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WMJ

2026 • volume 125 • issue 4



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Addressing Social Isolation and Loneliness

Turning Local Data Into Safer Roads

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COVER ART

Milky Way

Richard Abraham, MD

Photograph

Artist Statement:

"On a clear mountain night the Milky Way rises straight up between the trees. In medicine we use light to see what's hidden and to reach what no hand can. This view reminds me how far light travels to find us in the dark."

See page 435 for information about the artist.

• • •

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Medetomidine in the US Illegal Fentanyl Supply: An Emerging Threat Requiring Physician Awareness

To the Editor:

Medetomidine has recently emerged as an adulterant in the US illicit drug supply, prompting the Centers for Disease Control and Prevention to issue clinical advisories identifying it as a growing public health concern, particularly in urban areas. It is a veterinary sedative and α2-adrenergic agonist, pharmacologically related to xylazine and dexmedetomidine, and is traditionally used in animal medicine for sedation and analgesia. It is not approved for human use. Compared with xylazine, medetomidine may be up to 300 times more potent, potentially contributing to more profound sedation and greater clinical toxicity.[1] Since it is metabolized hepatically, plasma concentrations generally peak within 10 to 30 minutes after exposure. Its effects may last several hours, with concurrent opioid exposure prolonging sedation and clinical toxicity.[1,2]

Unlike opioids, medetomidine does not respond to naloxone; nevertheless, naloxone should be administered in all suspected overdose cases given the frequent co-ingestion of fentanyl.[2,3] Studies have demonstrated rapidly increasing detection of medetomidine in drug samples and overdose deaths across several US regions.[3,4] Its presence alongside fentanyl and other illicit substances has contributed to increasingly complex and potentially life-threatening overdose presentations.[4,5] Patients exposed to medetomidine may present with sedation, decreased responsiveness, respiratory depression, bradycardia, hypotension, and miosis. Medetomidine may also contribute to recurrent hypoxia, prolonged central nervous system depression, and increased airway management requirements.[3,5]

Diagnosis is challenging because medetomidine is not typically included in hospital rapid drug screens. Physicians should maintain a high index of suspicion when altered mental status or cardiovascular instability persists despite naloxone administration following a suspected fentanyl overdose.[2,3] When exposure is suspected, comprehensive screening should include medetomidine in blood or 3-hydroxy medetomidine with deconjugation in urine, recognizing that rapid metabolism may limit detection once withdrawal symptoms develop.

Beyond acute toxicity, abrupt cessation following regular exposure can precipitate a profound hyperadrenergic withdrawal syndrome that parallels severe clonidine withdrawal and, in some cases, surpasses it in severity. Withdrawal symptoms may begin within hours after cessation, peaking 18 to 36 hours after the last exposure. Clinical manifestations include severe tachycardia, hypertension, altered mental status, tremor, chest pain, and intractable nausea and vomiting. Vital signs may fluctuate rapidly as patients transition from α2-agonist intoxication with hypotension and bradycardia to hyperadrenergic withdrawal. Severe cases have been associated with end-organ complications, including non-ST elevation myocardial infarction (NSTEMI) and posterior reversible encephalopathy syndrome (PRES), underscoring the potential for rapid clinical deterioration.[2,3]

Management is primarily supportive, emphasizing airway protection, oxygenation, and cardiovascular monitoring, with naloxone continued when opioid co-exposure is suspected.[2] Increases in emergency department visits for nonalcohol, non-nicotine, and non-cannabis-related substance withdrawal have been temporally correlated with medetomidine detection in the regional drug supply, with sustained prevalence linked to substantial emergency department and intensive care unit utilization.[5] Treatment of medetomidine withdrawal includes α2-agonist therapy, such as clonidine, guanfacine, tizanidine, or intravenous dexmedetomidine in severe cases, with some patients requiring intensive care monitoring during dexmedetomidine administration.

Heightened clinical awareness is essential for early diagnosis and reducing mortality among patients exposed to medetomidine. Although medetomidine does not respond to naloxone, opioid overdose reversal agents should remain a treatment priority given the frequent co-ingestion of fentanyl. Prompt recognition of acute toxicity and of the potentially life-threatening hyperadrenergic withdrawal syndrome, including complications such as NSTEMI and PRES, facilitates timely escalation of care, improves outcomes, and strengthens public health surveillance efforts aimed at reducing overdose deaths.

—Priyanka Kaushal, BS; Farzana Hoque, MD, MSHA, MRCP

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Fahad Aziz, MD, FASN

Beyond the Crash Count: Turning Local Data Into Safer Roads

Fahad Aziz, MD

A motor vehicle crash unfolds in seconds. An ordinary trip can suddenly result in a life-changing injury, a family tragedy, and a challenge for emergency responders and health systems. The consequences may be especially profound in rural communities, where higher-speed roads, longer emergency response times, and greater distances to trauma care can influence survival. In 2023, rural areas accounted for 41% of US traffic fatalities despite representing approximately 20% of the population, and the fatality rate per vehicle mile traveled was 1.5 times higher on rural versus urban roads.[1] Longer emergency medical services response times also have been associated with greater motor vehicle crash mortality.[2]

Preventing these injuries requires recognizing a fundamental principle: not all crashes are alike, and not all locations along the same road carry the same risk.

In this issue of the *Wisconsin Medical Journal*, Rhodes-Lyons and colleagues demonstrate how local data can reveal these differences and guide practical solutions.[3] They examined motor vehicle collisions along a rural 4-lane segment of US Highway 10 in Wood County, Wisconsin, from January 1, 2019, through March 1, 2024. Using dispatch records, statistical analysis, and geospatial mapping, they asked which collision types were most likely to result in injury or death—and where those crashes occurred.

Frequency Is Not the Same as Severity

Among 239 collisions, 51 (21.3%) resulted in injury or death. Deer-related collisions accounted for 38.0% of all crashes, reflecting a familiar Wisconsin hazard. Statewide, more than 17,000 deer-related crashes occurred in 2024, causing 708 injuries and 9 deaths.[4] Yet on the corridor studied, only 4.3% of deer-related crashes resulted in injury or death, compared with 31.7% of nondeer collisions.[3]

Angle collisions showed the opposite pattern. Although less frequent, they were disproportionately associated with harm. After multivariable adjustment, angle collisions carried more than twice the odds of injury or death compared with other mechanisms (odds ratio, 2.52; 95% CI, 1.04-6.09). Daylight, dry road surfaces, and clear weather were not independently associated with injury outcomes.[3]

Wrong-way driving provided another concerning signal: 4 of 5 wrong-way collisions resulted in injury or death. The sample is too small for a precise risk estimate, but the pattern warrants attention. Together, these findings underscore a central lesson of injury prevention: the most common event is not necessarily the most harmful. Prevention priorities must reflect severity as well as frequency.

From Crash Counts to Precision Prevention

The study's geospatial analysis makes the findings particularly actionable. Nondeer and angle collisions clustered near major intersections, especially County Roads 80, A, and 186, whereas deer-related crashes were more broadly distributed along the corridor's rural eastern portion.[3] Different patterns therefore require different responses.

> This is translational research at its most practical—turning local evidence into meaningful change.

General safety messages—wear a seat belt, avoid impaired or distracted driving, obey speed limits, and remain alert—remain essential. But they cannot fully address risks created by a particular intersection, crossover, turning movement, or roadway design. Local data make precision prevention possible: identifying which crashes cause the greatest harm, where they occur, which roadway features may contribute, and which countermeasures are most likely to help.

From Research to Action

This is translational research at its most prac-

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tical—turning local evidence into meaningful change. Translation can mean moving findings from a spreadsheet to a safer intersection, from a map to a redesigned roadway, or from an observation to a community intervention. Achieving that change requires collaboration across disciplines, including researchers, clinicians, engineers, law enforcement, emergency medical services, public health, and transportation planning. When these perspectives come together, local research can move beyond describing a problem to becoming a catalyst for change.

Interpreting the Findings With Caution

The findings should be interpreted within the study's limitations. The analysis involved a single highway corridor and relied on sheriff's office dispatch records. Events could not be linked to hospital or trauma registry data, limiting assessment of injury severity, treatment, disability, and long-term outcomes. Alcohol and drug involvement was inconsistently documented, and the modest sample constrained the multivariable analysis.

The wrong-way driving findings should therefore be considered a safety signal rather than a stable estimate of risk. Likewise, the association between angle collisions and injury does not prove that roadway design caused those outcomes; speed, traffic volume, driver behavior, sight distance, and other unmeasured factors may have contributed. These limitations temper certainty but do not diminish the value of the approach. Meaningful change often begins by identifying a pattern, studying it systematically, and bringing the findings to those positioned to act.

If roadway changes are implemented, ongoing monitoring and before-and-after analyses will be essential to determine whether they reduce serious collisions and whether benefits are sustained.

Why Local Research Matters

National datasets and multicenter studies define broad patterns and shape policy, but they cannot answer every question facing an individual community. Wisconsin communities differ in geography, infrastructure, health care access, emergency response capacity, and resources. Some local problems may never become the subject of a national study, but that does not make them less important.

Local research can identify risks that may be missed when we look only at statewide data. It can also help communities move more quickly from understanding a problem to taking action. Rhodes-Lyons and colleagues studied 239 crashes along one section of a Wisconsin highway, but the lessons from their work reach far beyond Highway 10.

The true value of research is not simply its publication, but in what happens because of it. Sometimes research changes how we care for patients in a clinic or hospital. Sometimes, as this study shows, it can help make a rural Wisconsin road safer for everyone who travels it.

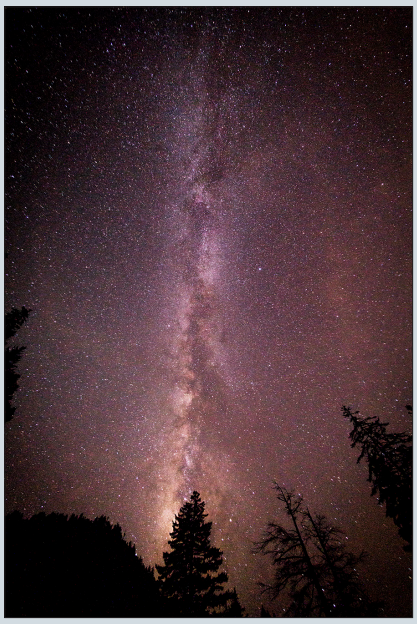
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"Milky Way, Vertical"

About the Artist

Richard Abraham, MD, is a pediatric anesthesiologist. "My work begins before I ever reach for a medication. It begins with a frightened child, a worried parent, and a few minutes to help them feel safe. Medicine has also deepened my appreciation for light's ability to reveal and heal. For more than a decade, I have photographed that light on location. I wanted to bring these views to people who might never have the opportunity to make the journey themselves."

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Looking Inward and Onward: Medical Humanities as a Tool for Understanding the Power of the Wisconsin Idea

Elizabeth A. Fleming, MD; Katherine Bakke, MD, MPH; Olivia Davies, MD; Liana Eskola, DO; Kevin Wyne, MPAS, MSc, PA-C; Nicole C. Nelson, PhD

"One of the longest and deepest traditions surrounding the University of Wisconsin, the Wisconsin Idea signifies a general principle: that education should influence people's lives beyond the boundaries of the classroom."[1]

These are challenging times for academic institutions. Decreased funding threatens ongoing research and the educational mission of health care training programs, including medical schools. There is increasing recognition that the academic community has not effectively communicated its value to the health and well-being of society at large. Even the Wisconsin Idea, one of the longest traditions of the University of Wisconsin (UW), has a problematic history that may contribute to this mistrust. To address these challenges and to harness the potential of the Wisconsin Idea, a thoughtful approach that incorporates deep reflection and storytelling is needed.

• • •

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Storytelling is increasingly recognized as a tool not only for creating connection and fostering empathy, but also for better disseminating scientific and medical knowledge.[2] As with other aspects of medical education, effective storytelling can be taught.[3] A narrative is a story that shares information while producing meaning and understanding for listeners.[4] As Transportation Theory suggests, the meaning a listener takes from a story is highly dependent on what the story makes them think about and how it makes them feel.[5]

Storytelling is increasingly recognized as a tool not only for creating connection and fostering empathy, but also for better disseminating scientific and medical knowledge.

Evidence suggests that feeling immersed in the details and context of a narrative produces emotional resonance – empathy – and affects how listeners process its meaning. While direct measurements of empathy are challenging, empathy can trigger oxytocin release, which can move people to feel more trusting and behave more generously.[6,7] Studies using functional magnetic resonance imaging and storytelling have revealed areas of the brain that impact cognitive and affective understanding as well as processing social information, like the ability to interpret others' desires, beliefs, and goals. Consuming a narrative may produce empathy as an integral part of understanding content.[8]

Consider how reading about the history of the Wisconsin Idea impacts your own thoughts and feelings. The Wisconsin Idea has its roots in the teachings of John Bascom, who served as the University of Wisconsin president from 1874 to 1887. A professor of rhetoric, he believed in the Social Gospel, a movement popular in the late 19th and early 20th centuries that used Christian morality as a vehicle for fighting social injustices. Indeed, he believed that one's Christian salvation depended on ridding the world of social evils.[9]

Charles Van Hise, UW president from 1903 to 1918, and Robert La Follette, Wisconsin governor from 1901 to 1906, were both students of Bascom. With Van Hise and La Follette as leaders of the state and its university, Wisconsin became nationally recognized for passing workers' compensation legislation, early adoption of the extension movement, and turning the state's failing wheat industry into a thriving dairy farming economy. The Wisconsin Idea emerged from their work.[10]

Not all Wisconsinites, however, experienced the application of academic knowledge to their lives as beneficial. Van Hise was also a strong advocate for eugenics, a scientifically inaccu-

rate and immoral theory of racial improvement and planned breeding. He lobbied for laws that empowered the state to forcibly sterilize those deemed unfit. Instruction in eugenics was integrated into UW sociology, criminology, genetics, and zoology coursework until 1948.[11]

Wisconsin physicians were deeply involved with the eugenics movement. They gave speeches to the eugenics club, conducted medical evaluations of "fitness," oversaw the state facilities where Wisconsinites were confined and sterilized, and coerced Indigenous women into involuntary sterilization.[11,12] This history is unknown to many in the Wisconsin medical community, but it remains omnipresent for families affected by the policies promoted by the university. While we tout the Wisconsin Idea, they hold this history in their perception of our institution.

It is tempting to consider the Wisconsin Idea from the perspective of extremes—either it is a laudable philosophical principle or a tainted relic. Instead, we propose that the Wisconsin Idea is best understood when carefully considered from multiple perspectives. Competence as a health care provider requires an understanding that health and illness are not only biological phenomena but are deeply rooted in human experiences and histories. Understanding our multifaceted, sometimes problematic past demands not only cognition, but perspective-taking, analysis, and an awareness of social contexts.

Medical humanities offer tools for learning to do all of this well. Studies of narrative medicine training in practicing clinicians have been shown to enhance observational skills, improve empathy, promote the ethical practice of medicine, and reduce provider burnout.[12-15]

One practical way we engage with medical history at UW Madison is by bringing our health care community to the archives. Reading about eugenics is a fundamentally different experience from physically holding a log of 1940s eugenic sterilizations by Wisconsin surgeons and developing a shared analysis. Participants can recognize the intersubjective understanding of sickness and health and better understand themselves in relation to patients and the larger systems in which care is provided.

The Wisconsin Idea charges us to work to improve the health and well-being of all people in Wisconsin, and beyond. Knowing the story of its history does not negate the potential good but can help us better understand the complexity of distrust of academic institutions. Engaging with narratives through arts-based medical humanities practices can not only improve our ability to tell effective stories but also promote a more nuanced understanding of our shared history, foster a sense of community, and cultivate a shared vision. We in academic medicine owe it to the people of Wisconsin to learn to both listen to and tell stories.

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The Diagnosis I Missed in Myself

Brian Burroughs, PA-C

On long family car rides when I was a child, I was often the reason we stopped so often. Before we had even reached the highway, I would already be asking how far it was to the next rest area. At the time, I assumed this was simply how my body worked. Only much later did I begin to wonder whether the pattern I had lived with for so long might have had a name.

As I grew older, the pattern remained. Urinary urgency and frequency were a constant presence. At times there was also a vague bladder discomfort that was difficult to explain, an uncomfortable pressure that sometimes resembled the early stages of a urinary tract infection, though the infection never quite arrived.

For most of my life, I accepted these symptoms as a minor inconvenience.

Like many people with chronic symptoms, I adapted. I planned ahead before long meetings. I learned where restrooms were located in unfamiliar buildings. Travel required a bit more preparation. The symptoms waxed and waned over time, sometimes barely noticeable, other times intrusive enough to shape the day.

When symptoms persist without a clear explanation, it becomes surprisingly easy to normalize them.

• • •

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Years later, as a physician assistant, I began caring for patients whose stories sounded familiar. Many described chronic urinary urgency, frequency, and bladder discomfort. They had often been treated repeatedly for presumed urinary tract infections despite negative cultures. Their symptoms persisted, sometimes fluctuating unpredictably. The experience was frustrating for them and perplexing for the clinicians who had previously cared for them.

Through these encounters, and through collaboration with a urogynecologist colleague, I became more familiar with a condition that had received little attention during my training: interstitial cystitis.

Interstitial cystitis is characterized by urgency, frequency, and bladder discomfort in the absence of infection. It is often recognized only over time, as patterns begin to emerge.

The condition is most often discussed in the context of women's health, and many clinicians rarely consider it when evaluating male patients. As a result, some patients spend years searching for explanations while more familiar diagnoses are repeatedly considered.

As I listened to my patients describe their experiences, parts of their stories began to feel uncomfortably familiar. The urgency without infection. The unpredictable flares. The quiet adjustments required to navigate daily life.

Eventually, a thought surfaced that I had never seriously considered before. What if the symptoms I had lived with for years were the same condition affecting my patients?

Interstitial cystitis is often described as uncommon in men. Yet uncommon is not the same as impossible. Like many conditions without a single diagnostic test, it can exist for years before anyone recognizes the pattern. Looking back, the pattern in my own symptoms had been present since childhood. I simply had not learned how to see it.

What if the symptoms I had lived with for years were the same condition affecting my patients?

Recognizing this possibility was both clarifying and humbling. It provided an explanation for something that had long seemed vague, but it also raised a more difficult question: how had I not recognized this sooner?

Clinicians often assume that medical knowledge protects us from diagnostic blind spots. In reality, we are subject to the same habits of thinking as anyone else. We normalize symptoms that have always been present. We attribute them to stress, diet, or coincidence. Perhaps most importantly, we assume that illness happens to other people.

This experience changed how I approach patients with similar symptoms.

Urinary urgency and discomfort are common complaints across clinical settings. The reflex is often to evaluate for infection, treat when appropriate, and move on. But for some

patients, the story does not end there. Now, when patients describe persistent urgency, frequency, or bladder discomfort despite negative testing, I listen differently.

Conditions that rely on pattern recognition rather than definitive testing are easy to miss. They require time, attention, and a willingness to reconsider initial assumptions. In settings where continuity allows patterns to emerge, this kind of listening matters.

I am more likely to consider diagnoses that are not immediately obvious. I take greater care to validate patients' experiences, even when objective findings are limited. For many, simply having a name for what they are experiencing can be reassuring. More importantly, it affirms that their symptoms are real.

Living with chronic symptoms, even relatively mild ones, offers a different understanding of illness. It is not just the symptoms themselves, but the way they shape daily life: The constant awareness of restroom locations. The small decisions about what to drink before a long meeting. The quiet hope that symptoms will remain manageable during travel or work.

These details rarely appear in the medical record, yet they are central to the patient's experience.

Perhaps the most important lesson from this experience has been humility.

Medicine often rewards certainty. We prefer clear diagnoses, definitive tests, and straightforward treatments. Yet many of the conditions encountered in everyday practice exist in shades of gray. Symptoms develop gradually. Diagnoses emerge slowly. Understanding often comes only after careful attention to patterns over time.

Now, when patients describe symptoms that do not fit neatly into familiar explanations, I listen a little more carefully. Sometimes we learn medicine from textbooks and training. Sometimes we learn it from our patients. And occasionally, we learn it from ourselves.

In clinical practice, not every diagnosis is confirmed by testing. Some are recognized through patterns that emerge over time. Recognizing those patterns requires curiosity, attention, and humility.

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February 2027

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Addressing Social Isolation and Loneliness in Hospital Settings

Sanjay Bhandari, MD, MS; Ronald Anguzu, PhD, MPH, MBChB; Pinky Jha, MD, MPH; Sara Kohlbeck, PhD, MPH; Adam Pfankuch, BS; Terri A deRoon Cassini, MS, PhD; Colleen Galambos, PhD, LCSW

Social isolation—an objective lack of social connection—and loneliness—the subjective feeling of disconnection—are surprisingly common yet serious health concerns.[1,2] They affect more people than many well-known conditions such as diabetes and obesity. About half of Americans report feeling lonely, and roughly 1 in 4 adults say they lack social and emotional support.

As an example, consider an older man admitted to the hospital who has spent days in his room without a single visitor or phone call from family or friends. His wife died several years earlier, and he now lives alone in a small apartment with his children living far away. Over the years, his social connections have dwindled, leaving him largely isolated and lonely. His medical chart lists common chronic conditions: diabetes, hypertension, and arthritis. During clinical encounters, his physicians move through their familiar routines: reviewing laboratory results, adjusting medications, and managing disease-specific concerns. Yet, beneath these comorbidities and laboratory values lies something that often goes unnoticed: a life affected by social isolation and loneliness.

Clinicians routinely track chronic diseases, but they rarely assess social isolation and loneliness, despite their profound impact on health.

While each patient's circumstances may differ, the underlying theme is often the same: social disconnection, the quiet "elephant in the room," frequently goes unrecognized. Clinicians routinely track chronic diseases, but they rarely assess social isolation and loneliness, despite their profound impact on health. Research shows that poor social connection is linked to increased risk of cardiovascular disease, depression, suicide, and premature mortality, as well as higher health care utilization and cost.[1,2] Recognizing their growing impact on health and well-being, the US Surgeon General declared isolation and loneliness a national epidemic in 2023.[1]

While these conditions are not routinely screened for in clinical practice, hospitalization represents a promising yet underutilized opportunity for assessment. For many patients, a hospital stay may be one of the few reliable points of contact with the health care system. A recent study found that more than 1 in 4 hospitalized adults report feeling lonely, and nearly a quarter experience social isolation,[3] highlighting the opportunity to identify and address these issues during hospitalization. Moreover, a longer inpatient stay offers health care professionals, including social workers, nurses, and physicians, more time to screen for and address these issues than is typically available during an outpatient visit.

How can hospital providers implement this screening opportunity? One approach is through brief, standardized instruments, such as the UCLA Three Item Loneliness Scale,[4] which is readily available for more structured screening. When formal screening is not feasible, asking a few open-ended questions may provide valuable information about how social isolation and loneliness are affecting a patient. Examples include the following:

1. How often do you talk with family or friends?
2. Is there someone you can call for help?
3. How connected do you feel to others?

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4. Do you ever feel lonely or left out?

The easiest approach in hospital setting may be to integrate these questions naturally into the social history interview rather than treating them as a checklist.

Once isolation or loneliness is suspected or identified, the next step is addressing it. While interventions for community-dwelling populations are better studied,[5] evidence specific to hospitalized patients remains limited. Nonetheless, several feasible strategies may help promote social connection during a hospital stay, including maintaining contact with family and friends through visits, phone, or video calls; offering group-based activities such as physical therapy sessions; encouraging therapy animal visits; and involving social workers early to address broader social needs. These efforts should extend beyond hospitalization through discharge planning that connects patients to community resources, such as adult day programs, peer support groups, and local organizations such as the Wisconsin Coalition for Social Connection.[6]

Ultimately, addressing isolation and loneliness is as much an art as a science, and there is no one-size-fits-all fix. Health care teams have the freedom to be thoughtful and creative, tailoring their approach to each patient's needs while drawing on both hospital and community resources to strengthen social connection. Nonetheless, rigorous evaluation of inpatient-specific screening approaches and interventions remains a critical unmet need.

