areas. We must continue to use our time, talents, human and financial resources, and shared knowledge to build and expand the entire pathway of rural physician development, starting in K-12 programs, extending through college and medical student recruitment, and with a growing emphasis on rural residency training programs.[8] The SMPH is fully committed to working with our partners in advancing this vision for Wisconsin, in a way that will serve as a national model. Together, we will move FORWARD! in advancing the health of our rural communities.

REFERENCES

1. *Painting the Picture of Wisconsin's Health: Wisconsin's 2020 Statewide Health Assessment*. Wisconsin Department of Health Services, Division of Public Health; 2022. P-03169. Accessed March 13, 2023. https://dhs.wisconsin.gov/publications/p03169.pdf

2. *Rural Wisconsin Health.* Wisconsin Office of Rural Health; 2017. Accessed March 19, 2023. https://worh.org/wp-content/uploads/2022/01/Rural-WI-Health-2017.pdf

3. *A Just Recovery of Rural Equity in Wisconsin. Wisconsin Community and Rural Response Task Force Report.* University of Wisconsin Population Health Institute; 2021. Accessed: March 19. 2023. https://uwphi.pophealth.wisc.edu/wp-content/uploads/sites/316/2021/02/A-Just-Recovery-for-Rural-Equity_FINAL.pdf

4. Topchik M, Gross K, Pinette M, Brown T, Balfour B, Kein H. *The Rural Health Safety Net Under Pressure: Rural Hospital Vulnerability*. The Chartis Center for Rural Health; 2020. Accessed March 19, 2023. www.chartis.com/sites/default/files/documents/Rural%20Hospital%20Vulnerability-The%20Chartis%20Group.pdf

5. *Obstetric Delivery Services and Workforce in Rural Wisconsin Hospitals.* Wisconsin Office of Rural Health; 2019. Accessed March 19, 2023. https://worh.org/wp-content/uploads/2019/09/ObstetricServicesReport2018Revised.pdf

6. Bowman RC, Penrod JD. Family practice residency programs and the graduation of rural family physicians. *Fam Med*. 1998;30(4):288-292.

7. Morken C, Bruksch-Meck K, Crouse B, Traxler K. Factors influencing rural physician retention following completion of a rural training track family medicine residency program. *WMJ*. 2018 Dec;117(5):208-210.

8. Crouse B, Golden RN. A strategic approach to addressing the rural Wisconsin physician shortage. *WMJ*. 2016 Aug; 115(4): 210-211.

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Thank You!
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