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Climate Challenges: Exploring How Climatic Shifts Affect Thyroid Function

Asad Allana, BDS, MSc; Ayesha Irfan, MBBS; Tooba Munir, MBBS; Muqadas Riaz, MBBS

Climate change, partially driven by human activities, has become an increasingly prominent concern in recent years.[1] Numerous human activities contribute to global climate change, including the burning of fossil fuels and subsequent accumulation of greenhouse gases in the atmosphere, land-use changes, deforestation, industrial processes, and certain agricultural practices.[2] Recent climate projections indicate a 47% likelihood that the global average temperature between 2024 and 2028 will exceed 1.5 °C above preindustrial levels, corresponding to approximately 0.9 °C above the 1991-2020 global average, underscoring the rapid pace of current warming.[3]

Climate change has been shown to disrupt various endocrine functions. Although the extent of these effects varies across populations and climatic regions, the thyroid appears particularly vulnerable to environmental stressors linked to temperature fluctuations, pollution, and nutritional changes associated with global warming.[4] Triiodothyronine (T3) and thyroxine (T4) are thyroid hormones that play essential roles in regulating various physiological functions.[5] Thyroid-stimulating hormone (TSH), the principal regulator of the hypothalamus-pituitary-thyroid axis, sustains adequate thyroid function by regulating hormone synthesis.[6]

Importantly, studies conducted in regions with pronounced seasonal variability, such as continental or high-latitude climates, have consistently shown greater fluctuations in TSH, free triiodothyronine (FT3), and free thyroxine (FT4) levels than those observed in equatorial or maritime temperate regions, where temperature changes are less extreme.[4]

Mechanistic Pathways

Rising and declining environmental temperatures interfere with the thyroid's ability to maintain hormonal balance, leading to metabolic changes and thyroid disorders.[6,7]

Over the last decade, the incidence of thyroid disorders has increased by approximately 1.1% annually, potentially reflecting, in part, environmental exposures associated with climate change.[7]

Recent research demonstrates clear seasonal and climate-driven variations in thyroid hormones. TSH levels consistently increase during winter and decrease in summer across diverse populations.[8-9] Conversely, FT3 and FT4 display inverse trends: FT3 typically declines during summer, whereas FT4 increases. The temperature-dependent activity of peripheral deiodinase enzymes, particularly type II iodothyronine deiodinase (DIO2), which converts T4 to FT3, is partially responsible for these patterns. Higher temperatures inhibit this conversion, whereas lower temperatures increase DIO2 activity, resulting in higher FT3 levels and FT3/FT4 ratios. Extensive epidemiological data have also demonstrated a strong inverse association between ambient temperature and the FT3/FT4 ratio. Additionally, photoperiod influences thyroid hormone regulation; longer daylight exposure is associated with higher FT3 levels and FT3/FT4 ratios, likely through light-sensitive regulation of deiodinase expression.[10] These physiological adaptations indicate that thyroid regulation is highly sensitive to both temperature and light variation.

Over the last decade, the incidence of thyroid disorders has increased by approximately 1.1% annually, potentially reflecting, in part, environmental exposures associated with climate change.

Beyond immediate hormonal responses,

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seasonal and climate-related influences may also trigger deeper molecular adaptations within the endocrine system. Environmental stressors such as heat can induce broad epigenetic "memory" through DNA methylation and histone modifications that reprogram gene transcription. Notably, thyroid hormone signaling acts as a key mediator of these processes, including through regulations of DNA methyltransferase activity, linking environmental exposures to lasting transcriptomic shifts in endocrine function. A better understanding of these pathways may improve interpretation of seasonal thyroid test variation and inform the clinical management of thyroid disorders.[11]

Broader Environmental and Societal Factors

Rising temperatures associated with climate change increase moisture loss in agricultural crops, resulting in the concentration of nitrates and nitrites – compounds known to interfere with iodine uptake and disrupt thyroid function. Global warming may also contribute to increased iodide volatilization from seawater, thereby reducing iodine availability in nearby plants, soil, and drinking water. These changes may increase the risk of iodine deficiency and associated thyroid disfunction, particularly among vulnerable populations.[6]

Climate-related shifts in agriculture and soil chemistry can substantially alter iodine and selenium bioavailability. For example, heavy rainfall and flooding can leach iodine from topsoil,[12] whereas humid, irrigated soils can reduce selenium content (arid soils generally retain more selenium).[13] Because iodide uptake and organification by thyroid peroxidase are required for thyroxine synthesis, and selenium-dependent deiodinases activate thyroid hormones, reductions in either micronutrient can impair T3 and T4 production. Thus, climate-related losses of iodine and selenium may reduce thyroid hormone production and increase the risk of deficiency-related disorders.[7]

Beyond nutrient availability, environmental exposures associated with climate change may also influence thyroid disease risk through additional pathological mechanisms. For example, certain climatic conditions, such as living in volcanic environments, have been associated with increased carcinogenic risk.[14] In addition, the prevalence of thyroid disorders, including autoimmune thyroiditis, has been reported to increase in regions experiencing climate-related environment changes.[3]

Protecting Vulnerable Populations

Pregnant women, infants, and older adults are particularly susceptible to complications arising from impaired thyroid function. Policies that prioritize protection of these populations are therefore essential. Targeted support systems and access to health care should be strengthened in regions most affected by climate-related environmental disruptions. For example, community-based iodine supplementation programs and universal salt iodization initiatives have been effective in reducing thyroid disorders among populations at risk for iodine deficiency.[12-13] Additionally, heat-health action plans implemented in countries such as France, incorporating public warning systems, expanded emergency services, and targeted resources for older adults, have demonstrated measurable reductions in heat-related endocrine and metabolic complications. These findings highlight the value of structured public health interventions for protecting vulnerable populations.[15]

Future Directions for Research, Surveillance, and Policy

Most environmental regulations focus on topics such as disaster preparedness and carbon emissions, yet thyroid health seldom is considered within these frameworks. Climate policies should incorporate the potential endocrine effects of environmental change. Urban planners should consider how urban design influences heat exposure and its potential effects on thyroid function. Clinical systems may also benefit from integrating relevant environmental data into thyroid function monitoring protocols, while governments should continue to strengthen regulations that limit exposure to substances known to disrupt thyroid hormone signaling.

Recent case studies provide examples of potential adaptation strategies. For example, in France and several Southern European countries, urban heat adaptation plans have been implemented to reduce the health effects of increasingly frequent heat waves. These initiatives include expanding urban green spaces, improving building ventilation standards, and establishing early warning systems for heat-related illness. Such policies have been shown to reduce cardiovascular and metabolic stress and may also mitigate thyroid dysregulation associated with extreme heat exposure.[15] These examples illustrate how climate-responsive public health interventions, including pollution-reduction strategies and temperature management, may help reduce thyroid-related health risks.

Technological advancements are also transforming the study of thyroid-environmental interactions. Wearable devices are being developed to collect continuous physiologic data beyond conventional laboratory testing, including biomarkers potentially indicative of thyroid stress. Concurrently, environmental sensor networks are being incorporated into health monitoring systems to identify populations and regions at increased risk of climate-related exposures. These innovations suggest that the thyroid gland could serve as a sensitive biological marker of environmental stress, providing new opportunities for early identification and prophylactic intervention.

Additional research is needed to better characterize the relationship between climate change and thyroid health. Longitudinal studies involving populations exposed to environmental stressors such as pollution, heat waves, and water instability may strengthen the evidence linking climate-related exposures to changes in TSH, T3, and T4 concentrations over time. Incorporating geospatial approaches, including GPS-based analyses and satellite mapping, may help identify geographic hotspots. Further investigation of molecular mechanisms, including gene expression and epigenetic modifications, may also provide insight into the biological pathways through which environmental exposures influence thyroid function.

Public health systems may ultimately benefit from a more proactive approach to thyroid surveillance. Achieving this goal will require collaboration among public health agencies, health systems, and climate researchers.

Although comprehensive thyroid hormone data are not routinely incorporated into many public health databases, biochemical data from clinical and laboratory networks could potentially be linked with environmental datasets. Such integration could strengthen population-level surveillance and advance understanding of climate-related thyroid health effects, without implying that thyroid disorders should be considered reportable public health conditions.

Implementation of these strategies will require adequate workforce and organizational capacity. In addition, health care professionals may benefit from additional training regarding the potential effects of climate-related environmental changes on thyroid disease. Greater coordination among local government and health departments is also necessary. If agencies work together and if thyroid issues are tracked more consistently, we will be better positioned to help mitigate climate-related thyroid health risks before they become more widespread.

Conclusions

As the intersection between climate change and thyroid health becomes increasingly evident, a multifaceted response is urgently needed. Addressing this emerging challenge will require coordinated efforts across research, clinical practice, public health, and policy. Proactive investments in research, policy development, and health care infrastructure may help mitigate the endocrine-related risks associated with climate change. Although many questions remain unanswered, available evidence suggests that climate-related effects on thyroid health warrant greater attention as part of broader climate resilience strategies. By strengthening surveillance systems, supporting targeted research, and integrating endocrine considerations into climate adaptation efforts, health systems may be better positioned to address these evolving challenges.

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Wrong-Way Driving and Injury Risk on a Rural Four-Lane Corridor: A Descriptive and Spatial Analysis of US Highway 10, 2019–2024

Heather Rhodes-Lyons, PhD; Rachel Symons, BSN; Gina Brandl, MSN; Erin Klarr, BSN; Lucy Martinek, MD

ABSTRACT

Introduction: Motor vehicle collisions (MVCs) on rural highways pose unique challenges due to high speed limits, limited access points, and varied environmental conditions. This study aimed to describe crash characteristics, identify predictors of injury and fatality, and evaluate geospatial trends along a rural segment of US Highway 10 in Wisconsin.

Methods: We conducted a retrospective analysis of MVCs reported on US Highway 10 from January 1, 2019, to March 1, 2024. Incident-level dispatch data were analyzed with corresponding environmental and temporal factors using descriptive statistics, geospatial analysis, and logistic regression. Geospatial mapping was used to identify high-risk roadway segments, and descriptive statistics and logistic regression were used to identify factors associated with injury or fatality.

Results: Among 239 MVCs, 21.3% (n = 51) involved injury or death. Angle collisions were significantly associated with increased odds of injury or fatality (OR 2.52; 95% CI, 1.04–6.09, *P* = .04). Wrong-way driving, though rare, was associated with a higher proportion of injury-producing crashes. Deer-related crashes comprised 38.0% of events but rarely resulted in injury (4.3%). Environmental factors, including lighting conditions, road surface conditions, and weather, were not independently predictive. Spatial clustering was observed near major intersections, transition zones, and roadway merging areas.

Conclusions: Collision mechanism, particularly angle collisions and wrong-way crashes, are key predictors of injury on this rural 4-lane highway corridor. In contrast, deer-related collisions were common but infrequently associated with injury. These findings support targeted roadway-engineering improvement, enhanced signage, and behavioral interventions to reduce crash-related injury along rural corridors such as Highway 10.

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INTRODUCTION

Motor vehicle collisions (MVCs) continue to be a leading cause of injury and death in the United States, with rural areas experiencing disproportionately high fatality rates due to factors such as excessive speed, prolonged emergency medical services (EMS) mobilization and response times, and limited access to trauma care facilities.[1-5] In Wisconsin, there is a high proportion of rural residents (32.9%), and the age-adjusted injury mortality rate exceeds the national rate, highlighting ongoing geographic disparities in injury risk and outcomes.[6] Rural highways such as US Highway 10 present unique hazards, including long stretches without interruption, high speed limits, limited lighting, and increased wildlife crossings, all of which contribute to crash risk and severity.[7,8] Despite widespread public health initiatives aimed at improving rural roadway safety, injury prevention efforts are often reactive and lack precise geospatial targeting.[9] Wrong-way driving incidents, though rare, have become particularly dangerous due to resulting high-speed, head-on collisions.[10] In Wisconsin, deer-related crashes are common on rural highways, particularly in wooded or agricultural corridors. While wildlife-vehicle collisions account for a substantial proportion of total crashes, they are less often associated with serious injury than multivehicle or angle collisions.[11-13]

The objective of this study was to identify environmental, temporal, and mechanistic factors linked to injury or death resulting from MVCs along a rural section of US Highway 10 in Wisconsin

from 2019 to 2024. We also analyzed the spatial clustering of high-risk crash locations to support targeted infrastructure improvements and prevention efforts.

METHODS

Study Design and Data Source

This retrospective cohort study analyzed motor vehicle collisions (MVCs) on the 4-lane rural segment of US Highway 10 in Wood County, Wisconsin, from January 1, 2019, to March 1, 2024. Incident-level data were collected from Wood County Sheriff's Office dispatch face sheets, which record real-time crash details including time, location, environmental conditions, crash mechanism, vehicle involvement, and EMS response.

Data abstraction was limited to events occurring within the designated Highway 10 corridor. Eligible cases included any reported MVC involving motorized vehicles (eg, passenger cars, trucks, and commercial vehicles) with complete information on crash location and outcome. Events involving only nonmotorized participants or those lacking injury or location data were excluded. For regression modeling, deer-related collisions were excluded to avoid attenuating associations between predictor variables and injury outcomes because of the high frequency and low severity of these events.

Dispatch records were reviewed manually for consistency and coded for variables including lighting (daylight, dawn/dusk, dark-unlit), road surface conditions (dry, wet, icy, or snowy), weather, direction of travel, number of vehicles, and crash type (eg, angle, front-to-rear, or wrong-way). When available, records also included information on alcohol or drug involvement and EMS response times.

This study was determined to be exempt from oversight by the [RHO10124] Institutional Review Board under institutional policies and federal guidelines for minimal-risk research. Analyses adhered to the principles of the Declaration of Helsinki and were reported according to the STROBE guidelines (Supplementary Table 1).

Outcomes of Interest

The primary outcome was whether an MVC resulted in an injury or fatality, based on dispatch documentation indicating medical evaluation or death at the scene or during transport. Crashes were classified as injury/fatality or noninjury events. Secondary outcomes included environmental, temporal, and mechanistic predictors of injury, as well as the geospatial distribution of injury-producing crashes along the study corridor (Figure).

Statistical Analysis

Descriptive statistics were used to summarize crash characteristics. Categorical variables were presented as frequencies and percentages, and continuous variables were reported as means, medians, and interquartile ranges. Group comparisons between injury/fatality and noninjury crashes were conducted using chi-square tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. Analyses were conducted using R version 4.4.1 (R Core Team, 2023). A descriptive geospatial analysis was performed in Power BI Desktop (version 2.143.878.0, Microsoft) to visualize crash clustering and identify high-frequency roadway segments.

Multivariable logistic regression was used to identify factors independently associated with injury or fatality. To minimize confounding from frequent but low-severity events, deer-related collisions were excluded from the regression model. Predictor variables included environmental, mechanistic, and temporal factors such as lighting conditions, road surface conditions, weather, direction of travel, and collision type. Variables were screened for multicollinearity using tolerance testing (threshold, > 0.5). Regression analyses were conducted using SPSS version 28 (IBM Corp). Model results were expressed as odds ratios (OR) with 95% confidence intervals (CI); significance was set at $P < .05$.

RESULTS

First Analysis: Crash Characteristics

A total of 239 MVCs were reported along the designated rural segment of US Highway 10 during 2019-2024. Of these, 51 crashes (21.3%) resulted in injury or fatality. Deer-related collisions accounted for 38.0% (n = 91) of all MVCs, while the remaining 61.9% (n = 148) were non-deer-related. Although deer collisions were common, they were significantly less likely to cause injury or death than non-deer-related MVCs (4.3% vs 31.7%, $P < .01$). See Table 1.

Crash timing showed a bimodal distribution in injury outcomes, with injury/fatality crashes peaking in 2021 (25.4%) and again in 2024 (17.6%). The mean crash time was 13:54 (SD, 6:05), with no significant difference between injury/fatality and noninjury groups ($P = .06$). EMS response time did not differ significantly between injury/fatality and noninjury groups (mean, 12:57 vs 13:30, $P = .69$).

Most crashes (69.0%) involved a single vehicle; however, 2-vehicle collisions were more likely to result in injury or fatality, although the association was not significant (62.7% vs 20.7%, $P = .06$). Nearly all deer-related crashes involved a single vehicle (97.8%).

Collision type was significantly associated with injury severity. Angle collisions accounted for 33.3% of injury/fatality events compared with only 7.4% of noninjury crashes ($P = .01$). Wrong-way collisions were rare (n = 5); however, 4 of the 5 events resulted in injury or fatality. Although the number of events was small, this finding suggests a potential association between wrong-way driving and injury risk that warrants further study.

Environmental factors also showed notable trends. Crashes occurring under dark or unlit conditions were more common among injury/fatality events (27.4% vs 21.8%, $P < .01$). Although dry roads were the most common overall, they were disproportion-

Table 1. Descriptive Characteristics of Motor Vehicle Crashes on US Highway 10, 2019–2024

		Environmental Hazard			Injuries and Fatalities		
	Total N = 239	**MVC-No Deer N = 148 (61.9%)**	**Deer-related MVC N = 91 (38.1%)**	***P* value**	**Incidents With Injury/Death N = 51 (21.3%)**	**Survived (N = 188)**	***P* value**
Year, n (%)							
2019	29 (12.1)	22 (14.9)	7 (7.7)	.14	11 (21.6)	18 (9.6)	<.01
2020	32 (13.4)	22 (14.9)	10 (11.0)	.51	8 (15.7)	24 (12.8)	<.01
2021	59 (24.7)	35 (23.6)	24 (26.4)	.74	13 (25.5)	46 (24.5)	<.01
2022	37 (5.5)	18 (12.2)	18 (19.8)	.10	2 (3.9)	34 (18.1)	<.01
2023	31 (13.0)	23 (15.5)	9 (9.9)	.36	8 (15.7)	24 (12.8)	<.01
2024	51 (21.3)	28 (18.9)	22 (24.2)	.49	9 (17.6)	41 (21.8)	<.01
Crash time, n = 234; mean, median [SD] IQR	13:54, 14:15 [6:05] 11:24	13:19, 13:14 [5:19] 8:29	14:48, 17:22 [6:21] 14:02	.07	13:27, 13:14 [5:12] 7:03	14:00, 14:58 [6:20] 11:44	.06
Elapsed arrival time, n = 148; mean, median [SD] IQR	0:37, 0:13 [2:17] 0:14	13:29, 13:10 [5:16] 8:26	12:15, 12:50 [9:21] 13:37	.69	12:57, 13:00 [5:06] 7:37	13:30, 13:36 [5:36] 10:13	.69
Vehicles involved, n (%)							
1 vehicle	165 (69.0)	76 (51.3)	89 (97.8)	<.01	18 (35.3)	147 (78.2)	.03
2 vehicles	71 (29.7)	71 (48.0)	0 (0)	—	32 (62.7)	39 (20.7)	.06
3 vehicles	1 (0.4)	1 (0.7)	0 (0)	—	1 (2.0)	0 (0)	—
Total injured, n (%)	51 (21.3)	47 (31.8)	4 (4.4)	.78	—	—	—
Total killed, n (%)	7 (2.9)	7 (4.7)	0 (0)	—	—	—	—
Event location, n (%)							
On roadway	199 (83.3)	108 (73.0)	91 (100)	<.01	42 (82.4)	157 (83.5)	<.01
Roadside	17 (7.1)	17 (11.5)	0 (0)	-	3 (5.9)	14 (7.4)	<.01
Manner of collision, n (%)							
No collision with vehicle in transport	165 (69.0)	76 (51.3)	89 (97.8)	<.01	19 (37.2)	146 (77.7)	.06
Angle	31 (13.0)	31 (20.9)	0 (0)	—	17 (33.3)	14 (7.4)	.01
Front to rear	15 (6.3)	15 (10.1)	0 (0)	—	6 (11.7) 11.8	9 (4.8)	<.01
Wrong-way driver	5 (2.1)	5 (3.4)	0 (0)	—	3 (5.9)	2 (1.1)	<.01
Lighting condition, n (%)							
Dark/Unlit	55 (23.0)	48 (32.4)	7 (7.7)	<.01	14 (27.4)	41 (21.8)	<.01
Dawn	7 (2.9)	6 (4.0)	1 (1.1)	.81	3 (5.8)	4 (2.1)	<.01
Daylight	87 (36.4)	87 (58.8)	0 (0)	—	32 (62.7)	55 (29.3)	.06
Dusk	4 (1.7)	4 (2.7)	0 (0)	—	2 (3.9)	2 (1.1)	<.01
Road surface, n (%)							
Dry	92 (38.5)	84 (56.8)	8 (8.8)	.04	36 (70.6)	56 (29.8)	<.01
Ice	32 (13.4)	32 (21.6)	0 (0)	—	9 (17.6)	23 (12.2)	<.01
Slush	1 (0.4)	1 (0.6)	0 (0)	—	—	1 (0.5)	—
Snow	14 (5.9)	14 (9.5)	0 (0)	—	1 (2.0)	13 (6.9)	<.01
Wet	14 (5.9)	14 (9.5)	0 (0)	—	5 (9.8)	9 (4.8)	<.01
Weather condition, n (%)							
Clear	72 (30.1)	65 (43.9)	7 (7.7)	.04	26 (51.0)	46 (24.5)	.88
Cloudy	46 (19.2)	45 (30.4)	1 (1.1)	.47	18 (35.3)	28 (14.9)	.03
Fog	4 (1.7)	4 (2.7)	0 (0)	—	1 (2.0)	3 (1.6)	<.01
Rain	8 (3.3)	8 (5.4)	0 (0)	—	3 (5.8)	5 (2.7)	<.01
Severe winds	2 (0.8)	2 (1.3)	0 (0)	—	—	2 (1.1)	—
Snow	19 (7.9)	19 (12.8)	0 (0)	—	2 (3.9)	17 (9.0)	<.01
Direction of travel, n (%)							
Eastbound	86 (36.0)	48 (32.4)	38 (41.8)	.23	18 (35.3)	68 (36.2)	.03
Northbound	29 (12.1)	23 (15.5)	6 (6.6)	.05	9 (17.6)	20 (10.6)	<.01
Southbound	25 (10.5)	24 (16.2)	1 (1.1)	<.01	7 (13.7)	18 (9.6)	<.01
Westbound	93 (38.9)	48 (32.4)	45 (49.4)	.01	17 (33.3)	76 (40.4)	.01
License status , n (%)							
Expired	1 (0.4)	1 (0.7)	0 (0)	—	—	1 (0.5)	—
Not Licensed	4 (1.7)	4 (2.7)	0 (0)	—	1 (2.0)	3 (1.6)	.56
Revoked	2 (0.8)	2 (1.3)	0 (0)	—	1 (2.0)	1 (0.5)	.56
Suspended	4 (1.7)	3 (2.0)	1 (1.1)	.76	1 (2.0)	3 (1.6)	.56
Alcohol test (N = 1 result, 0.17% BAC), n (%)	6 (2.5)	6 (4.1)	0 (0)	—	4 (7.8)	2 (1.1)	.12
Drug Test, n (%)	5 (2.1)	5 (3.4)	0 (0)	—	4 (7.8)	1 (0.5)	.18

Abbreviations: SD, standard deviation; IQR, interquartile range; BAC, blood alcohol count.

ately represented among injury/fatality crashes (70.5% vs 29.7%, $P < .01$). Similar patterns were observed for weather conditions: cloudy conditions and snow were more frequently associated with injury/fatality events (35.2% and 3.9%, respectively), although clear weather remained the most common condition overall. Direction of travel was also associated with injury outcomes, with most crashes occurring in the westbound direction (38.9%) and a greater proportion of injury/fatality events occurring among westbound vehicles (33.3%, $P = .01$).

Although alcohol and drug involvement were documented more frequently in injury/fatality crashes, these variables were recorded infrequently and did not reach statistical significance.

Second Analysis, Logistic Regression Model; Injury and Fatalities

A multivariable logistic regression model was developed to assess the relationship between crash characteristics and the risk of injury or death in MVCs on US Highway 10 during 2019-2024. The model included 7 potential predictors: EMS elapsed time to crash, roadway location, angle of impact, daylight conditions, dry road surface, clear weather, and westbound travel direction (Table 2).

Of these variables, only angle of impact was independently associated with increased odds of injury or death. Crashes involving an angle impact had 2.52 times greater odds of resulting in injury or fatality than other collision types of (OR, 2.52; 95% CI, 1.04–6.09; $P = .04$).

None of the environmental factors, including daylight conditions (OR, 1.22; 95% CI, 0.56–2.65; $P = .60$), dry road surface (OR, 1.41; 95% CI, 0.55–3.61; $P = .46$), or clear weather (OR, 1.10; 95% CI, 0.47–2.56; $P = .81$), were significantly associated with injury outcomes. Likewise, westbound travel direction (OR, 1.00; 95% CI, 0.46–2.16; $P = .99$) and roadway location (OR, 1.26; 95% CI, 0.47–3.34; $P = 63$) were not associated with increased injury risk.

EMS elapsed time, treated as a continuous variable, was not a significant predictor (OR, 1.00; $P = 87$), indicating that differences in response timing did not significantly affect injury outcomes in the study population.

Geospatial Analysis

Geospatial mapping revealed distinct crash clustering patterns along the Highway 10 corridor (Figure 1). Non-deer-related and angle collisions were tightly clustered around major intersections, particularly County Roads 80, A, and 186. Directional stratification showed that westbound non-deer-related crashes were concentrated in the western half of the corridor, whereas eastbound crashes occurred more frequently between County Roads 80 and 186. In contrast, deer-related crashes were more evenly distributed and occurred primarily in the rural eastern segment near the towns of Milladore and Sherry.

Table 2. Logistic Regression Among the Injuries and Fatalities by Motor Vehicle Crashes on US Highway 10, 2019 – 2024

	Standard Error	Odds Ratio (95% CI)	*P* value
Elapsed time to crash	0.00	1.00 (1.00–1.00)	.87
Event location on roadway	0.49	1.26 (0.47–3.34)	.63
Angle collision	0.45	2.52 (1.04–6.09)	.04
Daylight condition	0.39	1.22 (0.56–2.65)	.60
Dry road surface	0.47	1.41 (0.55–3.61)	.46
Clear weather condition	0.43	1.10 (0.47–2.56)	.81
Westbound direction	0.39	1.00 (0.46–2.16)	.99

DISCUSSION

This study provides a focused geospatial and mechanistic analyses of MVCs along a rural 4-lane corridor in central Wisconsin. Despite the high frequency of deer-related crashes, our findings suggest that collision mechanism and vehicle dynamics, rather than environmental conditions, are the most significant predictors of injury and fatality risk. Specifically, angle collisions were associated with more than a 2-fold increase in the odds of injury risk, consistent with national reports indicating that side-impact collisions are disproportionately fatal because of reduced structural protection and a higher likelihood of passenger-compartment intrusion.

Wrong-way driving events, although infrequent, were disproportionately represented among injury/fatality crashes in the univariate analysis. This finding is consistent with national data showing that wrong-way crashes are often head-on collisions and frequently involve older drivers or impaired driving, resulting in high-impact velocities and high lethality.[10,14] These findings underscore the need for improved detection and prevention infrastructure in rural settings, where long, uninterrupted roadways may increase the risk of driver disorientation or deliberate misuse of access points.

Environmental variables, including dry roads, daylight conditions, and clear weather, were not statistically significant predictors of injury or death in the multivariable model, despite being most common in the descriptive data. This finding supports previous research suggesting that crash severity is more strongly associated with crash type and vehicle interaction dynamics than with roadway surface or visibility conditions alone.[15] Although lighting and weather conditions are often linked to crash causation, their independent effects on injury severity appear limited after accounting for collision mechanism and vehicle count.[16]

A notable finding was the low severity of deer-related collisions, which accounted for more than one-third of all crashes but rarely resulted in injury (4.3%). Although deer-related crashes are often highlighted in rural road-safety campaigns, our findings suggest they pose a greater risk of vehicle damage than serious injury. These results are consistent with prior studies demonstrating that most deer-related MVCs involve single vehicles traveling at moderate speeds and rarely cause severe injury.[17]

Geospatial analysis identified clustering of injury-producing crashes--although not detailed in this regression model--near rural transition zones and at key intersections along Highway 10. Previous geospatial analyses similarly have demonstrated that high-speed rural corridors have concentrated patterns of crash risk that can be addressed with engineering interventions, including rumble strips, enhanced signage, or lane separation.[9,18] Although westbound crashes occurred more frequently and were more often associated with injury, geospatial mapping also suggested clusters of fatal events in eastbound travel segments; however, this trend did not reach statistical significance.

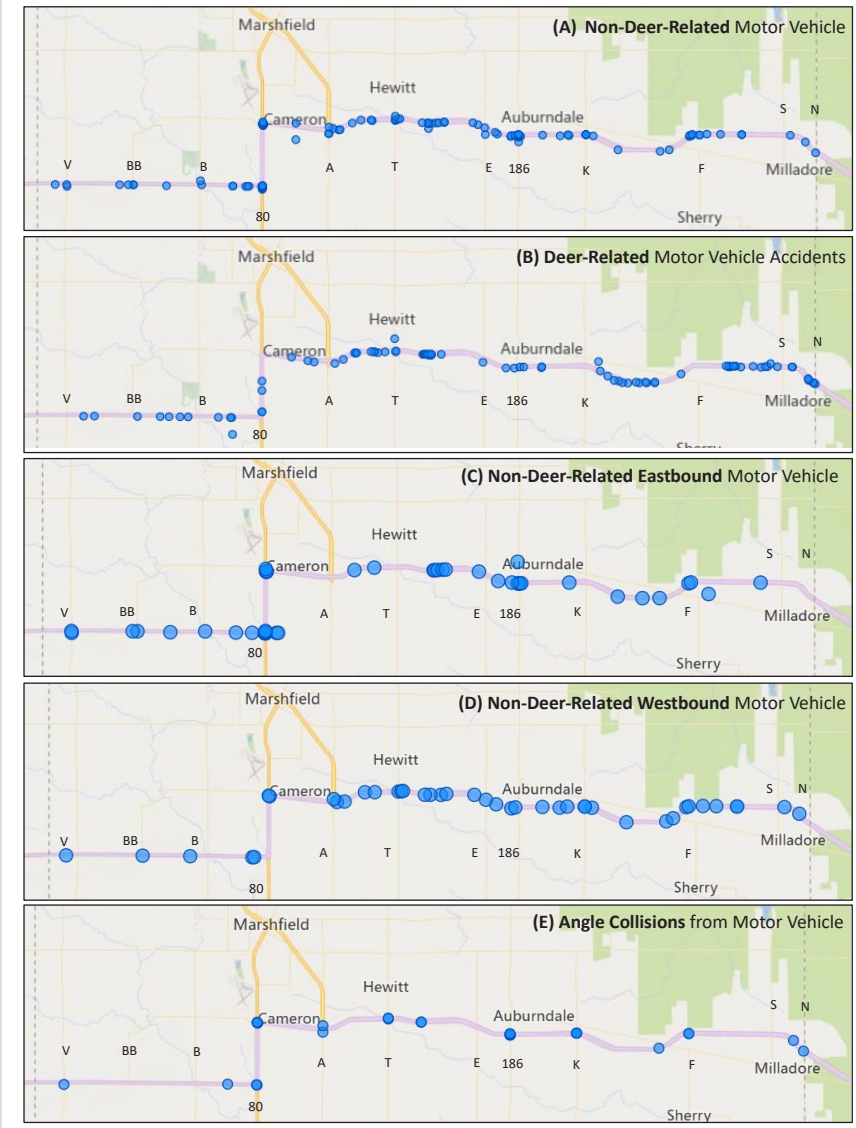
One possible explanation for the higher incidence of westbound crashes is increased commuter traffic entering Marshfield from the south, resulting in greater vehicle density and turning conflicts at key intersections. Further investigation using larger datasets is warranted to better clarify directional risk patterns along rural corridors.

In response to these findings, the study team shared results with transportation planners, local traffic engineers, and representatives from the Wisconsin Department of Transportation (WisDOT) to support corridor-specific safety interventions. Proposed countermeasures currently under consideration include J-turn intersection redesigns, enhanced signage at crossover points, high-reflectivity pavement markings, and rumble-strip installation along high-frequency crash segments. These measures align with Federal Highway Administration (FHWA) guidance on rural road safety improvements, particularly for divided highways with multiple uncontrolled access points.[19,20]

In addition to roadway design, behavioral strategies such as public education campaigns, dynamic warning signs, and targeted enforcement in identified injury hotspots may complement infrastructure improvements. These approaches may be particularly relevant for addressing the wrong-way driving and angle-impact risks observed in this study. The geospatial crash maps developed for this analysis have already been used during stakeholder meetings to support site-specific planning efforts. Future research could further integrate crash-clusters data with EMS response metrics and traffic-flow modeling to enhance rural road safety across Wisconsin.

Overall, this study highlights the need for prevention strategies tailored to specific collision mechanisms, with a particular focus on angle collisions and less common but potentially severe wrong-way driving events. Investments in passive infrastructure, such as median barriers and improved signage, as well as active technologies, including vehicle-based detection and warning systems, may help significantly reduce injuries along high-speed rural corridors.

Figure. Geospatial Distribution of Motor Vehicle Accidents Along Highway 10, Wisconsin, 2018-2023



Limitations

This study has several limitations. First, the data were obtained exclusively from Wood County Sheriff's Office dispatch face sheets and therefore may be affected by reporting inconsistencies, incomplete documentation, or classification errors, particularly for environmental variables such as lighting and weather. Injury status was recorded at the scene or during transport, and outcomes could not be verified using hospital records or trauma registry data, potentially resulting in underestimation of the true injury burden.

Second, the dataset lacked detailed clinical information regarding injury severity, medical interventions, and long-term outcomes, limiting the ability to categorize injuries by severity or health care resource utilization. In addition, toxicology testing was documented inconsistently and was not performed in all cases, limiting assessment of the effects of alcohol or drug impairment on crash outcomes.

Third, although the analysis intentionally focused on a rural segment art of US Highway 10, the findings may not be generalizable to other highway types, urban roads, or regions with different traffic patterns and enforcement practices.

Finally, although the multivariable model adjusted for key confounders, the limited sample size restricted the number of variables that could be included, potentially excluding other relevant predictors such as driver behavior, seat belt use, or vehicle type.

CONCLUSIONS

This analysis of MVs along a rural 4-lane corridor of US Highway 10 found that collision mechanism, particularly angle impacts, was the strongest predictor of injury or fatality, independent of environmental or time-related factors. Although deer-related crashes were common, they rarely resulted in injury, indicating a need to shift rural safety priorities towards high-severity but less frequent events such as angle and wrong-way collisions. These findings support targeted, mechanism-specific interventions, including roadway design changes, improved signage, and driver warning technologies, to reduce injuries on high-speed rural highways. Integration of dispatch-based data with clinical and geospatial analyses may provide a valuable framework for localized traffic-safety planning and injury prevention in rural areas.

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Appendix: Supplemental Table available at www.wmjonline.org

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Understanding the Associations Between Disordered Eating and Drinking Motives and Alcohol-Related Consequences in Community College Students Who Drink Alcohol

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ABSTRACT

Introduction: Disordered eating and alcohol use are common health risk behaviors among college students. Drinking motives and alcohol-related consequences may vary according to whether students experience body image concerns or engage in disordered eating behaviors. Little is known about these relationships among community college students. The purpose of this study was to evaluate the associations between disordered eating, drinking motives, and alcohol-related consequences among community college students who consume alcohol.

Methods: Community college students from 5 campuses in Washington and Wisconsin were recruited. Cross-sectional survey data were used to evaluate associations among body image concerns and disordered eating behaviors, drinking motives, and alcohol-related consequences.

Results: Among 181 participants, 82% were female, 78% were White, and the mean age was 22.9 years [SD, 3.2]. Participants who reported a fear of weight gain were more likely to drink alcohol to cope with anxiety (r=0.17; P=.0280), depression (r=0.17; P=.0214), and conformity-related motives (r=0.17; P=.0264) than those without this fear. Similarly, participants who reported fasting had significantly higher motivation to drink alcohol to cope with anxiety (mean [SD], 9.47 [3.77] vs 8.16 [3.48]; P=.0369) and depression (mean [SD], 17.70 [10.36] vs 13.62 [6.86]; P=.0191). Participants who reported a fear of weight gain and those who engaged in fasting also experienced more alcohol-related consequences (r=0.19, P=.0135 and mean [SD], 8.33 [5.01] vs 4.80 [5.10]; P=.0001), respectively).

Conclusions: Community college students who consume alcohol may benefit from targeted screening and intervention addressing the intersection of disordered eating, drinking motives, and alcohol-related consequences.

INTRODUCTION

Disordered eating and alcohol use are common health risk behaviors among college students. Approximately 7% of college students reported having been diagnosed with an eating disorder.[1] Risk factors and precursors of eating disorders, including body image concerns and disordered eating behaviors (DEBs), are frequently reported by college students. Among college freshmen, 50% reported a desire to lose weight, and 15% reported frequently skipping meals.[2] Compensatory eating behaviors, including self-induced vomiting, use of laxatives or diuretics, and overexercising, are also common among college students. In a study of undergraduate students, nearly half reported engaging in compensatory behaviors in the previous 28 days.[3] Thus, even among students without an eating disorder diagnosis, body image concerns and DEBs are common and concerning.

Despite the importance of these behaviors among college-aged individuals, little is known about disordered eating among young adults attending community colleges. Community colleges are postsecondary schools offering 2-year degrees; approximately 30% of all undergraduate students attend these institutions.[4] Community college students are a unique population that is typically older, more likely to attend school part-time, and more likely to come from racially and ethnically diverse backgrounds.[4] Although studies examining body image concerns and DEBs in community college students are limited, one study found that 32% of students weighed themselves at least weekly and 42% were dissatisfied or very dissatisfied with their weight.[5]

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Alcohol use is another health risk behavior commonly reported by college students. In prior work, the prevalence of past-year alcohol use among community college students was 84%[6] and past-month use was 63%.[7] The prevalence of heavy episodic alcohol use among community college students has been reported between 25% and 47%.[6,8]

Regular alcohol use and binge drinking can have negative effects on physical and mental health, as well as social and academic consequences. Alcohol intoxication can lead to immediate negative consequences by impairing decision-making capacity and impulse control.[9] Among students attending 2- and 4-year colleges, 18% of those who drank alcohol reported doing something they regretted while drinking during the past 12 months.[1] Given the consequences associated with alcohol use among college students, it is important to understand the factors that motivate alcohol consumption. Drinking motives have previously been explored through models that identify the most common reasons individuals consume alcohol, including enhancing positive mood, coping with negative mood, facilitating social interactions, and fitting in.[10,11]

Previous studies have explored the relationship between disordered eating and patterns of alcohol use and alcohol-related consequences among college students attending 4-year universities. For instance, college students who screened positive for eating disorders or engaged in DEBs were significantly more likely to binge drink.[12,13] In addition, undergraduate students who engaged in DEBs were significantly more likely to have positive expectations of alcohol use and to engage in riskier drinking behaviors than those who did not engage in DEBs.[13] Female college students who engaged in purging reported more frequent alcohol use and more negative alcohol-related consequences than those who did not purge.[14]

The relationship between disordered eating, drinking motives, and alcohol-related consequences has not been explored among community college students. As community college students represent a unique population of young adults with potential barriers to accessing care (eg, less access to on-campus health centers),[15] understanding these behaviors may help inform screening practices and intervention efforts.

The objective of this study was to evaluate the associations between disordered eating (body image concerns and DEBs), drinking motives, and alcohol-related consequences among community college students who consume alcohol.

METHODS

This cross-sectional, secondary analysis used data from an online survey of community college students originally conducted as part of a larger intervention study examining substance use and social media use. The study was approved by the University of Wisconsin Health Sciences Institutional Review Board and the 5 participating community colleges (2 in Washington and 3 in Wisconsin).

Table 1. Modified Survey Questions Adapted From the Eating Disorder Diagnostic Scale

Body image concerns questions:	
Over the past 3 months…	• Have you felt fat? • Have you had a definite fear that you might gain weight or become fat? • Has your weight or shape influenced how you judge yourself as a person?
Disordered eating behaviors (DEBs) questions:	
In order to prevent weight gain or counteract the effects of eating, how many times per month on average over the past 3 months have you…	• Made yourself vomit? • Used laxatives or diuretics? • Fasted (skipped at least 2 meals in a row)? • Engaged in more intense exercise specifically to counteract the effects of overeating?
During the past 3 months have there been times when you have eaten what other people would regard as an unusually large amount of food given the circumstances?	
During the times when you ate an unusually large amount of food, did you experience a loss of control?	

Data were collected from March 2018 through December 2019. Eligibility criteria included enrollment in a community college; age 18 to 29 years, English-speaking, ownership of a Facebook account, and current alcohol use (within the previous 28 days) with at least 1 episode of heavy episodic drinking in the previous year (≥4 drinks for females and ≥5 drinks for males on a single occasion).

Recruitment strategies included: (1) sharing study information on community college websites; (2) distributing study information through community college listservs in up to 3 emails; and (3) displaying study flyers in public locations on campus. Interested students completed an online eligibility screening survey and, if eligible, an online consent process. After providing consent, participants were invited to complete an online survey. The survey took approximately 45 to 60 minutes to complete, and participants received a $20 incentive upon completion.

Measures

Demographic information collected included age, sex assigned at birth, race, ethnicity, and state of community college attendance (Washington or Wisconsin).

Disordered Eating: Body Image Concerns and DEBs

A modified version of the Eating Disorder Diagnostic Scale (EDDS)[16] was used to evaluate body image concerns and DEBs. The EDDS is a self-report instrument that aids in the diagnosis of anorexia nervosa, bulimia nervosa, and binge-eating disorder. We examined specific items from the scale relevant to this study (Table 1). Three body image concerns were evaluated: having felt fat, having experienced fear of weight gain or becoming fat, and the extent to which weight or shape influenced self-judgment. Each item was assessed using a Likert scale (0 = not at all to 6 = extremely). DEBs included fasting, self-induced vomiting,

use of laxatives or diuretics, compensatory exercise, and binge eating. Two questions assessed binge eating: (1) whether a binge episode occurred and (2) whether loss of control was experienced during the binge episode. For the remaining DEBs, participants reported the number of occurrences during the previous 3 months. Reporting a behavior at least 4 times per month during the previous 3 months was considered a positive response. This cutoff was extrapolated from the *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition (DSM-5) criteria, which specify that compensatory behaviors occur at least weekly for 3 months.[17]

Drinking Motives

Participants' motives for drinking alcohol were assessed with the validated Modified Drinking Motives Questionnaire-Revised (MDMQ-R).[11] The MDMQ-R is a 28-item questionnaire that assesses drinking motives across 5 factors: social, coping with anxiety, coping with depression, enhancement, and conformity. Items are scored on a 5-point Likert scale (1 = almost never/never to 5 = almost always/always). Scores for each factor were calculated as the sum of the corresponding items. Higher scores indicate a greater likelihood of drinking alcohol for that reason.

Alcohol-related Consequences

Alcohol-related consequences were assessed with the validated Brief Young Adult Alcohol Consequences Questionnaire (B-YAACQ).[18,19] The B-YAACQ is a 24-item yes/no (yes = 1, no = 0) questionnaire that assesses the number of alcohol consequences experienced during the previous month. Consequences range in severity from "While drinking, I have said or done embarrassing things" to "I have neglected my obligations to family, work, or school because of drinking." The total score is calculated as the sum of all items and ranges from 0 to 2, with higher scores indicating a greater number of alcohol-related consequences during the previous month.

Statistical Analysis

Survey responses measured on a Likert scale were summarized using means and standard deviations. Pearson correlation analyses were conducted to evaluate the correlations between body image concerns and drinking motives and alcohol-related consequences. Two-sample *t* tests were used to compare drinking motives and alcohol-related consequences between students who engaged in DEBs and those who did not. All reported *P* values were 2-sided and a significance level of $P < .05$ used to define statistical significance. Statistical analyses were conducted using SAS software, version 9.4 (SAS Institute).

RESULTS

A total of 726 students completed the screening eligibility survey, of whom 254 met study criteria; 181 students completed the survey and were included in this secondary analysis. Of the 181 participants, 148 were assigned female sex at birth (82%), 141 identified as White (78%), 123 attended a community college in Washington (68%), and the mean age was 22.9 years [SD, 3.2] (Table 2).

Table 2. Demographics

Category	Participants (N = 181)
Age, y; mean [SD], median, range	22.9 [3.2], 22, 18-29
Birth sex, n (%)	
Female	148 (82)
Male	33 (18)
Community college state, n (%)	
Wisconsin	57 (31)
Washington	123 (68)
Other	1 (1)
Race, n (%)	
White	141 (78)
African American	3 (2)
Asian	9 (5)
Native American/Pacific Islander	4 (2)
More than one race/other	13 (7)
Not answered	11 (6)
Ethnicity, n (%)	
Hispanic	47 (26)
Non-Hispanic	132 (73)
Not answered	2 (1)

Descriptive Information: Disordered Eating

For body image concerns, the mean scores for having felt fat and fear of weight gain or becoming fat were both 3.8 [SD, 2.1] on a 0- to 6-point Likert scale. The mean score for weight or shape having influenced self-judgment was 4.0 [SD, 2.1]. During the previous 3 months, approximately 54% of participants reported regularly engaging in binge eating, 24% reported fasting, 17% engaged in compensatory exercise, 4% used diuretics or laxatives, and 3% engaged in self-induced vomiting.

Descriptive Information: Drinking Motives and Alcohol-related Consequences

Among all participants, the mean score for drinking for social reasons was 15.0 [SD, 4.9; social factor scale, 5-25], for coping with anxiety was 8.5 [SD, 3.6; anxiety factor scale, 4-20], for coping with depression was 14.6 [SD, 8.6; depression factor scale, 9-45], for enhancement was 11.9 [SD, 4.8; enhancement factor scale, 5-25], and for conformity was 6.9 [SD, 3.2; conformity factor scale, 5-25). Cronbach α values were 0.81 for the social factor scale, 0.73 for the anxiety factor scale, 0.96 for the depression factor scale, 0.85 for the enhancement factor scale, and 0.87 for the conformity factor scale.

For alcohol-related consequences, the overall mean score on the B-YAACQ was 5.7 [SD, 5.3] during the previous month, with scores ranging from 0 to 21 (Table 3). Participants commonly reported having a hangover the morning after drinking (60.8%), having said or done embarrassing things while drinking (54.7%),

Table 3. Participant Responses on the Brief Young Adult Alcohol Consequences Questionnaire

Consequences	No. (%) Endorsing
1. While drinking, I have said or done embarrassing things.	99 (54.7)
2. I have had a hangover (headache, sick stomach) the morning after I had been drinking.	110 (60.8)
3. I have felt very sick to my stomach or thrown up after drinking.	76 (42.0)
4. I often have ended up drinking on nights when I had planned not to drink.	63 (34.8)
5. I have taken foolish risks when I have been drinking.	52 (28.7)
6. I have passed out from drinking.	28 (15.5)
7. I have found that I needed larger amounts of alcohol to feel any effect, or that I could no longer get high or drunk on the amount that used to get me high or drunk.	28 (15.5)
8. When drinking, I have done impulsive things that I regretted later.	60 (33.15)
9. I've not been able to remember large stretches of time while drinking heavily.	34 (18.8)
10. I have driven a car when I knew I had too much to drink to drive safely.	25 (13.8)
11. I have not gone to work or missed classes at school because of drinking, a hangover, or illness caused by drinking.	29 (16.0)
12. My drinking has gotten me into sexual situations I have later regretted.	38 (21.0)
13. I have often found it difficult to limit how much I drink.	29 (16.0)
14. I have become very rude, obnoxious or insulting after drinking.	28 (15.5)
15. I have woken up in an unexpected place after heavy drinking.	13 (7.2)
16. I have felt badly about myself because of my drinking.	47 (26.0)
17. I have had less energy or felt tired because of my drinking.	90 (49.7)
18. The quality of my work or schoolwork has suffered because of my drinking.	29 (16.0)
19. I have spent too much time drinking.	30 (16.6)
20. I have neglected my obligations to family, work or school because of drinking.	33 (18.2)
21. My drinking has created problems between myself and my boyfriend/girlfriend/spouse, parents or other near relatives.	21 (11.6)
22. I have been overweight because of drinking.	23 (12.7)
23. My physical appearance has been harmed by my drinking.	20 (11.0)
24. I have felt like I needed a drink after I'd gotten up (that is, before breakfast).	9 (5.0)

Table 4. Associations Between Body Image Concerns and the Modified Drinking Motives Questionnaire-Revised and Brief Young Adult Alcohol Consequences Questionnaire

	Felt Fat Fat N = 177	Fear of Weight Gain Or Becoming Fat N = 177	Weight Influenced Self-judgement N = 177
MDMQ-R–social	*r* = 0.03 *P* = .6673	*r* = 0.11 *P* = .1405	*r* = 0.11 *P* = .1400
MDMQ-R–anxiety	*r* = 0.12 P=.1111	*r* = 0.17 *P* = .0280	*r* = 0.11 *P* = .1372
MDMQ-R–depression	*r* = 0.11 *P* = .1385	*r* = 0.17 *P* = .0214	*r* = 0.09 *P* = .2558
MDMQ-R–enhancement	*r* = 0.07 *P* = .3317	*r* = 0.08 *P* = .2751	*r* = 0.09 *P* = .2314
MDMQ-R–conformity	*r* = 0.07 *P* = .3509	*r* = 0.17 *P* = .0264	*r* = 0.14 *P* = .0557
BYAAC	*r* = 0.10 *P* = .1821	*r* = 0.19 *P* = .0135	*r* = 0.15 *P* = .0538

Abbreviations: MDMQ-R, Modified Drinking Motives Questionnaire-Revised; BYAAC, Brief Young Adult Alcohol Consequences.

Pearson correlation was used to evaluate associations between body image concerns and drinking motives and alcohol-related consequences.

and having less energy or feeling tired because of drinking (49.7%).

Disordered Eating and Drinking Motives

Participants who reported a fear of weight gain or becoming fat were significantly more likely to drink alcohol to cope with anxiety ($r = 0.17$; $P = .0280$), cope with depression ($r = 0.17$; $P = .0214$), and conform ($r = 0.17$; $P = .0264$) (Table 4) than participants who did not report this fear.

In addition, participants who engaged in fasting were significantly more likely to drink alcohol to cope with anxiety (mean [SD], 9.47 [3.77] vs 8.16 [3.48]; $P = .0369$) and cope with depression (mean [SD], 17.70 [10.36] vs 13.62 [6.86]; $P = .0191$) than those who did not fast.

Other body image concerns (feeling fat and weight or shape influencing self-judgment) and DEBs (binge eating, self-induced vomiting, laxative or diuretic use, and compensatory exercise) were not significantly associated with drinking motives (Table 4).

Disordered Eating and Alcohol-related Consequences

Reporting a fear of weight gain or becoming fat was associated with a higher number of alcohol-related consequences compared with not reporting this fear ($r = 0.19$; $P = .0135$) (Table 4). Fasting was significantly associated with a higher number of alcohol-related consequences than not fasting (mean [SD], 8.33 [5.01] vs 4.80 [5.10]; $P = .0001$).

Other body image concerns (feeling fat and weight or shape influencing self-judgment) and DEBs (binge eating, self-induced vomiting, laxative or diuretic use, and compensatory exercise) were not significantly associated with a higher number of alcohol-related consequences (Table 4).

DISCUSSION

This preliminary study explored the relationship between body image concerns and DEBs and drinking motives and alcohol-related consequences among community college students who consume alcohol. Our results highlight important associations between these health risk behaviors in this understudied population and underscore the importance of effective screening and intervention practices.

Participants in this study commonly reported DEBs, including binge eating and fasting. These findings provide preliminary evi-

dence that DEBs are common among community college students, similar to findings among students attending 4-year colleges.[20,21] Participants reported an average of nearly 6 alcohol-related consequences during the previous month. Prior studies have reported similar findings, with community college students who engaged in binge drinking experiencing higher rates of alcohol-related consequences than those who abstained or did not binge drink.[6]

In this study, participants who reported a fear of weight gain or becoming fat and those who engaged in fasting were both significantly more likely to drink alcohol to cope with symptoms of depression and anxiety. Mental health concerns are common among college students; in a national survey of students attending 2- and 4-year colleges, 35% reported ever having ever been diagnosed with anxiety and 27% reported ever having been diagnosed with depression.[1] Among community college students specifically, 33% of reported health concerns were related to mental health.[22] Prior studies have demonstrated the relationship between eating disorders and mental health conditions; among individuals with eating disorders, nearly two-thirds also have anxiety and more than half have a mood disorder.[23] Our study provides preliminary support for an association between disordered eating and mental health concerns among community college students. Addressing disordered eating and mental health concerns concurrently may reduce the likelihood that students use alcohol as a means of coping and may decrease high-risk alcohol consumption overall.

In examining alcohol-related consequences, participants who reported a fear of weight gain or becoming fat and those who engaged in fasting reported significantly more alcohol-related consequences than other participants. Although not directly assessed in this study, food-restricted alcohol consumption (intentional restriction of food intake before drinking alcohol) is common among college students, with 14% of US college freshmen engaging in this behavior.[24] Restricting food intake before alcohol consumption may lead to more rapid attainment of peak blood alcohol concentrations, increasing the risk of negative alcohol-related effects. Continued research and student education are needed regarding the potential consequences of fasting before consuming alcohol.

Understanding these associations in community college students may be particularly relevant for clinicians who work with young adults attending community colleges, both on campus and in the community. Given the significant negative effects associated with disordered eating and alcohol use, early identification and intervention are crucial. Nationwide data from 165 colleges and universities demonstrated that fewer than half offer eating disorder screening once per year or semester and fewer than 1 in 4 offer year-round screening.[25] Although prior research has demonstrated the benefits of screening and brief intervention for reducing alcohol-related consequences among college students,[26] a study exploring alcohol-related resources on community college campuses found limited staffing and resources.[27] Community colleges face unique barriers to screening and intervention, including limited budgets and increased difficulty engaging off-campus and part-time students.[28] Offering virtual screening and intervention may be a promising strategy for reaching community college students. Validated screenings tools can be delivered electronically to assess disordered eating[29] and alcohol use,[30] with interventions targeted to students at high risk. Preliminary studies suggest that virtual options may be acceptable, feasible, and effective for reducing alcohol use and alcohol-related consequences among community college students.[28]

Limitations

Limitations of this study include the small sample size, which made it difficult to evaluate associations involving less prevalent DEBs and drinking motives and alcohol-related consequences. In addition, most participants were female and White, limiting our ability to explore differences by sex and race. However, this preliminary study provides a foundation for larger studies evaluating these behaviors in this understudied population.

The study population was limited to 2 geographic regions and therefore may not be nationally representative. However, it provides insight into the experiences of community college students in Wisconsin and a geographically distinct state. Because of the cross-sectional study design, we were able to establish associations but not causation. In addition, the study design did not allow assessment of changes in these behaviors and their relationships over time.

This study was limited to students who consume alcohol and therefore may not be generalizable to all community college students. However, this was an intentional design element that allowed the study to focus on students with alcohol use experience. Future studies should consider including community college students who do not consume alcohol should consider longitudinal follow-up to further evaluate these relationships.

In addition, because the full EDDS was not administered in the original survey, analyses focused on selected items rather than the total questionnaire score. However, questions were selected a priori to examine body image concerns and DEBs in this population. Despite these limitations, this preliminary study contributes to understanding the intersection between disordered eating, drinking motives, and alcohol-related consequences among community college students.

CONCLUSIONS

Overall, these findings provide preliminary evidence of associations between body image concerns and DEBs and drinking motives and alcohol-related consequences among community college students who consume alcohol. Understanding the connection between disordered eating and drinking motives, including drinking to cope with mental health concerns, may help inform

interventions that address these co-occurring behaviors. Although recommendations already exist to screen college students for alcohol use and disordered eating, barriers to implementation remain, particularly on community college campuses. Further research is needed to identify and deliver effective interventions for community college students. Future studies should explore associations between disordered eating, motives for drinking alcohol, and alcohol-related consequences in larger samples of community college students to confirm and expand upon our findings.

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Use of Hypoglossal Nerve Stimulation for Obstructive Sleep Apnea in Adults With Intellectual and Developmental Disabilities

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ABSTRACT

Introduction: The objective of this study was to assess the safety, efficacy, and patient satisfaction of hypoglossal nerve stimulation (HNS) therapy as an alternative to continuous positive airway pressure therapy for obstructive sleep apnea in adults with intellectual and developmental disabilities (IDDs), including trisomy 21 and cerebral palsy.

Methods: We conducted an observational study of 4 adults with IDDs and moderate to severe obstructive sleep apnea who underwent implantation of an HNS device. Patient demographic characteristics, device usage, obstructive sleep apnea and daytime sleepiness outcomes, and patient satisfaction scores were retrospectively reviewed and analyzed.

Results: The mean adherence rate was 92.3%. The mean [SD] pretreatment apnea-hypopnea index was 39.0 [16.7] events per hour, which decreased to 8.5 [4.7] event per hour after treatment, representing a mean [SD] reduction of 77.5% [12.9%]. Epworth Sleepiness Scale scores decreased in 2 patients, were unchanged in 1 patient, and increased in 1 patient. Patient-reported satisfaction was high, with mean [SD] scores of 5.0 [0.0] for comfort, ease of deactivation, and effectiveness and 4.5 [0.6] for ease of activation.

Conclusions: Treatment of obstructive sleep apnea with HNS was associated with decreased apnea-hypopnea index values and was well tolerated among adults with IDDs, suggesting that it may be a viable alternative to continuous positive airway pressure therapy for patients who cannot tolerate conventional treatment. However, the variable Epworth Sleepiness Scale findings and small sample highlight the need for larger studies with long-term follow-up to further evaluate the safety and effectiveness of HNS in this population.

INTRODUCTION

Obstructive sleep apnea (OSA) is a prevalent sleep disorder that affects individuals of all ages. This condition is marked by repeated episodes in which the upper airway is either completely or partially blocked during sleep. Notably, the incidence of OSA is higher among patients with intellectual and developmental disabilities (IDDs), such as trisomy 21 and cerebral palsy, than in the general population. The prevalence of OSA ranges from 30% to 80% among individuals with trisomy 21 and as high as 54% among those with cerebral palsy.[1-5] OSA symptoms are generally more severe in patients with IDDs, and complications occur more frequently, negatively affecting quality of life.[2,6]

For many patients with IDDs, continuous positive airway pressure (CPAP) therapy is the first-line recommended treatment for moderate to severe OSA. Although up to 80% of patients who initiate CPAP therapy tolerate it well,[7] studies including patients with IDDs are limited, and a considerable proportion cannot adhere to CPAP therapy.[8] Reasons for poor adherence include anxiety, claustrophobia, skin irritation, and mask-related discomfort. Additionally, sensory sensitivities, cognitive impairments, and anatomic differences may complicate mask fitting.

Hypoglossal nerve stimulation (HNS) therapy is a novel alternative to CPAP for the treatment of OSA and has demonstrated promising results in the general population,[9] although it has not been extensively studied in adults with IDDs. With HNS therapy,

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a surgically implanted device engages the hypoglossal nerve during sleep. Most HNS devices employ a dual-component system consisting of a sensing electrode positioned between the intercostal muscles and a stimulation lead wrapped around the anterior branches of the hypoglossal nerve. This configuration allows for the delivery of electrical impulses to the muscles responsible for tongue protrusion during inspiration, which effectively mitigates upper airway obstruction.

Two previously published case series highlighted the efficacy of HNS for adolescents with trisomy 21 who had severe OSA despite adenotonsillectomy and were intolerant of positive airway pressure therapy.[10,11] HNS treatment was associated with an acceptable adverse event profile and significant improvements in both therapy response and quality of life for 42 adolescents.[10] Additionally, HNS was well received and effective.[11] Therefore, HNS may represent a promising treatment option for patients with IDDs who cannot tolerate CPAP therapy.

Despite recent advancements in HNS therapy, research regarding its safety and efficacy in adults with IDDs remains limited. Therefore, we assessed HNS treatment in adults with IDDs and moderate to severe OSA who could not tolerate CPAP therapy. Specifically, we evaluated the safety and efficacy of HNS, as well as the device's operational parameters, patient usage, adherence, and satisfaction. These findings may clarify the role of HNS as a treatment option for adults with IDDs and OSA.

METHODS

Ethical Considerations and Approval

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was deemed exempt by our institutional review board. The retrospective nature of the study ensured that no interference with patient care occurred, and all data were anonymized to protect patient confidentiality. All patients or their surrogate decision-makers provided authorization for the research use of their health records.

Study Design and Participants

We retrospectively reviewed the electronic health records of adult patients with IDDs who underwent implantation of an HNS device (Inspire II Implantable Pulse Generator, Model 3024; Inspire Medical Systems, Inc) within our regional health system in the Midwestern United States from November 2020 through January 2024. Inclusion criteria included adults (aged ≥18 years) with an IDD who underwent HNS device implantation for management of moderate to severe OSA, as determined by polysomnography or equivalent sleep study. Patients were identified using the following *Current Procedural Terminology* codes: 64582, 64568, and 0466T. IDDs were identified using the following search terms: "cognitive dysfunction," "Down syndrome," "cerebral palsy," "intellectual disability," "developmental disorder, unspecified," and "chromosomal deletion." Exclusion criteria included age younger than 18 years, absence of an IDD, mild OSA or another sleep disorder unrelated to OSA, or no HNS device implantation procedure.

OSA severity was quantified with apnea-hypopnea index (AHI), measured as events per hour and categorized as mild (5 to <15), moderate (15 to <30), or severe (≥30). Daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS), with scores of 11 or higher indicating excessive daytime sleepiness. ESS scores were used to assess symptom burden but were not used to determine treatment eligibility. HNS was pursued only after shared decision-making, confirmation of eligibility according to established criteria, and discussion of alternative therapies, including oral appliance therapy, which were deemed unsuitable because of disease severity or tolerability limitations.

Data Collection

Data were manually abstracted from health records accessed through the pulmonary, critical care, and sleep medicine departments. Abstracted variables included demographic characteristics (ie, age, sex, and body mass index [BMI] values), adverse events, and follow-up outcomes. Outcome measures included quantitative and qualitative assessments of HNS efficacy and patient satisfaction, device usage data (pause duration and voltage requirements), and immediate and long-term adverse events associated with the device. ESS scores and patient satisfaction data were collected via patient self-report and/or family member proxy report, depending on cognitive status.

Data Analysis

To evaluate HNS efficacy, we analyzed AHI values, ESS scores, and device usage data. AHI and ESS scores were obtained from assessments performed within 60 days before HNS device implantation (pretreatment). The device was activated 30 days after implantation. Posttreatment ESS scores were recorded 90 days after implantation, and posttreatment AHI values were recorded 120 days after implantation.

Patient satisfaction was assessed using a 4-item questionnaire administered 4 months after implantation. Responses were scored on a 5-point Likert scale, with 1 indicating poor and 5 indicating excellent.

All data analyses were descriptive. Data are presented as counts and percentages or as mean [SD] and median (range). The percentage decrease in AHI values was calculated as the difference between pretreatment and posttreatment values divided by the pretreatment value. Adherence was calculated as the percentage of nights during a 30-day period in which the HNS device was used for more than 4 hours

RESULTS

We identified 4 adult patients with IDDs and moderate to severe OSA who underwent HNS implantation at our regional hospital during the study period; 3 (75%) were men and 1 (25%) was a

woman. One patient had trisomy 21 (Down syndrome), 1 had Asperger syndrome, 1 had cerebral palsy, and 1 had Koolen-de Vries syndrome. The mean [SD] age was 44.8 [5.9] years, with a median (range) of 44 (39-52) years. The mean [SD] BMI value was 32.0 [1.5], with a median (range) of 32.2 (30.1-33.5).

Usage and Adherence

The patient with Koolen-de Vries syndrome and the patient with Asperger syndrome were able to turn on and use the HNS device independently, whereas the patients with Down syndrome and cerebral palsy required assistance from family members. All patients used the device consistently each night, with a mean [SD] nightly usage of 6.6 [0.9] hours. The mean adherence rate was 92.3%, and the median adherence rate was 90.0%.

Operational Parameters

The implanted HNS devices required relatively low stimulation voltages and had minimal pause durations (Table 1). The mean [SD] voltage requirement was 2.2 [0.7] V, with a median (range) of 1.9 (1.8-3.3) V. The mean [SD] pause duration was 0.25 [0.50] second, with a median (range) of 0.00 (0.00-1.00) second.

AHI Outcomes

The mean [SD] pretreatment AHI was 39.0 [16.7] events per hour, whereas the mean [SD] posttreatment AHI was 8.5 [4.7] events per hour (Table 2). This constituted a mean [SD] decrease of 77.5% [12.9%]. The median (range) pretreatment AHI was 31.5 (29.0-64.0) events per hour, compared with 8.5 (4.0-13.0) events per hour after treatment.

ESS Scores

For the patient with Koolen-de Vries syndrome, ESS data were primarily self-reported and corroborated by her parents. The patient with Asperger syndrome completed the ESS independently. For the patients with Down syndrome and cerebral palsy, ESS data were obtained through family-member proxy reports.

The mean [SD] ESS score decreased from 10.5 [7.3] before treatment to 5.8 [4.9] after treatment (Table 3). Median (range) scores were 12.5 (0.0-17.0) before treatment and 5.0 (1.0-12.0) after treatment, highlighting substantial variability among the patients. Two patients (1 with Koolen-de Vries syndrome and 1 with cerebral palsy) had decreased ESS scores following HNS device implantation, whereas the score was unchanged in the patient with trisomy 21 and increased in the patient with Asperger syndrome.

Patient-Reported Satisfaction

For the patient with Koolen-de Vries syndrome, satisfaction data were reported primarily by her parents. The patient with Asperger syndrome provided satisfaction data independently. For the patients with Down syndrome and cerebral palsy, satisfaction data were obtained through family-member proxy reports.

Table 1. Operational Parameters of the Implanted HNS Device

Patient	Mean Pause Duration, s	Voltage Requirement, V
1	0.00	1.9
2	0.00	1.8
3	0.00	1.8
4	1.00	3.3
Mean [SD]	0.25 [0.50]	2.2 [0.7]
Median (range)	0.00 (0.00–1.00)	1.9 (1.8-3.3)

Abbreviation: HNS, hypoglossal nerve stimulation; s, second; V, volts.

Table 2. AHI Values Before and After HNS Therapy

		AHI, events/h		
Patient	IDD	Pretreatment	Posttreatment	Decrease, %
1	Trisomy 21	64.0	13.0	79.7
2	Asperger syndrome	31.0	4.0	87.1
3	Cerebral palsy	32.0	5.0	84.4
4	Koolen-de Vries syndrome	29.0	12.0	58.6
Mean [SD]		39.0 [16.7]	8.5 [4.7]	77.5 [12.9]
Median (range)		31.5 (29.0–64.0)	8.5 (4.0–13.0)	82.1 (58.6–87.1)

Abbreviations: AHI, apnea-hypopnea index; HNS, hypoglossal nerve stimulation; h, hour; IDD, intellectual and developmental disability.

Table 3. ESS Scores Before and After HNS Therapy

		ESS score	
Patient	IDD	Pretreatment	Posttreatment
1	Trisomy 21	12.0	12.0
2	Asperger syndrome	0.0	1.0
3	Cerebral palsy	17.0	7.0
4	Koolen-de Vries syndrome	13.0	3.0
Mean [SD]		10.5 [7.3]	5.8 [4.9]
Median (range)		12.5 (0.0–17.0)	5.0 (1.0–12.0)

Abbreviations: ESS, Epworth Sleepiness Scale; HNS, hypoglossal nerve stimulation; IDD, intellectual and developmental disability.

No short-term or long-term adverse events, including infection, pain, hematoma or seroma, pneumothorax, device migration and lead issues, stimulation-related discomfort, neuropraxia, or transient tongue paresis, were noted.

All patients reported a high level of satisfaction with the HNS device. Mean [SD] scores were 5.0 [0.0], the maximum possible score, for comfort, ease of deactivation, and effectiveness compared with CPAP therapy (Table 4). The only questionnaire item that did not receive the maximum score from all patients was ease of activation, which had a mean [SD] score of 4.5 [0.6].

DISCUSSION

In this small observational study, we investigated the use of HNS for the treatment of moderate to severe OSA among adults with IDDs. Our findings underscore the potential of HNS as an effec-

tive and patient-preferred alternative to CPAP therapy, particularly for individuals with IDDs, who have a higher prevalence and severity of OSA and often experience challenges using conventional OSA therapies.

Table 4. Posttreatment Patient Satisfaction Scores[a]

	Patient				
Question	1	2	3	4	Mean [SD]
How comfortable is the device?	5.0	5.0	5.0	5.0	5.0 [0.0]
How easy is it to activate the device?	5.0	4.0	5.0	4.0	4.5 [0.6]
How easy is it to deactivate the device?	5.0	5.0	5.0	5.0	5.0 [0.0]
How effective is the device compared to CPAP?	5.0	5.0	5.0	5.0	5.0 [0.0]

Abbreviation: CPAP, continuous positive airway pressure.
[a]Responses were reported with a 5-point Likert scale in which a score of 1.0 represents poor and a score of 5.0 represents excellent.

The considerable reduction in AHI values is consistent with previous evidence supporting the effectiveness of HNS in mitigating upper airway obstruction during sleep, not only in the general population but also in patients with trisomy 21 and potentially other IDDs.[12-14] Importantly, the high patient satisfaction scores relating to comfort, ease of use, and perceived effectiveness highlight the potential of HNS to improve quality of life in this patient population.

The first reported case of HNS device implantation in an adolescent involved a 14-year-old patient with Down syndrome and a baseline AHI of 49 events per hour.[12] After device implantation, the AHI decreased to 3.4 events per hour. The patient's voltage requirement was 1.4 V, similar to the voltage requirements observed in our cohort (mean, 2.2 V; median, 1.9 V).

In a large cohort of adults, adherence to HNS was generally high, with mean nightly use of approximately 5 to 6 hours at 12 months after implantation.[15] Early acclimatization is also typically favorable in neurotypical adults, with an objective early-use study reporting average nightly use exceeding 7 hours during the first month after activation.[16] Factors that may have reduced effective nightly use included stimulation-related discomfort, particularly during titration to higher therapeutic amplitudes, sleep disruption or arousals, difficulty acclimating to therapy, insomnia symptoms, and perceived lack of benefit when residual sleep-disordered breathing persisted.

Few studies have evaluated HNS efficacy in patients with Down syndrome. Although these patients often require substantial caregiver involvement, adherence can be high when patients and families are well supported. In a multicenter trial including adolescents with Down syndrome, mean [SD] nightly HNS use was 9.0 [1.8] hours, and 95.2% of patients used the device for at least 4 hours per night on 70% or more of nights.[10] Similarly, in a small prospective trial including adults with Down syndrome, objective adherence exceeded 4 hours on nearly all nights shortly after HNS activation, with a median nightly use of more than 8 hours.[17] Those findings suggest that caregiver engagement may mitigate certain adherence barriers and underscore the importance of counseling regarding acclimatization, troubleshooting, and realistic expectations for incremental programming changes over time.

The therapeutic efficacy and tolerability of HNS are closely related to device programming parameters—particularly stimulation amplitude (voltage), which is adjusted to promote tongue protrusion and improve airway patency while minimizing arousals and discomfort. In clinical practice, higher amplitudes may be required to optimize control of obstructive events; however, higher settings may be less comfortable and contribute to interruptions in use during sleep and reduced adherence. Common early, typically transient adverse effects include tongue or oral discomfort and stimulation-related sensations. Among a cohort of adolescents with Down syndrome, temporary tongue or oral discomfort was the most frequently reported complication.[10] Although no published studies have demonstrated that higher HNS voltage settings directly contribute to tongue discomfort or pose challenges with tolerance and adherence, this remains a potential concern, particularly in patients with IDDs. Nevertheless, the minimal pause durations and low-voltage requirements observed in our cohort suggest that HNS was well tolerated and operationally efficient in this population.

ESS scores decreased after HNS device implantation in 2 patients. The patient with Koolen-de Vries syndrome had a substantial decrease, from 13 to 3, and the patient with cerebral palsy had a decrease from 17 to 7. However, the patient with trisomy 21 had no change in ESS score, and the patient with Asperger syndrome had a marginal increase from 0 to 1. These variable findings suggest that ESS may not be a fully reliable measure of daytime sleepiness in patients with IDDs because of differences in baseline characteristics and the subjective nature of self-reported or proxy-reported assessments. Additionally, the small sample size limited our ability to identify consistent changes. Therefore, these findings should be interpreted with caution. Future studies with larger cohorts and objective measures of daytime sleepiness and alertness are needed to better characterize the effects of HNS on daytime symptoms in patients with IDDs.

Although our findings are promising, several limitations warrant consideration. First, the retrospective design limits the generalizability of the results. Second, the absence of a control group and reliance on self-reported satisfaction measures may have introduced bias. Finally, the relatively short follow-up period precludes insights into long-term efficacy, adherence, and potential sequelae of HNS therapy. Despite these limitations, our findings provide valuable preliminary data regarding the use of HNS in a population with unique therapeutic challenges. Future research should aim for larger, randomized controlled trials with long-term fol-

low-up data to validate the efficacy and safety of HNS in adults with IDDs. Additional research examining the effects of HNS on other aspects of sleep quality, daily functioning, and the economic implications of adopting this technology in clinical practice may also be valuable.

CONCLUSIONS

The preliminary findings of this observational study suggest that HNS may be an effective and well-tolerated treatment alternative for moderate to severe OSA in adults with IDDs. High patient-reported satisfaction, favorable adherence, and improvements in clinical outcomes suggest that HNS may be a reasonable option for patients who cannot tolerate CPAP therapy. However, larger prospective studies with control groups and long-term follow-up are needed to confirm these findings and to establish HNS as a standard treatment for OSA in this population.

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Incidence of Electrolyte Abnormalities in Emergency Department Patients Presenting With Ethanol Intoxication

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ABSTRACT

Introduction: Ethanol intoxication is the most common substance use-related emergency department (ED) presentation in the United States, and the proportion of ethanol-related ED visits is increasing. Although ethanol ingestion can lead to electrolyte abnormalities, ethanol intoxication is often diagnosed on the basis of physical examination, and clinicians frequently defer laboratory testing in clinically intoxicated patients. The purpose of this study was to describe the incidence of electrolyte abnormalities in a cohort of patients evaluated in the ED for ethanol intoxication.

Methods: A retrospective cohort study was performed on Veteran Affairs (VA) ED visit data from 2010 through 2019. Eligible encounters included ED visits with a serum ethanol concentration greater than 50 mg/dL and available electrolyte results.

Results: A total of 223456 encounters involving 83178 patients were included in the analysis. The study population was 94.2% male, and the median age was 55 years. Overall, 48.8% of encounters had at least 1 electrolyte abnormality, and 2.9% had a severe electrolyte abnormality. Hypokalemia was associated with hypomagnesemia (OR, 2.64; 95% CI, 2.56-2.73) and hypophosphatemia (OR, 2.51; 95% CI, 2.21-2.84).

Discussion: The prevalence of electrolyte derangements was substantial among patients with ethanol intoxication. Abnormalities in commonly measured electrolytes were associated with abnormalities in less frequently measured electrolytes.

Conclusions: Routine serum chemistry testing should be considered in patients presenting with ethanol-related complaints to screen for electrolyte abnormalities. In particular, hypokalemia should increase concern for hypomagnesemia and hypophosphatemia.

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INTRODUCTION

Approximately 8.6 million emergency department (ED) visits in the United States were related to ethanol use from January 2021 through September 2023, with 80% attributed solely to ethanol without coingestants.[1] Multiple electrolyte abnormalities are associated with both acute and chronic ethanol ingestion, including hypoglycemia, hyponatremia, hypokalemia, hypomagnesemia, hypocalcemia, and hypophosphatemia.[2] These electrolyte abnormalities can have serious consequences, as demonstrated by a recent case report of central pontine myelinolysis after sodium correction in a patient with chronic ethanol use.[3] Despite the prevalence of electrolyte abnormalities, emergency medicine providers may be hesitant to obtain serum chemistries in patients presenting with presumed ethanol ingestion because of the perception that these presentations are low acuity[4] or concern for prolonging ED length of stay.[5]

This study aimed to better define the incidence of electrolyte abnormalities and identify factors associated with more severe electrolyte derangements among patients presenting with ethanol ingestion. We performed a retrospective study of patients presenting to Veterans Affairs (VA) EDs from 2010 through 2019 for ethanol intoxication.

METHODS

An automated Microsoft Structured Query Language query was conducted using the VA Corporate Data Warehouse to identify

Table 1. Demographics Characteristics of Study Population, N = 83 178

Sex	n (%)
Male	78 346 (94)
Female	4832 (6)
Race	
White	54 585 (66)
Black	20 852 (25)
Other	2096 (3)
Unknown	5645 (7)
Ethnicity	
Non-Hispanic	74 244 (89)
Hispanic	5101 (6)
Unknown	3833 (5)
Median age	55 (IQR 45-62)

Abbreviation: IQR, interquartile range.

all ED visits within the VA hospital network from January 1, 2010, through December 31, 2019, as previously reported.[6] Any ED visit at which the patient had a serum ethanol concentration greater than 50 mg/dL was included. Visits without available serum chemistry data were excluded.

Demographic data, including age, sex, race, and ethnicity, were collected. Laboratory measurements of serum ethanol, sodium, potassium, calcium, magnesium, phosphorus, glucose, and creatinine were obtained. ED disposition data also were obtained. Glucose and electrolyte abnormalities were categorized as mild, moderate, or severe based on predefined cutoffs shown in Table 2. Calcium values were not corrected for serum albumin. Hypoglycemia was defined as a serum glucose concentration below 70 mg/dL.

Descriptive statistics and odds ratio were calculated for variables of interest. To quantify effect size, odds ratios were converted to Cohen's *d* using established methods, with larger absolute values indicating greater effect magnitude. The primary outcome was a composite of any electrolyte abnormality or hypoglycemia. Secondary outcomes included any severe electrolyte abnormality, hospital admission, and disposition among admitted patients (medical admission, including intensive care unit admission, vs hospital discharge or psychiatric admission). We also examined rates of electrolyte abnormalities among patients with renal insufficiency, defined as a serum creatinine concentration greater than 1.4 mg/dL, versus those with a creatinine concentration of 1.4 mg/dL or less. A sensitivity analysis excluding patients with a creatinine greater than 1.4 mg/dL also was performed. This study was approved by the VA Milwaukee Institutional Review Board (protocol #1598912).

RESULTS

There were 223 456 distinct encounters during the study period, encompassing 83 178 individual patients. The median age was 55 years, and 109 119 encounters (48.8%) resulted in hospital admission. Most patients were male (94.2%), White (65.6%), and non-Hispanic (89.3%). Patients younger than 60 years accounted for 64.3% of visits. Additional demographic characteristics are shown in Table 1.

Table 2. Electrolyte and Glucose Abnormalities

Electrolyte Abnormalities	**N**	**%**
Total sodium assays	220 210	
Low (< 135 mEq/L)	30 251	13.7
Mild (130–134 mEq/L)	21 876	9.9
Moderate (120–129 mEq/L)	7754	3.5
Severe (< 120 mEq/L)	621	0.3
High (> 145 mEq/L)	14 367	6.5
Mild (145–149 mEq/L)	13 486	6.1
Moderate (150–159 mEq/L)	873	0.4
Severe (> 160 mEq/L)	8	<0.01
Total potassium assays	219 314	
Low (< 3.5 mEq/L)	43 686	19.9
Mild (3.0–3.4 mEq/L)	37 620	17.2
Moderate (2.5–2.9 mEq/L)	5450	2.5
Severe (< 2.5 mEq/L)	616	0.3
High (> 5.0 mEq/L)	2474	1.1
Mild (5.0–5.4 mEq/L)	1610	0.7
Moderate (5.5–5.9 mEq/L)	600	0.3
Severe (> 6 mEq/L)	264	0.1
Total calcium assays	198 555	
Low (< 8.5 mg/dL)	39 949	20.1
Mild (8.0–8.4 mg/dL)	25 773	13.0
Moderate (7.0–7.9 mg/dL)	10 589	5.3
Severe (< 7.0 mg/dL)	3627	1.8
Total magnesium assays	118 120	
Low (< 1.7 mg/dL)	20 452	17.3
Mild (1.5–1.6 mg/dL)	11 962	10.1
Moderate (1.2–1.4 mg/dL)	6667	5.6
Severe (< 1.2 mg/dL)	1823	1.5
Total phosphorus assays	11 124	
Low (< 2.5 mg/dL)	1217	10.9
Mild (2.0–2.4 mg/dL)	856	7.7
Moderate (1.0–1.9 mg/dL)	346	3.1
Severe (< 1.0 mg/dL)	15	0.1
Glucose Abnormalities	**N**	**%**
Total glucose assays	214 661	
Low (< 70 mg/dL)	6706	3.1
Severe (< 55 mg/dL)	1853	0.9
High (> 200 mg/dL)	9450	4.4
> 300 mg/dL	3645	1.7
> 500 mg/dL	532	0.2

The prevalence of various electrolyte abnormalities is summarized in Table 2. Sodium, potassium, calcium, magnesium, and phosphorus concentrations were obtained in 98.6%, 98.2%, 88.9%, 52.9%, and 5.0% of all encounters, respectively. Overall, 48.8% of tests performed identified at least 1 electrolyte abnormality, and 2.9% demonstrated a severe electrolyte abnormality (n = 6529). There were 12 467 encounters with a severely elevated ethanol concentration (> 400 mg/dL). Serum creatinine values were available for 83.5% of encounters, and renal insufficiency was identified in 4.4%.

Hyponatremia and hypernatremia were observed in 30 251 and 14 367 sodium assays, respectively. Severe hyponatremia was present in 621 assays, whereas severe hypernatremia occurred in 8 assays. Hypokalemia occurred in 43 686 cases, including 616 cases of severe hypokalemia. Serum magnesium concentrations were measured in 26 230 (60%) of hypokalemia cases. Hyperkalemia occurred in 2474 potassium assays, including 264 cases of severe hyperkalemia.

Table 3. Assessment of Factors Associated With Electrolyte Abnormalities

Variable (n)	Any electrolyte abnormality, %	Odds Ratio (95% CI)	Severe electrolyte abnormality, %	Odds Ratio (95% CI)
Age > 60 years (75 099)	55.9	1.41 (1.39–1.44)	3.38	1.48 (1.41–1.56)
10+ ED visits (39 468)	54.1	1.21 (1.18–1.23)	2.72	1.02 (0.96–1.09)
Serum ethanol > 400 mg/dL (12 467)	59.3	1.47 (1.42–1.53)	2.54	0.94 (0.85–1.06)
Serum creatinine > 1.4 mg/dL (8228)	59.2	1.55 (1.48–1.62)	9.7	3.94 (3.64–4.26)
Female (4832)	50.1	1.02 (0.99–1.07)	2.60	0.97 (0.86–1.10)
Admitted to hospital (108 952)	54.9	1.64 (1.62–1.67)	74.2	3.10 (2.93–3.29)

Abbreviation: ED, emergency department.

Among calcium assays, 39 949 were consistent with hypocalcemia, including 3627 cases of severe hypocalcemia. Hypomagnesemia was present in 20 452 cases, of which 1823 were severe. Among phosphorus assays, 1217 were consistent with hypophosphatemia, including 15 cases of severe hypophosphatemia.

Patients with hypokalemia were more likely to have hypomagnesemia (OR, 2.64; 95% CI, 2.56-2.73; Cohen's $d = 0.535$) and hypophosphatemia (OR, 2.51; 95% CI, 2.21-2.84; $d = 0.507$). In contrast, patients with hyponatremia were less likely to have hypomagnesemia (OR, 0.37; 95% CI, 0.35-0.40; $d = 0.548$) or hypophosphatemia (OR, 0.35; 95% CI, 0.27-0.47; $d = 0.579$).

Serum glucose concentrations are summarized in Table 2. Glucose concentrations were obtained in 96.1% of all encounters. Among all glucose assays, 6706 were consistent with hypoglycemia, including 1853 cases of severe hypoglycemia. Hyperglycemia was identified in 9450 samples, with 3645 and 532 glucose concentrations exceeding 300 and 500 mg/dL, respectively.

Several factors were associated with electrolyte abnormalities (Table 3). Patients with 10 or more study-related visits during the 10-year period accounted for 39 468 encounters (17.7%). These patients were more likely to have an electrolyte abnormality than patients with fewer visits (OR, 1.21; 95% CI, 1.18-1.23; $d = 0.105$). However, frequent ED visits were not associated with severe electrolyte abnormalities (OR, 1.02; 95% CI, 0.96-1.09; $d = 0.011$).

Similarly, patients with a severely elevated ethanol concentration (> 400 mg/dL) were more likely to have an electrolyte abnormality than those with lower ethanol concentrations (59.3% vs 49.7%; OR, 1.47; 95% CI,1.42-1.53; $d = 0.212$) but were not more likely to have a severe electrolyte abnormality (OR, 0.95; 95% CI, 0.85-1.06; $d = 0.014$).

Patients aged 60 years or older were more likely than those younger than 60 years to have any electrolyte abnormality (55.9% vs 47.4%; OR, 1.41, 95% CI, 1.39-1.44; $d = 0.189$) and any severe electrolyte abnormality (3.38% vs 2.31%; OR, 1.48; 95% CI, 1.41-1.56; $d = 0.216$). Older patients also were less likely to have an ethanol concentration greater than 400 mg/dL (OR, 0.39; 95% CI, 0.36-0.40; $d = 0.519$). Sex was not significantly associated with electrolyte abnormalities. Patients with electrolyte abnormalities were more likely to be admitted to the hospital (OR, 1.64; 95% CI, 1.62-1.67; $d = 0.273$), particularly those with severe electrolyte abnormalities (OR, 3.10; 95% CI, 2.93-3.29; $d = 0.624$).

In a sensitivity analysis excluding 8228 encounters involving patients with renal insufficiency, results were similar to those of the primary analysis, except that older age was no longer associated with electrolyte abnormalities or severe electrolyte abnormalities.

DISCUSSION

Alcohol was involved in an estimated 1.8% of ED visits in the United States in 2020 (52 174 507 total visits), and there is a global trend toward increased hospitalization for alcohol-related reasons.[7,8] In this study, nearly half of patients presenting with ethanol intoxication who underwent laboratory testing had at least 1 electrolyte abnormality. Although patients who underwent laboratory testing may have been more likely to have abnormalities than those who did not, it is noteworthy that most intoxication cases in the database from which this cohort was derived were identified by ethanol assays (78.3%) without associated ICD-9 or ICD-10 codes related to alcohol intoxication. Therefore, the incidence of these abnormalities is likely substantial despite the potential for selection bias.

Our findings are generally consistent with existing data regarding the most common electrolyte abnormalities among patients with alcohol use disorder,[9] although previous studies have primarily focused on long-term ethanol use rather than acute ethanol intoxication. A single-center study from Austria evaluating laboratory abnormalities in acute ethanol intoxication found elevated serum electrolytes more frequently than electrolyte deficiencies. Hypernatremia, hyperchloremia, and hypermagnesemia were the most common abnormalities, occurring in 41%, 21%, 17% of patients, respectively. In contrast, hypokalemia and hypophosphatemia were each identified in fewer than 5% patients.[10] The authors speculated that suppression of antidiuretic hormone release and subsequent polyuria may have contributed to the high prevalence of hypernatremia and hyperchloremia and suggested that electrolyte deficiencies may be less common when laboratory testing is performed shortly after acute ingestion.[10,11]

The marked differences between their findings and ours may have several explanations. First, our study included a substantially larger cohort drawn from a national health care system. Second, many patients in our cohort had multiple ED visits, suggesting a population with chronic ethanol intoxication.

Many clinicians are reluctant to pursue diagnostic workup in patients who are clinically intoxicated because observation periods, particularly when medicolegal concerns arise regarding discharge of patients with markedly elevated ethanol concentrations, can place additional demands on EDs already facing boarding and staffing challenges.[4] As a result, discharging patients once they appear clinically sober may be preferred. However, studies have shown that physicians are often inaccurate when estimating blood alcohol concentrations based on clinical assessment alone.[12] Accordingly, deferring laboratory testing in patients presenting with ethanol-related complaints may result in missed electrolyte abnormalities in a population that is often medically underserved. Interestingly, a multicenter study from Minnesota found that obtaining laboratory studies increased ED length of stay by approximately 23%; however; specific ethanol concentrations had no effect on total time to discharge among intoxicated patients.[5]

Point-of-care electrolyte testing may be a reasonable option for patients with suspected ethanol intoxication when a serum ethanol concentration is not clinically necessary. Although a complete electrolyte and metabolic panel may not be necessary in all patients, a two-tiered approach to laboratory evaluation may be useful when abnormalities are identified on a basic metabolic panel or point-of-care testing. In particular, patients with hypokalemia were more likely to have concomitant hypomagnesemia and hypophosphatemia. Therefore, hypokalemia should prompt a lower threshold for additional testing. Although the association between hypomagnesemia and hypokalemia is well established,[13] our finding suggest that additional electrolyte evaluation should be considered when hypokalemia is identified.

We also found that older patients with ethanol intoxication were more likely than younger patients to have electrolyte abnormalities overall and severe electrolyte derangements specifically, a finding that parallels observations older adults presenting to the ED.[14] Based on our sensitivity analysis, this association appears to be largely driven by the higher prevalence of renal insufficiency among older patients. Regardless of the underlying mechanism, suspected ethanol intoxication in patients aged 60 years or older should prompt heightened concern for electrolyte disturbances and may justify a lower threshold for routine laboratory evaluation.

Limitations

This study has several limitations. Given its retrospective design, causal relationships cannot be established, and the data may be subject to errors or omissions. We were only able to identify patients with documented serum ethanol concentrations of 50 mg/dL or greater; therefore, clinically intoxicated patients who did not undergo ethanol testing were not included.

In addition, because of the nature of database review, we were limited to predefined electrolyte abnormalities and could not adjust for factors such as pseudohyponatremia related to hyperglycemia or abnormalities associated with acute kidney injury or concurrent chronic kidney disease. Consequently, we cannot definitively conclude that all observed electrolyte abnormalities were directly attributable to ethanol consumption, and the underlying etiologies are likely multifactorial. We also were unable to determine how many patients received electrolyte repletion as therapy.

As noted previously, although we found a high prevalence of electrolyte abnormalities, patients who underwent laboratory testing may have been inherently more likely to have such abnormalities than those who did not. Furthermore, there was discordance between factors predictive of any electrolyte abnormality and those with severe electrolyte abnormalities, the reasons for which remain unclear. This analysis included all patients with serum ethanol concentrations greater than 50 mg/dL, including those with incidental ethanol intoxication who presented for unrelated complaints. We also lacked morbidity and mortality data for the study population. Finally, because the study population was limited to patients treated at VA facilities, generalizability of these findings to other patient populations may be limited.

CONCLUSIONS

This retrospective study found that ethanol intoxication is frequently associated with electrolyte derangements, many of which are clinically significant and can be readily identified in the ED using routine serum chemistry testing. Older patients, frequent ED users, and those with markedly elevated ethanol concentrations were more likely to have electrolyte derangements, with older patients also at increased risk for severe derangements. Clinicians should consider expanding laboratory evaluation to include less commonly tested electrolytes when abnormalities are identified on a basic chemistry panel. In particular, hypokalemia was associated with both hypomagnesemia and hypophosphatemia and may warrant additional testing.

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Culturally Tailored Support to Improve Breastfeeding Initiation and Duration in Black Birthing Communities

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ABSTRACT

Introduction: Black birthing individuals have lower breastfeeding initiation and duration rates than non-Hispanic White birthing individuals. Breastfeeding provides health benefits for both mothers and infants, and increased access to breastfeeding support may help reduce disparities in infant mortality and chronic disease. Understanding perceptions, motivators, barriers, and knowledge related to breastfeeding in Black birthing communities is vital to improving breastfeeding rates. This study examined how breastfeeding experiences differed between birthing individuals who did and did not receive culturally tailored peer support.

Methods: We used an adapted, validated survey to assess perceptions of breastfeeding, and survey findings informed focus group discussions. We recruited birthing individuals who self-identified as Black and received or declined breastfeeding support within the previous year. Qualitative data were coded to identify themes and compared between groups. t tests were used to compare Likert-scale scores measuring breastfeeding beliefs and barriers between supported and unsupported groups.

Results: Twenty-one Black women (mean [SD] age, 30.1 [6.7]) participated in 3 focus groups; 13 received breastfeeding and birthing support, and 8 reported no formal support. Themes differed by support status, suggesting several benefits associated with support. Participants who received support expressed fewer concerns about pain and reported greater support from family, friends, and employers. Participants also identified opportunities to strengthen breastfeeding support, including addressing workplace barriers, enhancing family and community support, and increasing access to culturally tailored education.

Conclusions: Culturally tailored support was associated with greater breastfeeding knowledge, confidence, and perceived support among Black birthing individuals. These findings highlight the potential value of community-based, culturally tailored interventions in addressing breastfeeding disparities and improving maternal and infant health outcomes.

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INTRODUCTION

Breastfeeding offers benefits for both mothers and infants. For infants, breastfeeding reduces the risk of infections, allergies, and chronic conditions while supporting development.[1,2] For mothers, breastfeeding lowers the risk of postpartum hemorrhage, certain cancers, and type 2 diabetes and supports postpartum weight loss and bonding.[3-5] Black women have lower breastfeeding initiation (75% vs 83%) and duration (49% vs 57% at >6 months) rates than non-Hispanic White women.[6] In Milwaukee County, where 70% of Wisconsin's Black population resides, breastfeeding initiation rates are 78.6%, compared with the national average of 86.1%.[7,8] Across Wisconsin, breastfeeding initiation rates are 54% among Black women and 87% among non-Hispanic White women.[9]

These disparities stem from structural racism and sexism and encompass cultural, sociological, and health-related factors.[10-13] Our community partner addresses these disparities by promoting breastfeeding awareness, building community allies, and reducing reliance on formula.[14] Its mission is to improve maternal health, champion breastfeeding through systems- and policy-level changes, build partnerships with community allies, and provide family-centered health education and support services. These efforts align with initiatives of the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC). In 2016, these initiatives encouraged participants to initiate and continue exclusive breastfeeding, increased

referrals to WIC for breastfeeding support, and promoted public acceptance and support of breastfeeding.[15] These changes were implemented in response to evidence suggesting that provision of formula vouchers reduced breastfeeding initiation and acceptance among low-income populations nationwide.[16,17]

More than 80% of Black birthing individuals in Wisconsin deliver in southeastern Wisconsin, where our community partner provides services to improve maternal and infant health.[18] Mothers who receive support are significantly more likely to initiate breastfeeding, and fathers who participate in peer-led education have partners with substantially higher rates of exclusive breastfeeding.[19,20] This study examined differences in breastfeeding experiences among women who did and did not receive this level of support.

METHODS

This study employed a mixed-methods design to explore breastfeeding experiences among Black women in southeastern Wisconsin. Quantitative data were collected using an adapted, validated survey assessing perceptions, motivators, barriers, and self-efficacy. Survey findings informed focus group data collection, providing contextual insights into participants' experiences. The mixed-methods approach integrated quantitative trends and qualitative themes to provide a comprehensive understanding of how support influences breastfeeding initiation, duration, and exclusivity.[21]

Recruitment

Participants were recruited through referrals to support services from health care organizations and nonprofit partners. Women who had been referred but did not respond to outreach or participate in support services were classified as "Unsupported." Staff confirmed that these women were not receiving breastfeeding support through any other program. Three focus groups were conducted in Milwaukee, Wisconsin. All participants were less than 1 year postpartum. They were classified as either recipients of breastfeeding support ("Supported") or as women not receiving support from a community- or government-based breastfeeding organization ("Unsupported"). Of 25 invited participants, 21 agreed to participate. The first focus group was designated for Unsupported women, and 7 of 8 attended. The eighth participant was only able to attend the second focus group, which otherwise consisted entirely of Supported participants. The third focus group included only Supported participants.

Facilitation and Data Collection

Two facilitators led community-based focus groups, while a researcher documented participants' affect and nonverbal cues. The research team comprised women and nonbinary individuals, and 3 of the 4 team members self-identified as Black. The focus groups lasted 90 minutes and were audio-recorded and transcribed.

Table 1. Selected Participant Demographic Characteristics, N = 21

Characteristic	n	%	Mean [SD]
Race			
Black	21	100.0	
Sex			
Women	21	100.0	
Age, years			30.1 [6.7]
18–25	6	28.6	
26–35	10	47.6	
36–45	5	23.8	
Relationship status			
Single, no partner	5	23.8	
Partnered, living separately	9	42.9	
Living with partner	7	33.3	
Education			
No high school diploma/GED	3	14.3	
High school diploma/GED	8	38.1	
Some college	6	28.6	
College degree	3	14.3	
Advanced degree	1	4.8	
Household income			
< $50,000/year	18	85.7	
≥ $50,000/year	3	14.3	
Time since last delivery (months)	21		7.2 [2.9]
Any experience breastfeeding			
Yes	11	52.4	
No	10	47.6	
Intend to breastfeed next child			
Yes	15	71.4	
No	0	0	
Unsure	6	28.6	

Staff reviewed survey responses to identify metrics relevant to funding, program improvement, and organizational planning. A previously validated Likert-scale survey developed for Black women to assess perceived risk, benefits, self-efficacy, and barriers related to mammography was adapted for this study because of its accessible language relevant constructs.[21] At the recommendation of the community-based organization, additional questions regarding breastfeeding experiences were added while maintaining the original survey format. For example, participants were asked to rate agreement with the statement, "When I think about breastfeeding, I feel excited, happy, and/or peaceful" (Table 2).

Participants completed the survey before beginning the focus group. Two participants arrived too late to complete the survey and therefore participated only in the focus group. Aggregate survey results were projected on a screen and used to guide focus group discussion.

Quantitative Study Measures and Analysis

Participants' breastfeeding beliefs were assessed using a 5-point Likert scale measuring agreement with statements related to breastfeeding motivations and barriers.

Descriptive statistics were used to summarize responses for variables measuring perceived breastfeeding benefits and self-reported

Table 2. Adapted Survey on Breastfeeding Beliefs

Breastfeeding Questions	Support Mean [SD]	No support Mean (SD)	*P* value
For me, convenience (no need to prepare bottles with formula) is a motivator to breastfeed.	4.29 [1.25]	3.17 [0.75]	.0832
For me, losing weight is a motivator to breastfeed.	3.57 [1.62]	3.00 [1.10]	.4800
For me, the benefits to my baby's health is a motivator to breastfeed.	4.86 [0.38]	4.33 [0.52]	.0586
For me, bonding with my baby is a motivator to breastfeed.	5.00 [0]	4.69 [0.82]	.0522
For me, the benefit to my own health is a motivator to breastfeed.	4.86 [0.38]	3.83 [1.47]	.1018
For me, saving money is a motivator to breastfeed.	4.43 [0.98]	3.83 [1.17]	.3380
For me, cost is a barrier to breastfeeding.	2.29 [1.60]	2.33 [1.03]	.9514
For me, finding time is a barrier to breastfeeding.	1.86 [0.90]	2.83 [1.33]	.1441
For me, inconvenience is a barrier to breastfeeding.	2.29 [0.49]	2.83 [0.75]	.1421
For me, pain is a barrier to breastfeeding.	1.57 [0.53]	2.83 [1.33]	.0408
For me, a lack of support from family and friends is a barrier to breastfeeding.	1.57 [0.53]	3.50 [1.22]	.0030
For me, lack of support from employment or education is a barrier to breastfeeding.	2.29 [0.95]	3.33 [0.52]	.0351
For me, a lack of resources (pump, bag, refrigerated storage) is a barrier to breastfeeding.	2.14 [1.35]	2.67 [1.21]	.4794
When I think about breastfeeding, I feel anxious, depressed, upset, nervous and/or scared.	2.29 [0.49]	3.17 [0.98]	.0597
When I think about breastfeeding, I feel excited, happy and/or peaceful.	5.00 [0]	3.17 [0.98]	.0004

breastfeeding barriers. *t* tests were used to compare mean scores between groups (Stata/MP version18.5 [StataCorp, LLC]). A 2-sided *P* value <.05 was considered statistically significant.

Qualitative Data Analysis

Transcripts were analyzed using ATLAS.ti version v8.4 (ATLAS.ti Scientific Software Development GmbH). Participants were identified using randomized initials. Two research team members independently conducted open coding to identify themes and develop a preliminary codebook. Coding continued until no new codes emerged. A team codebook was then developed by consolidating codes to overarching themes. Discrepancies in coding were resolved through discussion with a third researcher until consensus was reached.

Theme Validation

One month after the focus groups, participants were reconvened for member checking. Themes and conclusions from the analysis were presented, with participants were given opportunities to provide feedback verbally and nonverbally. An executive summary was distributed to accommodate participants who preferred to review the information privately and provide feedback at a later time.

Ethical Considerations and Protection of Human Subjects

All study procedures were approved by the designated Institutional Review Board [Protocol # 00032076]. A waiver of informed consent was granted because the study posed minimal risk. Participants received an informational letter describing the study and their rights as research participants.

RESULTS

Twenty-one Black birthing individuals, all of whom identified as women/female, were included in the analysis. The mean age was 30.1 years [SD, 6.7], and most participants reported household incomes below $50,000 (85.7%). Nearly half had some college education or higher (47.6%), 33.3% lived with a partner, 42.9% were partnered but living separately, and 23.8% were single without a partner. Eleven women (52.4%) had breastfed previously, and 15 (71.4%) intended to breastfeed their next child (Table 1). Among those who had not previously breastfed, 3 had attended only 1 support event, were unsuccessful in their breastfeeding attempts, and subsequently engaged more fully in support programming while preparing for another pregnancy. Only 2 of the 8 women in the Unsupported group reported that they were considering breastfeeding during their next pregnancy.

Survey Results

Table 2 summarizes participants' breastfeeding beliefs. Compared with unsupported women, supported women were significantly less likely to identify pain ($P = .04$) and lack of support from family and friends ($P = .003$) and employers ($P = .04$) as barriers to breastfeeding. Supported women were also more likely to report positive feelings about breastfeeding ($P < .001$). Unsupported women more frequently reported negative emotions, whereas supported women more often identified infant health benefits as a motivator for breastfeeding.

Thematic Analysis

Content analysis identified themes related to barriers and motivators to breastfeeding, sources of advice and information, uncertainty and anxiety, and confidence and knowledge in breastfeeding (Table 3).

Barriers to Breastfeeding: Breastfeeding-related pain was discussed in all groups; however, supported participants generally viewed pain as preventable or manageable. Time- and work-related constraints were also discussed across groups. Workplace barriers included limited opportunities for pumping breaks,

scheduling difficulties, inadequate facilities, and lack of support from supervisors or colleagues. Outside of work, participants identified competing demands on their time, including household responsibilities, caregiving duties, and a desire for personal freedom. They described the need for support with breastfeeding techniques, maintaining milk supply, emotional well-being, and advocacy in personal and professional settings. Supported women typically described insufficient support as a barrier experienced by others rather than themselves.

Table 3. Barriers and Motivators to Breastfeed: Representative Quotes

Barriers	Quote
Pain or fear of pain	"That thing [the pump] hurt, it was almost 19 years ago, I don't know if it was the wrong size or what, but that thing hurt. And I was like, okay, I'm not pumping, I'm just going to feed my baby. I didn't like the pump at all. If I was someone that didn't know about breastfeeding and I thought – the pump, that's how this would feel, I probably wouldn't want to breastfeed." *–JS, Group 3, Supported*
Time constraints or work-related barriers	"We had to set up times and split the room or whatever it was and share the space, but it was a huge barrier for me. And really, I probably would have pumped a little bit longer if I felt like I had more support and freedom at work, to um, continue to do it but, that, that was a barrier for me for sure." *–PL, Group 2, Supported*
Motivators	
Low cost and convenience	"It's like, yeah, it's convenient, it's cost-effective, those are ALL motivators for me, anything that's gonna make my life easier in this transition to being a mom, I'm like, all for it." *—CB, Group 1, Unsupported*
Health and emotional benefits for the baby	"I never knew that. But they can have all the milk they want if it helps me lose some weight. They can have it all." *–LW Group 1, Unsupported*
Support system	"Not just education in the Black community, and within the Black community and support from the Black community to the Black community, but also systems we use. Whether that's stores, public events that we frequent, but systems changing in the medical profession so that they honor our bodies and our decisions to support our babies with our milk." *–RJ Group 3, Supported*
Beautiful and natural process	"it's magical, because, like, my body makes food for my baby, and it didn't have to grow out of the ground, you know, and just I mean all of the science-y stuff behind it, but it's also magical. Like, the oxytocin, and you know, I could be so mad about something, like, girl come get on your booby, and after a few minutes, I'm like, all right, that's fine, everything's fine (laughter)." *–EB, Group 3, Supported*

Motivators to Breastfeed: Unsupported women most commonly identified low cost and convenience as motivations for breastfeeding. Participants perceived the costs associated with formula and supplies for bottle preparation to be substantially greater than those associated with pumping equipment and milk storage. Among supported women, motivations included maternal-infant bonding, nutritional and immune benefits for the infant, and maternal benefits such as weight loss and chronic disease prevention. Many supported women also spoke about the beauty and naturalness of breastfeeding, the importance of celebrating it, and their commitment to breastfeeding despite potential barriers.

Sources of Advice about Breastfeeding: Women in all groups discussed their experiences obtaining breastfeeding information and their perceptions of various sources of information. Unsupported women relied heavily on observations and advice from family members and friends. Participants across groups expressed both positive and negative views of individual health care providers. Some reported strong trust and confidence in their clinicians and relied on them for guidance. However, perceptions of the health care system overall were generally negative. Women frequently shared personal experiences of family members as reasons for general distrust of the health care system (Table 4).

Uncertainty and Anxiety About Breastfeeding: Unsupported women expressed uncertainty regarding breastfeeding techniques, including latching and pumping. They reported concerns about pain, cost, supplies, latching, breastfeeding with piercings, and the potential effects on intimacy with a partner. Although most recognized that breastfeeding was less expensive than formula feeding, many were uncertain about proper breast milk storage and appropriate formula supplementation. Unsupported women generally understood that breastfeeding benefits infants but often could not identify specific benefits. Some were unaware of maternal health benefits associated with breastfeeding. Participants also described employers who failed to provide adequate space, storage, or time for pumping. Although several examples suggested potential violations of workplace protections, unsupported women generally demonstrated limited awareness of their breastfeeding rights.

Confidence and Knowledge About Breastfeeding: In contrast, supported women demonstrated greater knowledge and confidence regarding breastfeeding. They used appropriate terminology for breastfeeding techniques, benefits, and advocacy. Responses regarding cost and preparation were detailed and differentiated between breastfeeding, formula feeding, and pumping. Additionally, they spoke confidently and accurately regarding workplace breastfeeding protections and described advocating for these rights in employment settings. These participants expressed conviction and pride when discussing their commitment to breastfeeding rights, initiation, and exclusivity. Several noted that the maternal-infant bond alone would have motivated them to breastfeed regardless of any other benefits or deterrents (Table 5).

DISCUSSION

This study demonstrates that women who received support expressed greater confidence in breastfeeding. Although participants reported varying levels of support, themes of uncertainty were more common among women who received less support.

While women in all groups indicated that pain was a barrier, only unsupported women expressed fear of pain and identified it as a personal barrier to breastfeeding. These findings were consistent with the quantitative results, in which pain was identified as a significant barrier only among unsupported women ($P = .04$).

It is important to contextualize these findings within broader clinical patterns related to pain and breastfeeding difficulty. Nipple pain is a common reason for breastfeeding cessation. It is often associated with inflammation resulting from to incorrect latching and too much force on the nipple during lactation.[22] Studies indicate that 40% to 70% of mothers experience breastfeeding difficulties, including sore or cracked nipples and pain.[23] These issues have been associated with lower breastfeeding self-efficacy and reduced self-perceived knowledge.[24] Continued, tailored breastfeeding support through professional guidance or community-based programming may be needed to ensure women learn proper latching techniques and feel confident in their breastfeeding abilities.[25]

Unsupported women frequently identified time constraints as a significant barrier to breastfeeding, both at work and at home. One participant worked on construction sites without access to clean, running water. Another worked in food service and could not take breaks. Addressing such barriers will require systems-level changes, including employer education, workplace assessments, and clear standards for breastfeeding accommodations.[26,27] In occupations where breastfeeding is difficult to incorporate into traditional workplace schedules, colleague support has been associated with longer breastfeeding duration and greater exclusivity.[28]

Although supported women report greater confidence in advocating for workplace rights, opportunities remain to improve advocacy on behalf of birthing women. As of 2020, 25 states had enacted workplace breastfeeding legislation that allows mothers to express and store breast

Table 4. Sources of Advice About Breastfeeding: Representative Quotes

Source	Quote
Family and friends	"But my mom and my aunties, they always use Similac. They said that was the best formula, so I was going to go with that. At the end of the day, it is my decision, but I don't really know." *–TM, Group 1, Unsupported*
Government-sponsored programs	"I don't believe the people [government office]. I don't." *–CB, Group 1, Unsupported* "She told me she never breastfed so how you gonna tell me?"*–LW, Group 1, Unsupported*
Community programs	"How she [community partner leader] teaches us breastfeeding, the differences between what formula have [sic] in it, what breastmilk have [sic] in it, the position, all I knew was I was just holding my baby in the cradle, the crosshold, I didn't know all of that. I was just doing it before and now I'm educated." *–HC, Group 2, Supported*
Health care providers (positive)	"I was just gonna say having a good relationship with your doctor is, is important. Um, having a doctor that you can trust, confide in, um, that actually listens to what you're saying, someone you can, I mean, my doctor, I can literally FaceTime her." *–DD, Group 2, Supported*
Health care providers (negative)	"They value business over the people. That's how I look at it, that's been my experence like my parents are on all these types of medications for the same thing, but no one's dealing with the initial issue." *—KS, Group 3, Supported*

Table 5. Uncertainty and Confidence in Breastfeeding: Representative Quotes

Uncertainty/Anxiety	Quote
How to breastfeed:	"I feel like there's a lot of questions like is the baby getting enough food, I don't know. Cuz my sister's baby, when she was breastfeeding, she breastfed him, give him some milk, then he like hungry soon as he got off it, like screaming to the top of his lungs, so I don't know." *—SP, Group 1, Unsupported*
Cost, preparation, and supplies	"They say that babies clench on, and sometimes they don't take it, so if they're not taking it, what do you do if they don't want it? Then how do we know what formula to give them if they don't clench on?" *–ML, Group 1, Unsupported*
Health benefits	"Helps baby not being sick so often and stuff like that…but you're gonna be sick one day in your life, ain't you? They gonna get chicken pox, they gonna be sick, so I mean why is it they gotta suck on you just to not be sick?" *–LW, Group 1, Unsupported*
General unease	"It makes me nervous cuz I don't know what it's gonna feel like, that's the main thing. I don't know how it's gonna work." *–TM, Group 1, Unsupported*
Workplace rights	"At my last job, I went and they told, and I sat there and told them, like you know, about maternity leave. They were like, uh we don't do maternity leave, you just have to leave. Okay, I'll just leave right now if that's how y'all feel like. I'm not gonna work for y'all." *–ML, Group 1, Unsupported*
Confidence/Knowledge	**Quote**
How to breastfeed	"People call me and say, 'my baby, they're forcing me to give him formula, my baby's not gaining weight, they didn't tell me to massage my breasts so that I could integrate the hind milk with the foremilk and my baby can get calorically rich milk'." *—SS, Group 3, Supported*
Cost and preparation:	"When I used to pump, and it wasn't a lot, but it took a lot of energy to make sure that I had enough bottles cleaned. I had to clean the bottles, store milk for her, I had to make sure that the milk was coming correctly, it was just a whole lot of extra stuff that I didn't have to do when I was just breastfeeding. I was just there, no bottles, no fuss." *–EB Group 3, Supported*
Workplace rights	"Then when I got into the workplace, they didn't have any space for me to pump, and so I had to advocate for myself based on the standard with the law that they need to provide me with space to pump, it needs to be private, it needs to have access to running water, I need to be able to pump as many times as I need to and they are not included in my breaks." *–MG, Group 3, Supported*
Positivity and commitment:	"I think it's invigorating because you get that connection with the child, you get that connection with kind of like the world at the same time. You, you're like the tree, and they are like the roots, or you're the roots, and they're the tree. You just grow with your child a little bit more." *–RJ, Group 3, Supported*

milk at work, contributing to improved breastfeeding rates.[29,30] All participants reported work-related barriers. However, supported women appeared more confident about navigating their rights in the workplace. While barriers persist, support may equip women to manage these challenges more effectively ($P = .0351$).

Participants also described limited or no support within their households, competing caregiving responsibilities with other children, and being too tired to devote time to breastfeeding. Nationally, breastfeeding rates are lower among single-parent household and those with lower socioeconomic status.[31,32] Research examining breastfeeding perceptions among women of socioeconomic status has identified positive influences such as shared narratives, improved knowledge, and a supportive social networks, whereas negative influences include lack of guidance, opinions from family and friends, limited support, and conflicting messages from health care professionals.[33]

Unsupported women recognized that breastfeeding benefited infant health but often could not describe specific benefits. In contrast, supported women easily listed the health benefits of breastfeeding and identified their personal motivations with conviction and pride. Notably, only the focus group composed entirely of supported women discussed breast cancer risk reduction as a benefit of breastfeeding. Although greater knowledge does not necessarily translate into stronger motivation, it may help women determine what matters most to them. These findings are consistent with previous research demonstrating that women who are more knowledgeable about the mechanics, benefits, and challenges of breastfeeding are more likely to feel confident in their ability to breastfeed, which is associated with longer breastfeeding duration and greater exclusivity.[34,35]

A notable difference between groups was the extent to which women relied on anecdotal information from their friends and family, with reliance inversely related to support. Unsupported women frequently referenced others' experiences rather than drawing on personal knowledge, whereas supported expressed confidence in their own expertise. In some cases, referencing the experience of friends led to more questions. One unsupported woman referred to friend who claimed that breastfeeding hurt, but she had heard from another source that pain occurred only if breastfeeding was done incorrectly, and she did not know who to believe. Similar studies have shown that social networks play an important role in shaping breastfeeding beliefs and behaviors, particularly among Black women and women with limited access to culturally responsive care.[36,37] When trusted information from health care systems is unavailable or inconsistent, family narratives may fill the gap, even when inaccurate or outdated. Community-based organizations can bridge these gaps by providing accurate, culturally relevant information in trusted settings.

Supported women exhibited clear, confident beliefs and were better equipped to evaluate conflicting information and make informed breastfeeding choices. These findings are consistent with broader evidence demonstrating that breastfeeding self-efficacy is influenced by factors including birth preparedness, socioeconomic conditions, anxiety, and relationship status.[38] Although the Breastfeeding Self-Efficacy Scale was not used in this study, it may be valuable in future research to better tailor breastfeeding support strategies.[39]

Differences in perceptions of health care providers emerged across all focus groups, regardless of support status. Although participants sought information from physicians and other clinicians, distrust of individual providers and the health care system was prevalent. Participants frequently described providers as "disconnected" from the realities of their daily lives. Even women who were happy with their own clinician reported difficulty finding providers with similar values or cultural backgrounds. A previous study of 130 Black mothers similarly identified gaps in breastfeeding education and support throughout pregnancy, childbirth, and the postpartum period and emphasized the importance of trust, continuity of care, and consistent breastfeeding education.[40] While support programs do not replace health care professionals, they may help bridge these gaps by connecting women with individuals who share common experiences and values. Participants also express frustration when breastfeeding guidance came from individuals without personal breastfeeding experience.

Overall, these findings suggest that community-tailored breastfeeding support may improve confidence, knowledge, and attitudes toward breastfeeding. Such support may empower women to make informed decisions, advocate for their needs, and promote breastfeeding within the Black birthing community.

Strengths and Limitations

This study highlights the strengths of a culturally tailored and community-centered approach to breastfeeding support among Black birthing individuals. A key strength was the use of a mixed-methods design, which integrated quantitative trends with qualitative insights to provide a comprehensive understanding of breastfeeding experiences. Partnering with a community-based organization facilitated culturally tailored, person-centered care and enhanced participant trust and engagement. However, the study was limited by its relatively small sample size, which may limit generalizability, and by possible self-selection bias, as supported participants may have been more motivated or had greater access to resources.

Future Directions

Focus groups were conducted in late 2018, and data were analyzed in 2019. Following the onset of COVID-19, our community partner prioritized transitioning to virtual services and ensuring the safety of birth workers. Data from this study have informed multiple funding proposals, and our partner has continued to expand its reach and support services. Future efforts should focus on broad

dissemination of these findings and program successes to support other community-based organizations working to improve breastfeeding initiation, duration, and sustainability.

CONCLUSIONS

This study demonstrates the impact of culturally tailored support on breastfeeding knowledge and intentions among Black/African American birthing individuals. Supported women expressed fewer concerns and demonstrated greater understanding of breastfeeding benefits and breastfeeding-related rights. These findings highlight the importance of community-driven interventions that provide comprehensive, person-centered care. Community-based breastfeeding support programs may offer a replicable approach for reducing breastfeeding disparities and improving maternal and infant health outcomes.

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Vitamin D Supplementation During COVID-19 Infection Is Associated With an Unfavorable Impact of Increased Total Number of Organ Systems Involved

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ABSTRACT

Introduction: COVID-19 is a systemic disease that affects multiple organ systems. We investigated the association between vitamin D supplementation and the number of organ systems involved in hospitalized patients with COVID-19.

Methods: This retrospective study included 808 consecutive patients with COVID-19 treated at a tertiary care hospital in the metropolitan New York City area between March 2020 and May 2020. The outcome variable was the total number of involved organ systems, defined as a score reflecting involvement of the respiratory, neurologic, renal, cardiovascular, hepatic, endocrine, musculoskeletal, and hematologic organ systems.

Results: Overall, 249 patients (30.8%) received vitamin D supplementation. The number of organ systems involved was significantly greater among patients who received vitamin D supplementation (mean [SD], 4.7 [1.82]) than among those who did not (mean [SD], 3.5 [1.93]; $P < .001$). Vitamin D supplementation was significantly associated with an increased number of organ systems involved (B,0.30; SE, 0.11; $P = .01$).

Conclusions: Vitamin D supplementation was associated with a greater number of involved organ systems among hospitalized patients with COVID-19. Prospective studies, including randomized clinical trials, are needed to confirm this association.

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INTRODUCTION

COVID-19 is a systemic disease that affects multiple organ systems, most commonly the respiratory system, but also the endocrine, musculoskeletal, hematologic,[1] neurologic, renal, cardiovascular, and hepatic systems.[2] COVID-19 symptoms range from asymptomatic to severe illness.[3,4] Increased disease severity and mortality are associated with age older than 70 years, male sex, and the Black and Hispanic race/ethnicities.[5,6] Increased disease severity is also associated with comorbidities, including obesity, diabetes, hypertension, lipid disorders, cardiovascular disease, chronic lung disease, and immunodeficiencies.[7,8]

Vitamin D supplementation has been investigated in patients with COVID-19 across several organ systems. Findings for the respiratory system are mixed. Some studies report that vitamin D supplementation is associated with respiratory improvement, including a decreased need for noninvasive and invasive mechanical ventilation, increased oxygen saturation, decreased respiratory rate, an increased ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2),[9] decreased breathing difficulty, decreased chest congestion, decreased cough,[10] and a lower Pneumonia Severity Index score.[11] However, others report no association between vitamin D supplementation and duration of respiratory support.[12]

Findings for the hematologic system are also mixed. Some studies report that vitamin D supplementation is associated with increased anti-inflammatory cytokines,[13] increased T-helper lymphocytes,[14] decreased fibrinogen,[15] and decreased occurrence of sepsis,[9] suggesting hematologic improvement. However, another

study found no association between vitamin D supplementation and sepsis.[16]

For the renal system, vitamin D supplementation is associated with a lower risk of COVID-19 infection, severe COVID-19 infection, and mortality among patients with advanced chronic kidney disease,[17] as well as decreased blood urea nitrogen levels.[18] For the hepatic system, vitamin D supplementation is associated with lower alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels[9] and decreased alkaline phosphatase (ALP).[19] For the musculoskeletal system, vitamin D supplementation is associated with lower creatine kinase levels, suggesting improved muscle function.[20]

The vitamin D endocrine system creates an active form of vitamin D, which acts on multiple systems, including the endocrine,[21,22] neurologic,[23,24] and cardiovascular systems.[25] Because vitamin D deficiency is associated with increased COVID-19 disease severity,[26] several review articles have suggested that vitamin D supplementation may improve COVID-19-related health concerns involving the endocrine,[27] neurologic,[28] and cardiovascular[29] systems. However, studies examining vitamin D supplementation in patients with COVID-19, regardless of baseline vitamin D status, and its association with endocrine, neurologic, and cardiovascular system involvement have not been reported. Furthermore, we are unaware of any studies evaluating the association between vitamin D supplementation and multisystem organ involvement in hospitalized patients with COVID-19. Therefore, we examined the association between vitamin D supplementation and the number of organ systems, including the respiratory, neurologic, renal, cardiovascular, hepatic, endocrine, musculoskeletal, and hematologic systems.

METHODS

Setting

This retrospective study included 808 consecutive patients with COVID-19 treated at a public tertiary care hospital in the metropolitan New York City area. All patients were admitted from March through May 2020. Ethical approval was obtained from the hospital institutional review board. A waiver for informed consent was granted because of the retrospective study design.

Variables

Demographic variables included age (years), sex (male/female), and race/ethnicity (White, African American, Hispanic, East Asian, Southeast Asian [eg, India, Pakistan], and Other). Comorbidities included obesity (body mass index >30 kg/m^2) and the Charlson Comorbidity Index (CCI), which is based on the presence of multiple comorbidities.[30]

Disease severity variables included the quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA) score[31] (range, 0-3; 1 point each for respiratory rate >22 breaths/min, systolic blood pressure <100 mmHg, and Glasgow Coma Scale <15[32]), intensive care unit (ICU) admission at any point during hospitalization, invasive mechanical ventilation at admission, and oxygen requirements during hospitalization (none, low FiO_2 [≤55%], high FiO_2 [>55%], and invasive mechanical ventilation).

Treatment management variables included the use of vasopressors (phenylephrine, dobutamine, norepinephrine, epinephrine, or dopamine) and other treatments (defined as receipt of 1 or more of the following: therapeutic anticoagulation, glucocorticoids, or antibiotics at admission; remdesivir; interleukin-6 inhibitors; and convalescent plasma).

We investigated the involvement of 8 organ systems: respiratory, cardiovascular, endocrine, hematologic, hepatic, musculoskeletal, neurologic, and renal. Respiratory involvement was defined as a new requirement for supplemental oxygen or nadir oxygen satura-

Table 1. Sample Characteristics of Vitamin D Supplementation and Patients With COVID-19 (N = 808)

Variables	No Vitamin D Mean [SD] or Frequency (%) (n = 559)	Vitamin D Mean [SD] or Frequency (%) (n = 249)	*P* value
Demographics			
Age (years), mean	59.3 [17.13]	61.1 [15.06]	.16
Female sex	250 (44.7)	77 (30.9)	<.001
Race/ethnicity			.01
White	130 (23.3)	74 (29.7)	
African American	137 (24.5)	55 (22.1)	
Hispanic	259 (46.3)	95 (38.2)	
East Asian	18 (3.2)	8 (3.2)	
Southeast Asian	9 (1.6)	7 (2.8)	
Other	6 (1.1)	10 (4.0)	
Comorbidities			
Obesity	215 (38.5)	86 (34.5)	.29
CCI, mean	2.7 [2.46]	3.1 [2.46]	.02
Disease severity			
qSOFA, mean	1.5 [0.63]	1.5 [0.61]	.78
Intensive care unit admission	222 (39.7)	164 (65.9)	<.001
Invasive mechanical ventilation admission	23 (4.1)	21 (8.4)	.01
Oxygen requirement hospitalization			<.001
None	117 (20.9)	20 (8.0)	
Low FiO_2 (≤55%)	217 (38.8)	72 (28.9)	
High FiO_2 (>55%)	135 (24.2)	59 (23.7)	
Invasive mechanical ventilation	90 (16.1)	98 (39.4)	
Treatment management			
Vasopressor	56 (10.0)	68 (27.3)	<.001
All other treatments	521 (93.2)	244 (98.0)	.01
Organ system involvement			
No. of organ systems involved, mean	3.5 [1.93]	4.7 [1.82]	<.001

Abbreviations: CCI, Charlson Comorbidity Index; qSOFA, quick Sequential/Sepsis-related Organ Failure Assessment.

Note: Fisher exact test comparisons performed for race/ethnicity due to expected cell size less than 5.

tion <95%. Cardiovascular involvement was defined as a new elevation in troponin I (>0.04 ng/mL), new supraventricular tachycardia, new or worsening atrial fibrillation, new atrioventricular block, new ventricular tachycardia, new-onset or acute-on-chronic heart failure, or new use of inotropes or vasopressors. Endocrine involvement was defined as a new or increased baseline insulin requirement or blood glucose level < 60 mg/dL or >140 mg/dL. Hematologic involvement was defined as an absolute neutrophil count <1.8 × 109/L or >7 × 109/L, hemoglobin < 9.2 g/dL, platelet count <110×109/L, or a white blood cell count (WBC) < 4 × 109/L or >11 × 109/L. Hepatic involvement was defined as a total serum bilirubin level >1.1 mg/dL or an ALT level greater than 1.5 times the upper limit of normal limit (> 60 IU/L). Musculoskeletal involvement was defined as a creatine kinase (CK) level >1000 U/L. Neurologic involvement was defined as a change in baseline mental status, a new decrease in Glasgow Coma Scale score,[32] or new-onset cerebrovascular accident, transient ischemic attack, or seizure. Renal involvement was defined as a 1.5-fold increase in serum creatinine from baseline according to Acute Kidney Injury Network criteria[33] or an absolute increase in serum creatinine > 0.3 mg/dL.

Organ system involvement was summarized as a score ranging from 0 (no organ systems involved) to 8 (all 8 organ systems involved).

Statistical Analysis

Continuous variables were summarized using means and standard deviations. Categorical variables were summarized using frequencies and percentages. Analysis of variance was used to compare patients who did and did not receive vitamin D supplementation with respect to potential continuous covariates. The chi-square test or Fisher exact test was used to compare vitamin D supplementation status with potential categorical covariates.

Any variable that was statistically significant in the univariable analyses was included in the multivariable linear regression analysis for the outcome variable of number of organ systems involved.

Four additional sensitivity analyses were conducted. The first added qSOFA as a continuous predictor to the multivariable model. The second added qSOFA as a categorical predictor (not high risk, scores of 0-1; high risk, scores of 2-3). This cut-off was based on previous literature indicating that qSOFA scores of 2 and 3 are associated with a high risk of organ dysfunction.[34] The third analysis consisted of a stratified analysis of patients with non-high-risk qSOFA scores. The fourth consisted of a stratified analysis of patients with high-risk qSOFA scores.

Forest plots are presented for the multivariable regression analyses shown in the Tables. All *P* values were 2-sided, and statistical significance was set at $P < .05$. IBM SPSS Statistics, Version 29 (IBM Corporation) was used for the statistical analyses. Stata/SE Version 17 (StataCorp LLC) was used to generate the forest plots.

Table 2. Multivariate Linear Regression Analysis for Number of Organ Systems Involved

Variables	Vitamin D B (SE)	95% CI	*P* value
Vitamin D supplementation	0.30 (0.11)	0.10 to 0.52	.01
Female sex	-0.29 (0.10)	-0.48 to -0.10	.003
Race/ethnicity			
White	ref	ref	
African American	0.04 (0.13)	-0.22 to 0.30	.77
Hispanic	-0.32 (0.12)	-0.56 to 0.08	.01
East Asian	-0.34 (0.28)	-0.88 to 0.20	.22
Southeast Asian	0.11 (0.34)	-0.54 to 0.81	.76
Other	-0.43 (0.34)	-1.13 to 0.23	.21
CCI	0.12 (0.02)	0.08 to 0.16	<.001
Intensive care unit admission	0.56 (0.24)	0.07 to 1.02	.02
Invasive mechanical ventilation admission	0.03 (0.03)	-0.03 to 0.10	.08
Oxygen requirement hospitalization			
None	ref	ref	
Low FiO_2 (≤55%)	0.71 (0.14)	0.40 to 0.96	<.001
High FiO_2 (>55%)	1.48 (0.27)	0.88 to 1.97	<.001
Invasive mechanical ventilation	2.28 (0.30)	1.69 to 2.89	<.001
Vasopressor	1.09 (0.18)	0.75 to 1.45	<.001
All other treatments	0.30 (0.22)	-0.14 to 0.72	.17
Constant	1.80 (0.24)	1.33 to 2.27	<.001

Abbreviations: B, unstandardized beta; SE, standard error; CCI, Charlson Comorbidity Index; ref, reference.

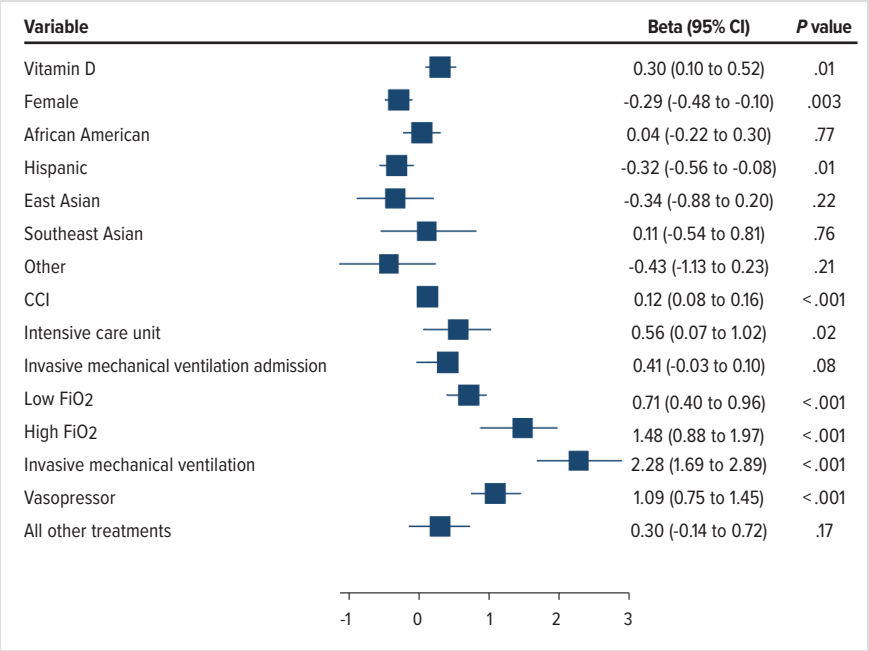
Note: adjusted R square = 0.56.

RESULTS

The sample included 249 patients (30.8%) who received vitamin D supplementation and 559 (69.2%) who did not. Table 1 compares patients who did and did not receive vitamin D supplementation. Patients who received vitamin D supplementation had a lower percentage of females and Hispanic individuals than those who did not receive vitamin D supplementation. Patients who received vitamin D supplementation had a higher mean CCI than those who did not receive vitamin D supplementation. They also had a higher frequency of ICU admission, invasive mechanical ventilation at admission, and invasive mechanical ventilation during hospitalization. In addition, patients who received vitamin D supplementation had a higher frequency of vasopressor use and receipt of other treatments than those who did not receive vitamin D supplementation.

Table 2 shows the multivariable linear regression analysis for the number of organ systems involved. Vitamin D supplementation was significantly associated with an increased number of organ systems involved. Female sex and Hispanic race/ethnicity were significantly associated with a decreased number of organ systems involved. Higher CCI, ICU admission, and all levels of oxygen support during hospitalization were significantly associated with an increased number of organ systems involved. Vasopressor use was also significantly associated with an increased number of

Figure. Forest Plot for Predictor Variables in the Multivariate Linear Regression Analysis for Number of Organ Systems Involved



Abbreviation: CCI, Charlson Comorbidity Index.

Table 3. Multivariable Linear Regression Analysis for Number of Organ Systems Involved From the Subset of Patients With Non-High-Risk Quick Sequential/Sepsis-Related Organ Failure Assessment Scores

Variables	Vitamin D B (SE)	95% CI	*P* value
Vitamin D supplementation	0.32 (0.14)	0.04 to 0.60	.03
Age (years)	0.02 (0.01)	0.004 to 0.03	.01
Female sex	-0.44 (0.12)	-0.68 to -0.20	.003
Race/ethnicity			
White	ref	ref	
African American	0.15 (0.18)	-0.20 to 0.49	.41
Hispanic	-0.24 (0.16)	-0.54 to 0.07	.13
East Asian	-0.06 (0.52)	-1.08 to 0.96	.91
Southeast Asian	0.27 (0.52)	-0.75 to 1.29	.61
Other	-0.51 (0.73)	-1.95 to 0.92	.48
CCI	0.01 (0.04)	-0.07 to 0.08	.82
Intensive care unit	0.74 (0.34)	0.07 to 1.02	0.03
Oxygen requirement hospitalization			
None	ref	ref	
Low FiO_2 (≤55%)	0.56 (0.16)	0.25 to 0.88	<.001
High FiO_2 (>55%)	1.08 (0.37)	0.37 to 1.80	.003
Invasive mechanical ventilation	2.22 (0.40)	1.44 to 3.00	<.001
Vasopressor	1.01 (0.25)	0.52 to 1.49	<.001
All other treatments	0.51 (0.25)	0.02 to 1.00	.04
Constant	0.99 (0.37)	0.26 to 1.72	.01

Abbreviations: B, unstandardized beta; SE, standard error; CCI, Charlson Comorbidity Index; ref, reference.

Note: adjusted R square = 0.60.

organ systems involved. The Figure shows the corresponding forest plot.

Sensitivity analyses were conducted with qSOFA included as a predictor variable (data not shown). In the analysis that included qSOFA as a continuous variable, vitamin D supplementation (B, 0.33; SE, 0.11; 95% CI, 0.12-0.53, $P = .002$) and qSOFA (B, 0.29; SE, 0.08; 95% CI; 0.14-0.45, $P < .001$) were each significantly associated with an increased number of organ systems involved. In the analysis that included qSOFA as a categorical variable, vitamin D supplementation (B, 0.32, SE, 0.11; 95% CI, 0.11-0.53; $P = .003$) and a high-risk qSOFA score (B, 0.33; SE, 0.10; 95% CI, 0.14-0.52; $P < .001$) were each significantly associated with an increased number of organ systems involved.

Supplemental Table 1 shows comparisons between patients who did and did not receive vitamin D supplementation among those with non-high-risk qSOFA scores. The pattern of significant findings was similar to that of the overall sample, except that age was significantly different, with a higher mean age among patients who received vitamin D supplementation, and invasive mechanical ventilation at admission no longer differed significantly between groups. Supplemental Table 2 shows comparisons between patients who did and did not receive vitamin D supplementation among those with high-risk qSOFA scores. The pattern of significant findings was similar to that of the overall sample, except that race/ethnicity, CCI, and receipt of other treatments did not differ significantly between groups.

Additional sensitivity analyses were conducted separately among patients with non-high-risk and high-risk qSOFA scores. Table 3 shows the multivariable linear regression analysis for the number of organ systems involved among patients with non-high-risk qSOFA scores. Vitamin D supplementation was significantly associated with an increased number of organ systems involved. Table 4 shows the multivariable linear regression analysis among patients with high-risk qSOFA scores. Vitamin D supplementation was again significantly associated with an increased number of organ systems involved. Supplemental Figures 1 and 2 show the corresponding forest plots.

DISCUSSION

In this study, vitamin D supplementation was significantly associated with a greater number of organ systems involved. Female sex and Hispanic race/ethnicity were significantly associated with a lower number of organ systems involved. CCI, ICU admission, oxygen requirements (low FiO_2 ≤55%, high FiO_2 >55%,

invasive mechanical ventilation), and vasopressor use were significantly associated with a greater number of organ systems involved.

Previous studies have reported either no association[12] or a favorable association between vitamin D supplementation and reduced COVID-19 disease severity when examining individual organ systems.[9-11,13,35] Our findings differ from this pattern. The COVID-19 virus enters the body by binding to the angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed on endothelial and epithelial cells throughout the body.[36,37] The ACE2 receptor is involved in the breakdown of angiotensin II.[38,39] Angiotensin II helps maintain blood pressure through vasoconstriction and may contribute to fibrosis, inflammation, and cellular hypertrophy.[39-42] Elevated angiotensin II levels are associated with more severe COVID-19 symptoms.[43,44] Binding of the virus to ACE2 results in decreased ACE2 expression and a subsequent increase in angiotensin II levels.[45-47] Vitamin D upregulates ACE2 receptor expression, resulting in increased breakdown of angiotensin II.[48,49] Because SARS-CoV-2 binds to ACE2 receptors, it is possible that increased ACE2 expression associated with vitamin D supplementation could facilitate viral spread to additional organs and contribute to more extensive disease involvement.[50] A greater number of involved organ systems has been associated with worse prognosis in patients with COVID-19.[51] Thus, this hypothesis may help explain our finding that vitamin D supplementation was associated with a greater number of organ systems involved.

Female sex was associated with a lower number of organ systems involved compared with male sex. Previous research shows that COVID-19 severity and mortality are increased in males compared with females.[52,53] Our findings regarding the number of organ systems involved are consistent with this pattern and may reflect lower disease severity among females.

Hispanic patients had a lower number of involved organ systems than White patients. Individuals older than 65 years are at increased risk for severe COVID-19 infection.[54] In our sample, Hispanic patients had a mean age of 54.2 (SD, 14.47) years compared with 65.6 (SD, 18.07) years among White patients. Because Hispanic patients in our sample were substantially younger, age may partially explain their lower number of involved organ systems.

Higher CCI, ICU admission, oxygen requirements, and vasopressor use were each associated with a greater number of involved organ systems. These measures are markers of greater COVID-19 severity.[8,55-57] Accordingly, the observed association with a higher number of organ systems involved is consistent with this pattern. These findings may also reflect confounding by indication, whereby patients with more severe illness experience greater multisystem involvement.

Strengths, Limitations, and Future Research

This study has several strengths. To our knowledge, it is the first study to report an association between vitamin D supplementation and a greater number of involved organ systems among hospitalized patients with COVID-19. A second strength is the use of the novel outcome measure of number of organ systems involved.

The study also has several limitations. First, the dose of vitamin D dose supplementation was not recorded. Second, we did not determine whether vitamin D supplementation was initiated during hospitalization or represented continuation of prehospital supplementation. However, the primary research question was whether vitamin D supplementation during hospitalization was associated with improvement, no change, or worsening of physiologic manifestations of COVID-19 during acute illness. Third, baseline vitamin D levels were unavailable; therefore, vitamin D deficiency status could not be determined. Fourth, as an observational study, the findings cannot establish causality. Future randomized clinical trials are needed to evaluate causal relationships. Fifth, because the study was conducted at a single tertiary care hospital, generalizability may be limited. Sixth, although the outcome measure is novel, it is not a standardized clinical endpoint such as mortality. Finally, although sensitivity analyses were conducted to address potential unmeasured confounders of disease severity, other unmeasured confounders may exist that could introduce potential bias.

Table 4. Multivariable Linear Regression Analysis for Number of Organ Systems Involved From the Subset of Patients With High-Risk Quick Sequential/Sepsis-Related Organ Failure Assessment Scores

Variables	Vitamin D B (SE)	95% CI	*P* value
Vitamin D supplementation	0.39 (0.16)	0.06 to 0.71	.02
Female sex	0.09 (0.15)	-0.21 to 0.39	0.55
Intensive care unit	0.39 (0.35)	0.31 to 1.08	0.27
Invasive mechanical ventilation admission	0.54 (0.30)	-0.04 to 1.12	0.07
Oxygen requirement hospitalization			
None	ref	ref	
Low FiO_2 (≤55%)	0.63 (0.29)	0.06 to 1.19	.03
High FiO_2 (>55%)	1.60 (0.43)	0.76 to 2.44	<.001
Invasive mechanical ventilation	2.21 (0.47)	1.28 to 3.13	<.001
Vasopressor	1.10 (0.27)	0.57 to 1.62	<.001
Constant	2.37 (0.27)	1.85 to 2.90	<.001

Abbreviations: B, unstandardized beta; SE, standard error; CCI, Charlson Comorbidity Index; ref, reference.

Note: adjusted R square = 0.44.

CONCLUSIONS

Vitamin D supplementation was associated with a greater number of organ systems involved among hospitalized patients with COVID-19. Prospective studies, including randomized clinical trials, are needed to determine whether this association is causal and to confirm these findings.

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Appendices: Supplemental Tables and Figures are available at www.wmjonline.org

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Utilizing Coronary Artery Calcification and the COVID-GRAM Score to Predict Critical Illness in COVID-19 Patients

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ABSTRACT

Introduction: Coronary artery calcification (CAC), identified on routine chest computed tomography (CT), has been associated with worse outcomes in hospitalized patients with COVID-19. The COVID-GRAM Score is a risk stratification tool developed to predict critical illness in this population. This study compared the predictive performance of CAC identified on chest CT with that of the COVID-GRAM Score for intensive care unit (ICU) admission among hospitalized patients with COVID-19 and evaluated whether combining these measures improved identification of high-risk patients. We hypothesized that CAC would outperform the COVID-GRAM Score.

Methods: This retrospective cohort study includes 238 adults hospitalized with COVID-19 at a large academic medical center in Milwaukee, Wisconsin, between July 1, 2020, and July 1, 2021. Data were obtained through electronic medical record database queries and chart review. Eligible patients had confirmed COVID-19 infection and no prior history of coronary artery disease.

Results: Statistical analyses included descriptive statistics, sensitivity and specificity analyses, and receiver operating characteristic (ROC) curve analysis. The mean age was 64 [SD, 15] years, and 46.2% of patients were women. Patients admitted to the ICU had higher mean COVID-GRAM Scores than those not admitted to the ICU (mean [SD], 168 [45.4] vs 150 [44]; $P = .01$). Any CAC was present in 54.2% of ICU-admitted patients compared with 39.1% of patients not admitted to the ICU, and severe CAC was more common among ICU-admitted patients (18.6% vs 5.6%). The area under the ROC curve (AUC) was 0.61 for illness risk score derived from the COVID-GRAM model, compared with 0.58 for any CAC and 0.57 for severe CAC. Composite measures combining CAC and illness risk score did not improve discriminatory performance.

Conclusions: Neither the COVID-GRAM Score nor CAC effectively predicted ICU admission among hospitalized patients with COVID-19. Combining CAC with the illness risk score did not significantly improve predictive performance, highlighting the need for more robust risk stratification tools.

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INTRODUCTION

COVID-19 has caused more than 700 million cases and over 7 million deaths globally and was the 10th leading cause of death in the United States in 2023 (approximately 75 000 deaths).[1-3] Growing evidence points to its impact on cardiovascular health, increasing the risk of myocarditis, arrhythmias, and thromboembolic events in addition to known respiratory complications.[4,5] Using scoring systems to identify patients at risk for deterioration early could lead to better patient outcomes and more efficient use of health care resources.[6]

Coronary artery calcification (CAC) is detectable on computed tomography (CT) and reflects the burden of atherosclerotic disease. Elevated CAC levels signify heightened cardiovascular risk and are associated with greater susceptibility to adverse events. CT scans and the Agatston scoring system quantify CAC, aiding risk assessment and prompting interventions such as lifestyle changes and pharmacotherapy.[7-9] CAC identified on routine chest CT independently predicts worse outcomes among hospitalized patients with COVID-19, including higher mortality, more severe acute coronary syndromes, and increased need for mechanical ventilation.[1,10] This association persists even after accounting for established risk factors, suggesting the unique value of CAC in refining prognosis.

The COVID-GRAM Score is a risk tool developed to stratify hospitalized patients with COVID-19 according to their likelihood of adverse outcomes, with higher scores associated with a worse prognosis. The score's effectiveness at hospital admission may facilitate early risk stratification and potentially inform treat-

ment decisions.[11] A retrospective cohort study involving patients from 575 hospitals in China used data collected through January 31, 2020, to develop the score; however, it requires further evaluation in diverse external populations to establish validity.

While both CAC and the COVID-GRAM Score are potentially valuable tools for predicting outcomes in patients with COVID-19, studies evaluating their utility are scarce and have limitations. Building on our prior work demonstrating an association between CAC and worse COVID-19 outcomes,[1] this study compares the predictive ability of CAC detected on chest CT scans with that of the COVID-GRAM Score. We hypothesized that CAC would outperform the COVID-GRAM Score in predicting critical illness, defined by intensive care unit (ICU) admission. As a secondary objective, we assessed whether combining CAC and the COVID-GRAM Score would improve discrimination of ICU-level care.

METHODS

The Medical College of Wisconsin Institutional Review Board approved this retrospective cohort study and waived individual informed consent on May 21, 2020.

Data Source and Study Population

To identify eligible patients, researchers used the Clinical Research Data Warehouse tools, including i2b2 and the Honest Broker tool, provided by our institution's Clinical and Translational Science Institute. Researchers conducted a chart review using the institution's electronic health record to collect data.

Patients aged 18 years or older without a history of coronary artery disease (prior myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting) who were hospitalized at a large academic medical center in Milwaukee, Wisconsin, with active COVID-19 infection confirmed by reverse transcription-polymerase chain reaction (RT-PCR) between July 1, 2020, and July 1, 2021, were included. Patients who had previously tested positive for COVID-19 but did not have active symptoms during hospitalization and those who did not undergo chest CT during hospitalization were excluded.

The original dataset contained 464 participants. Individuals with missing lactate dehydrogenase values (n = 236) were excluded because the COVID-GRAM Score could not be calculated without this variable.[1] After application of these criteria, the final sample comprised 238 individuals.

Independent Variables and Outcome

The independent variables included demographic characteristics (age, sex, ethnicity, race, marital status, and employment status), CAC, and COVID-GRAM Score-related variables. Variables required to calculate the COVID-GRAM Score included chest radiograph abnormalities, age, hemoptysis, dyspnea, unconsciousness, number of comorbidities (chronic obstructive pulmonary disease, hypertension, diabetes, coronary artery disease, heart failure, chronic kidney disease, cancer, cerebrovascular disease, hepatitis B, immunodeficiency), cancer history, neutrophil-to-lymphocyte ratio, lactate dehydrogenase, and direct bilirubin. The points assigned in the COVID-GRAM Score are converted to an illness risk score, defined as risk of ICU admission, invasive ventilation, or death.[11]

Table 1. Demographic Characteristics (n = 238)

Variable	ICU – No (n = 179)	ICU – Yes (n = 59)	Overall (n = 238)	*P* value
Age, mean [SD], y	62.7 [15.1]	65.6 [13.7]	63.5 [14.8]	.2
Sex, n (%)				.94
Female	83 (46.4)	27 (45.8)	110 (46.2)	
Male	96 (53.6)	32 (54.2)	128 (53.8)	
Ethnicity, n (%)				.86
Hispanic	7 (3.9)	2 (3.4)	9 (3.8)	
Non-Hispanic	172 (96.1)	57 (96.6)	229 (96.2)	
Race, n (%)				.27
Black/African American	31 (17.4)	16 (27.1)	47 (19.8)	
White	130 (73.0)	38 (64.4)	168 (70.9)	
Other	17 (9.6)	5 (8.5)	22 (9.3)	
Marital status, n (%)				.37
Married	103 (57.5)	30 (50.8)	133 (55.9)	
Not married	76 (42.5)	29 (49.2)	105 (44.1)	
Employment status, n (%)				<.01
Employed	70 (39.3)	11 (18.6)	81 (34.2)	
Not employed	108 (60.7)	48 (81.4)	156 (65.8)	

Based on the illness risk score, patients were categorized into 1 of 3 risk groups: low, intermediate, and high risk. The low-risk group included patients with an illness risk score of <1.7%. The intermediate-risk group included patients with an illness risk score of 1.7% to <40.4%, and the high-risk group included patients with an illness risk score of ≥40.4%. For this study, the high-risk group (illness risk score of ≥40.4%) was classified as positive as a binary variable (positive illness risk score).

In addition to COVID-19-related factors, the severity of CAC detected on CT was evaluated. Radiologists assigned CAC severity as none, mild, moderate, or severe. These categories were subsequently grouped into 3 classifications for analysis: any CAC, moderate-to-severe CAC, and severe CAC.

Composite scoring systems were created by combining CAC severity and positive illness risk score. The first composite score combined any CAC and positive illness risk score (Composite 1). The second combined moderate-to-severe CAC and positive illness risk score (Composite 2). The third combined severe CAC and positive illness risk score (Composite 3). The binary dependent (outcome) variable was whether participants required ICU admission.

Statistical Analysis

Descriptive analyses were conducted to summarize the demographic and clinical characteristics of the study population.

Continuous variables were summarized as means with standard deviations, and categorical variables were summarized as frequencies and percentages. Differences between patients admitted to the ICU and those not admitted were evaluated using *t* tests for continuous variables and chi-square tests for categorical variables.

To assess the discriminatory performance of clinical measures for predicting ICU admission, binary classification analyses were performed. ICU admission was treated as a binary outcome (yes/no). The illness risk score (derived from the COVID-GRAM model) was evaluated as a continuous variable and dichotomized using a threshold of 0.404 to define high-risk versus non-high-risk groups.[11] CAC was examined using 3 binary categorizations: (1) any CAC versus none, (2) moderate-to-severe CAC versus none or mild CAC, and (3) severe CAC versus all other CAC categories.

For each predictor variable, 2x2 contingency tables were generated to classify ICU admission as true positive, false positive, true negative, or false negative, from which sensitivity and specificity were calculated. Composite predictors that combined clinical risk and CAC burden also were evaluated: (1) high illness risk score with any CAC, (2) high illness risk score with moderate-to-severe CAC, and (3) high illness risk score with severe CAC. Receiver operating characteristic (ROC) analyses were performed by comparing predictor values with observed ICU admission status. ROC curves were constructed by plotting sensitivity against 1 – specificity, and the area under the ROC curve (AUC) was used to summarize discriminative accuracy.

All statistical analyses were performed using R version 4.2.3 (R Foundation for Statistical Computing), and *P* values <.05 were considered statistically significant.

Table 2. COVID-GRAM Score, Illness Risk Score, CAC Scores, and Composite Scores

Variable	ICU – No (n = 179)	ICU – Yes (n = 59)	Overall (n = 238)	*P* value
COVID-GRAM Score, mean [SD]	150 [44.0]	168 [45.4]	155 [44.9]	.01
X-ray abnormality, n (%)				.77
No	51 (28.5)	18 (30.5)	69 (29.0)	
Yes	128 (71.5)	41 (69.5)	169 (71.0)	
Hemoptysis, n (%)				.99
No	167 (93.3)	59 (100)	226 (95.0)	
Yes	12 (6.7)	0 (0)	12 (5.0)	
Dyspnea, n (%)				.2
No	48 (26.8)	21 (35.6)	69 (29.0)	
Yes	131 (73.2)	38 (64.4)	169 (71.0)	
Unconsciousness, n (%)				.81
No	174 (97.2)	57 (96.6)	231 (97.1)	
Yes	5 (2.8)	2 (3.4)	7 (2.9)	
No. of comorbidities, mean [SD]	3.08 [1.66]	3.76 [1.50]	3.25 [1.65]	<.01
Cancer history, n (%)				.53
No	129 (72.1)	45 76.3)	174 (73.1)	
Yes	50 (27.9)	14 23.7)	64 (26.9)	
Neutrophil-lymphocyte ratio, mean [SD]	8.50 [7.83]	14.4 [18.8]	9.98 [11.8]	<.01
Lactate dehydrogenase, mean [SD]	369 [164]	472 [188]	394 [175]	<.001
Direct bilirubin, mean [SD]	2.61 [2.96]	2.78 [2.84]	2.65 [2.92]	.69
Illness risk score, mean [SD][a]	51 [31.7]	62.7 [27.7]	53.9 [31.1]	.01
Any CAC (mild/moderate/severe), n (%)				.04
No	109 (60.9%	27 (45.8)	136 (57.1)	
Yes	70 (39.1)	32 (54.2)	102 (42.9)	
Moderate-to-severe CAC, n (%)				.22
None or mild	144 (80.4)	43 (72.9)	187 (78.6)	
Moderate or severe	35 (19.6)	16 (27.1)	51 (21.4)	
Severe CAC, n (%)				<.01
None or mild or moderate	169 (94.4)	48 (81.4%)	217 (91.2)	
Severe	10 (5.6)	11 (18.6%)	21 (8.8)	
Composite 1, n (%)				<.01
Positive illness risk score[b] and any CAC	54 (30.2)	30 (50.8)	84 (35.3)	
Other	125 (69.8)	29 (49.2)	154 (64.7)	
Composite 2, n (%)				.06
Positive illness risk score[b] and moderate-to-severe CAC	29 (16.2)	16 (27.1)	45 (18.9)	
Other	150 (83.8)	43 (72.9)	193 (81.1)	
Composite 3, n (%)				<.01
Positive Illness Risk Score[b] and severe CAC	9 (5.0)	11 (18.6)	20 (8.4)	
Other	170 (95.0)	48 (81.4)	218 (91.6)	

Abbreviations: CAC, coronary artery calcification.

[a]Illness Risk is defined as intensive care unit admission, invasive ventilation, and death.

[b]Positive Illness Risk Score = high-risk group (illness risk score of ≥ 40.4%).

RESULTS

Demographic Characteristics

The study cohort consisted of 238 patients hospitalized with active COVID-19 who underwent chest CT during hospitalization and had laboratory testing sufficient to calculate the COVID-GRAM Score.

Table 1 summarizes the demographic characteristics of the study population. The mean age was 64 [SD, 15] years. Among the 238 participants, the distribution by sex was nearly even, with 110 females (46.2%). Most participants were non-Hispanic (96.2%) and identified as White (70.9%). Analysis of demographic variables revealed no statistically significant differences in age, sex, ethnicity, race, or marital status between patients admitted to the ICU and those not admitted. However, employment status was significantly associated with ICU admission, with 81% of patients

admitted to the ICU being unemployed compared with 61% of patients not admitted to the ICU ($P < .01$). Patients admitted to the ICU also had a higher mean number of comorbidities (mean, [SD], 3.76 [1.50] vs 3.08 [1.66]; $P < .01$).

COVID-GRAM Score and Coronary Artery Calcification

Table 2 summarizes the study population's COVID-GRAM scores, illness risk scores, CAC severity, and composite scores. The mean COVID-GRAM Score was 155 [SD, 44.9], and the mean illness risk score was 53.9 [SD, 31.1]. Participants admitted to the ICU exhibited higher mean COVID-GRAM Scores (168 [45.4] vs 150 [44.0]) and illness risk score (62.7 [27.7] vs 51 [31.7]) than patients not admitted to the ICU ($P = .01$ for both comparisons).

Among COVID-GRAM Score-related variables, patients admitted to the ICU had higher neutrophil-to-lymphocyte ratios (14.4 [18.8] vs 8.50 [7.83]) and higher lactate dehydrogenase levels (472 [188] vs 369 [164]) than patients not admitted to the ICU ($P < .01$ for all). Hemoptysis, chest radiograph abnormalities, dyspnea, loss of consciousness, cancer history, and direct bilirubin levels did not differ significantly between the groups.

ICU admission was associated with positive CAC findings, particularly severe CAC. Among patients admitted to the ICU, 18.6% had severe CAC compared with 5.6% patients not admitted to the ICU ($P < .01$) (Table 2). Likewise, any CAC was positively associated with ICU admission. Although 42.9% of the study population had any CAC, 54.2% of patients requiring ICU admission had CAC ($P = .04$). However, the association was not statistically significant when moderate-to-severe or severe CAC was compared with non or mild CAC ($P = .22$).

To assess whether combining the COVID-GRAM Score and CAC would better predict outcomes, 3 composite variables were evaluated. Composite 1 (any CAC and a positive illness risk score) was positive in 50.8% of ICU-admitted patients compared with 30.2% of patients not admitted to the ICU ($P < .01$). Likewise, Composite 3 (severe CAC and a positive illness risk score) was positive in 18.6% of ICU-admitted patients compared with 5% of patients not admitted to the ICU ($P < .01$). There was no statistically significant association between Composite 2 (moderate-to-severe CAC and a positive illness risk score) and ICU admission ($P = .22$).

Table 3. Sensitivity, Specificity, and AUC Analysis

Variable		ICU (Yes/No)		Sensitivity	Specificity	AUC
Illness risk score[a]		Positive	Negative	0.8	0.41	0.61
	Positive	47	105			
	Negative	12	74			
Any CAC (mild/moderate/severe)		Positive	Negative	0.54	0.61	0.58
	Positive	32	70			
	Negative	27	109			
Moderate-to-severe CAC		Positive	Negative	0.27	0.8	0.54
	Positive	16	35			
	Negative	43	144			
Severe CAC		Positive	Negative	0.19	0.94	0.57
	Positive	11	10			
	Negative	48	169			
Composite 1[b]		Positive	Negative	0.51	0.7	0.6
	Positive	30	54			
	Negative	29	125			
Composite 2[b]		Positive	Negative	0.27	0.84	0.55
	Positive	16	29			
	Negative	43	150			
Composite 3[b]		Positive	Negative	0.19	0.95	0.57
	Positive	11	9			
	Negative	48	170			

Abbreviations: AUC, area under the receiver operating characteristic curve; ICU, intensive care unit; CAC, coronary artery calcification.

Note: positive = yes; negative = no.

[a]Positive illness risk score = ≥ 40.4%; negative illnes risk score = 1.7% to <40.4%.

[b]Composite 1 (any CAC and positive illness risk score); Composite 2 (moderate-to-severe CAC and positive illness risk score); Composite 3 (severe CAC and positive illness risk score).

Sensitivity, Specificity, and AUC analysis

Table 3 summarizes the sensitivity, specificity, and the area under the receiver operating characteristics curve (AUC) for the COVID-GRAM Score, CAC categories and composite. ROC analysis is a valuable tool for assessing the ability of index tests to accurately diagnose diseases or conditions. The AUC was selected as the primary metric because it summarizes overall discriminatory performance across all possible thresholds.[12] An AUC score of 0.50 indicates that a test's predictive ability is no better than chance, whereas values above 0.80 generally considered clinically useful.[12]

Among the 238 patients analyzed, AUC values were close to 0.50 for all predictors evaluated, including the illness risk score and all CAC levels. As shown in the Figure, the AUC was 0.61 for the illness risk score, 0.58 for any CAC, 0.54 for moderate-to-severe CAC, and 0.57 for severe CAC. Although the illness risk score had the highest AUC (0.61), its performance was not significantly different from that of the CAC-based measures.

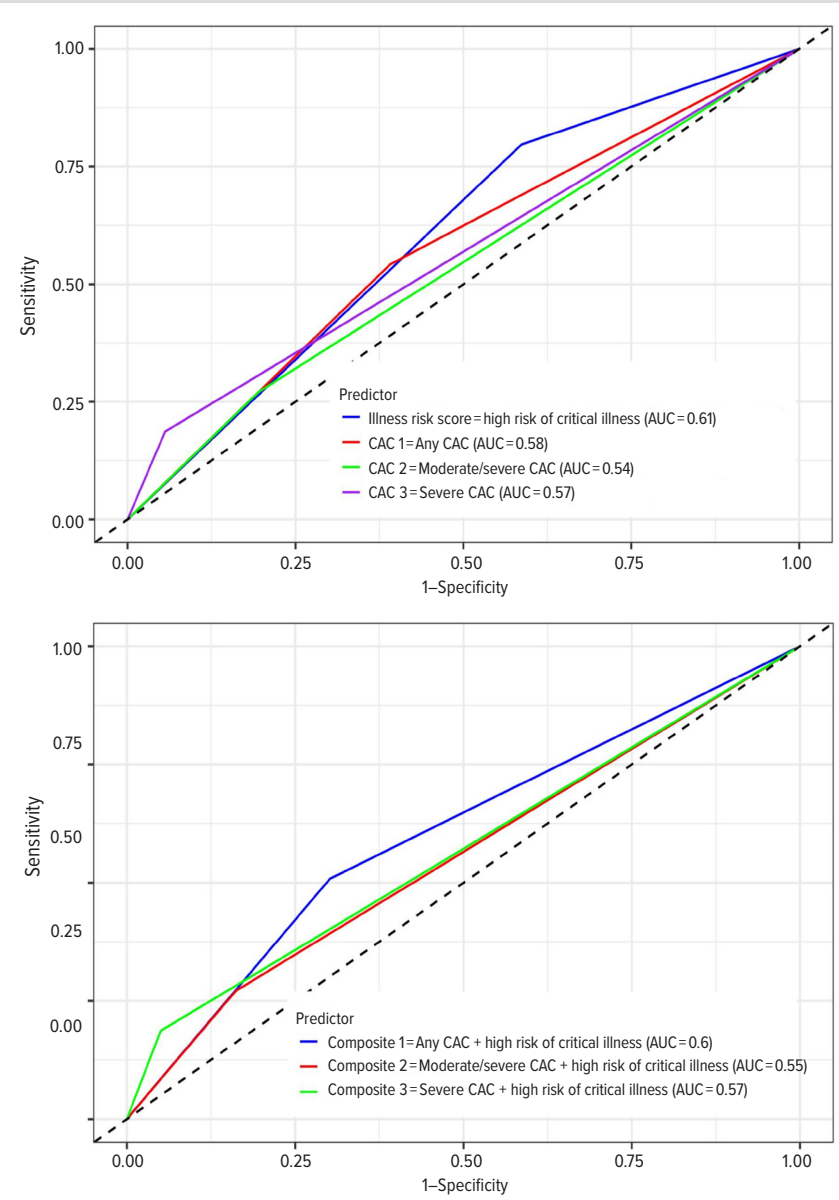
Composite scores did improve predictive performance. The AUC was 0.6 for Composite 1 (any CAC and positive illness risk score), 0.55 for Composite 2 (moderate-to-severe CAC and positive illness risk score), and 0.57 for Composite 3 (severe CAC and positive illness risk score).

DISCUSSION

At a single US academic medical center, the COVID-GRAM Score, incidental CAC identified on CT chest, and their composite measures demonstrated limited discrimination for predicting ICU-level care among hospitalized patients with COVID-19 and no prior clinical coronary artery disease. AUC values ranged from 0.54 to 0.61. Although severe CAC demonstrated high specificity (94%), its low sensitivity limited its utility as a stand-alone predictor. Nevertheless, severe CAC may have value for identifying a small subset of patients at higher risk for ICU admission. The novelty in this study lies in its direct comparison of these 2 risk stratification tools and its evaluation of whether a combining them improves prediction of ICU admission.

Although several comparisons were statistically significant in our cohort, including higher COVID-GRAM and illness risk scores, higher neutrophil-to-lymphocyte ratios, higher lactate dehydrogenase levels, and a greater prevalence of severe CAC and any CAC among ICU-admitted patients, overall discrimination for ICU admission remained poor. AUC values were 0.61 for the illness risk score, 0.58 for any CAC, 0.54 for moderate-to-severe CAC, 0.57 for severe CAC, and 0.60, 0.55, and 0.57 for the 3 composite measures, respectively. These findings are not contradictory. Whereas *P* values from group comparisons test whether mean or proportion differences exist between groups, the AUC assesses how effectively a measure distinguishes individual patients by risk across the sample. In our sample of 238 patients, modest differences between groups were sufficient to yield statistically significant *P* values but did not translate into clinically meaningful discrimination.

Figure. ROC Curves With Binary Outcome Intensive Care Unit (yes/no)



Abbreviations: AUC, area under the receiver operating characteristics curve; CAC, coronary artery calcification; ROC, receiver operating characteristic.

The operating characteristics shown in Table 3 further illustrate this distinction. Predictors with more specific thresholds, such as severe CAC and Composite 3 (specificity, 0.94-0.95; sensitivity, 0.19), identified a relatively small subset of higher-risk patients but failed to detect many ICU admissions. In contrast, the illness risk score (sensitivity, 0.80; specificity, 0.41) identified more patients who required ICU care but produced a substantial number of false-positive results. Accordingly, statistically significant associations should be interpreted as evidence of group-level differences rather than evidence of strong predictive performance. Taken together, the AUC, sensitivity, and specificity findings do not support the use of the COVID-GRAM Score, CAC, or their composite measures alone for triage or prognostication in this setting.

Our findings are consistent with those of Al Hassan et al,[13] who evaluated the COVID-GRAM Score, CALL score, and a nomogram in a multicenter study in the United Kingdom. The reported AUC values were 0.636, 0.500, and 0.628, respectively. The authors attributed the low predictive power of these tools to differences in the patient populations in the United Kingdom and

China. Similarly, the mean age of patients in our study was 63.5 years [SD, 14.8], compared with 48.9 years [15.7] in the original derivation cohort. The outcome of COVID-19 infection is also strongly influenced by underlying comorbidities.[14] In the cohort used to develop the COVID-GRAM Score, 75% of patients had no comorbid conditions, and only 2.5% had 3 or more comorbidities.[11] In contrast, participants in our study had a mean of 3.25 [1.65] comorbidities. These differences likely reduced the generalizability and performance of the COVID-GRAM model in our population.

Multiple previous studies have reported an association between CAC and adverse COVID-19 outcomes, particularly mechanical ventilation and mortality.[10,15,16] Most of these studies were conducted early in the pandemic, outside the United States, and over relatively short study periods when treatment options were limited.[10,15,16] The RECOVERY trial and CoDEX trial demonstrated improvement in mortality associated with dexamethasone in patients with severe COVID-19, leading to changes in treatment protocols.[17,18] Our study spanned July 2020 through July 2021, a period during which treatment strategies evolved substantially. These changes in treatment practices may partially explain the differences in CAC performance observed between our study and earlier reports.

The original study by Kotlo et al[1] analyzed the same patient population and found positive associations between CAC and ICU admission, mechanical ventilation, and mortality. Our analysis was restricted to the subset of patients with available lactate dehydrogenase data, resulting in the exclusion of 226 patients and reducing statistical power. This reduction in sample size may have altered the observed relationships. In addition, comparison of our cohort with the original Chinese derivation cohort highlights the differences in clinical practice patterns. Lactate dehydrogenase was obtained in the Chinese cohort but was not consistently measured in our institution's patient population.[11]

A strength of this study is the inclusion of patients hospitalized over a 12-month period, with a relatively even distribution of men and women. The study also captured patients treated later in the pandemic, when treatment options had become more standardized.

Limitations

A limitation of this study is that it included only patients who underwent nongated chest CT and had the complete laboratory data required to calculate a COVID-GRAM Score. These inclusion criteria may have selected for a sicker patient population. In addition, they resulted in the exclusion of a large subset of eligible patients, reducing the final sample size to 238 and limiting the representativeness of the cohort.

Another limitation is the assessment of CAC using nongated chest CT to diagnose and assess COVID-19 severity and a semiquantitative classification of none, mild, moderate-to-severe, and severe CAC rather than the quantitative Agatston scoring. This approach is potentially subjective and may vary among radiologists. Furthermore, only a limited number of studies have validated CAC assessment against the Agatston score, which remains the reference standard.[7,19]

The study may also have been underpowered. The calculated sample size required to achieve a power of 80% and acceptable AUC values was 252 participants. Because the final sample included only 238 participants, the possibility of a type II error cannot be excluded, meaning that potentially important associations may have gone undetected.[20,21] Accordingly, these findings should be considered preliminary and warrant confirmation in larger, prospective, multicenter studies.

CONCLUSIONS

The presence of incidental severe CAC in patients with COVID-19 and no prior history of clinical coronary artery disease may indicate an increased likelihood of requiring ICU-level care and should prompt heightened clinical awareness. However, our finding also highlight the limitations of the COVID-GRAM Score for predicting severe COVID-19 illness necessitating ICU admission. Because the score was developed and validated in specific patient populations, its performance may not generalize to other clinical settings. In our cohort, a high COVID-GRAM Score demonstrated limited ability for predicting ICU admission, and CAC did not outperform the COVID-GRAM Score. Furthermore, combining CAC with the COVID-GRAM Score did not meaningfully improve predictive performance. Accordingly, these tools should be used cautiously and should not serve as stand-alone determinants of clinical decision-making. Further large-scale, prospective, multicenter studies are needed to better define the role of CAC and COVID-19 risk prediction models in identifying patients at risk for severe illness.

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Small Drapes, Big Impact: Rethinking Drape Size for Infection Control in Cataract Surgery

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ABSTRACT

Introduction: The American Academy of Ophthalmology has reported that each cataract surgery in the United States produces 2.3 to 3.9 kg of waste. Studies from the Aravind Eye Care System in India have shown that, despite reusing surgical supplies between patients, postoperative endophthalmitis rates were lower than those reported in the United States. This suggests that much of the surgical material used in the United States may be unnecessary to prevent endophthalmitis. Identifying strategies to reduce waste generated by ophthalmic surgery is important. The purpose of this study was to determine whether postoperative endophthalmitis rates differed between cataract surgeries performed using full- or three-quarter-size surgical drapes.

Methods: We conducted a retrospective review comparing the use of Alcon full-size (6500 in^2) and three-quarter-size (3465 in^2) surgical drapes for phacoemulsification cataract surgery at a university-affiliated ambulatory surgery center between 2020 and 2024. Outcomes included postoperative endophthalmitis rates, surgical waste generated (in^2), and cost.

Results: A total of 21469 cataract surgeries were completed at the University of Wisconsin-Madison (UW Health's) ambulatory surgery center between 2020 and 2024. A total of 4897 (22.81%) cases used three-quarter-size surgical drapes and 16 572 (77.19%) used full-size surgical drapes. There were no cases of endophthalmitis in either group. Compared with full-size drapes, the three-quarter-size drapes reduced material use by 47% and saved $17,139.50.

Conclusions: No difference in postoperative endophthalmitis rates was observed between groups. Therefore, three-quarter-size surgical drapes may represent an acceptable alternative to full-size drapes for improving the sustainability of cataract surgery.

INTRODUCTION

According to the World Health Organization, climate change is a significant threat to human health, contributing to an estimated 13 million climate-associated deaths annually.[1] Globally, the health care sector is estimated to be responsible for 5% of all greenhouse gas emissions.[2] In the United States, the health care sector accounts for 10% of all greenhouse gas emissions and is the second-largest contributor to landfills after the food industry.[3] Operating rooms account for almost 70% of health care-sector emissions.[4]

Cataracts are the leading cause of visual impairment and blindness, making cataract surgery one of the most commonly performed procedures worldwide.[5] An estimated 20 million cataract surgeries are performed annually, with 3.7 million performed in the United States alone.[6] In resource-rich countries, cataract surgery utilizes single-use products that generate substantial waste. In 2016, the American Academy of Ophthalmology reported that each cataract surgery in the United States produces 2.3 to 3.9 kg of waste, all of which is landfill or biohazardous material.[7,8]

In resource-limited countries, the cost of surgery is a significant barrier for patients seeking cataract treatment.[9] To make eye care more accessible, the Aravind Eye Care System (AECS) in India developed an innovative model of care centered on time and resource efficiency.[7] As a result, surgeries are performed on multiple patients simultaneously within a single operating room, without changing surgical gowns or gloves between cases, and surgical

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and pharmaceutical supplies are routinely reused.[10] AECS produces 250 g of waste per phacoemulsification case, less than 11% of the waste generated by a comparable case in the United States.[7]

Despite reusing surgical supplies between patients and managing a high patient volume, AECS maintains a lower rate of postoperative endophthalmitis (0.01%) than that reported in the United States (0.04%).[7,10,11] These findings suggest that much of the single-use surgical equipment and supplies used in the United States may not prevent postoperative endophthalmitis. This observation is supported by published practice guidelines indicating that the primary measures associated with reducing postoperative endophthalmitis are preoperative preparation with povidone-iodine, intracameral antibiotic injection at the conclusion of surgery, and meticulous surgical technique.[12] Therefore, because ophthalmology has one of the highest surgical volumes in medicine, identifying strategies to reduce surgical waste is imperative.

We argue that full-size surgical drapes are unnecessary for cataract cases; shorter surgical drapes provide the same level of sterility given that they adequately cover the surgical field. The primary source of intraocular infection is bacteria from the patient's ocular surface, including the cornea and conjunctiva, and adnexa, including the eyelids, lacrimal glands, and extraocular muscles.[13] Eyelids and eyelashes remain covered with shorter surgical drapes, while areas distal to the patient's knee, which are not sources of endophthalmitis-causing infection, remain exposed.

This report presents a 5-year comparison of endophthalmitis rates, surgical waste, and cost savings between cataract surgery cases using full and three-quarter-size surgical drapes to determine whether smaller drapes are an acceptable alternative to reduce surgical waste.

METHODS

A retrospective review was performed to compare the use of Alcon full-size (6500 in^2) and three-quarter-size (3465 in^2) surgical drapes for cataract surgery at the University of Wisconsin-Madison ambulatory surgery center. Only phacoemulsification cases performed between 2020 and 2024 were included. Analysis included a comparison of postoperative endophthalmitis rates, surgical waste generated (in^2), and cost. Combined phacoemulsification cases with corneal, glaucoma, or other concurrent procedures were excluded. Use of surgical drape size was based on surgeon preference. The operating surgeon draped all patients.

This study was exempt from Institutional Review Board oversight.

RESULTS

A total of 21 469 cataract surgeries were completed at the University of Wisconsin-Madison ambulatory surgery center from 2020 through 2024; 4897 (22.81%) cases used three-quarter-size surgical drapes, and 16 572 (77.19%) used full-size surgical drapes. Ten surgeons used full-size surgical drapes. All cases using three-quarter-size drapes were performed by a single surgeon. There were no cases of endophthalmitis in either group.

Cases using full-size drapes resulted in a total of 107 718 000 in^2 of waste from surgical drapes alone, whereas cases using three-quarter-size drapes generated 16 968 105 in^2 of waste. Each three-quarter-size drape contains 47% less material than a full-size drape, resulting in a savings of 14 862 395 in^2 of material over the 5-year study period. The facility saved $17,139.50 by using the smaller drapes.

DISCUSSION

In 2021, the World Health Organization declared climate change to be the single biggest threat facing humanity.[14] If the health care system were a country, it would be the fifth-largest contributor to carbon emissions in the world, with emissions stemming primarily from power consumption in operating rooms, medication production, medical supply packaging, and transportation of patients, staff, and supplies.[15] Ophthalmology has one of the highest surgical volumes of any medical specialty and is therefore thought to contribute substantially to these emissions. Furthermore, because of the world's aging population, the demand for eye care is expected to increase significantly over the next 20 years.[16] Consequently, adopting more sustainable practices is an important priority within ophthalmology,

In a 2020 survey of more than 1300 cataract surgeons and nurses by the Ophthalmic Instrument Cleaning and Sterilization (OICS), 93% of respondents stated that operating room waste is excessive and should be reduced.[17] Several sources of unnecessary waste in cataract surgery have been identified in the literature. The use of water-based scrub techniques for surgical antisepsis was reported to use 61 000 L of water annually per operating room at a large ophthalmic surgical hospital.[18] Packaging associated with intraocular lenses (IOLs) and viscoelastic materials contributes more than 30% of the waste generated during cataract surgery, despite the IOL itself weighing approximately 1 g.[19] Drug waste management also contributes substantially, producing an estimated 30 kg of carbon emissions per cataract surgery.[20]

We identify full-size surgical drapes as another source of excess waste in cataract surgery. We hypothesized that because the sterile field remains completely covered by the drape regardless of whether it extends to the patient's feet or mid-thigh, shorter surgical drapes would be appropriate for cataract surgery. Our findings demonstrated no cases of postoperative endophthalmitis during the 5-year study period among phacoemulsification cases using three-quarter-size drapes. Similarly, no cases occurred among surgeries using full-size drapes, suggesting that shorter surgical drapes do not increase infection risk.

A recent study reported that over 50% of energy consumption during cataract surgery at a British academic institution was associated with the production, use, and disposal of surgical materials,

highlighting the substantial environmental burden of these materials.[21] Three-quarter-size surgical drapes use 47% less material than full-size drapes and can reduce the amount of waste generated. Over the 5-year study period, their use saved 14.8 million in^2 of material, an area approximately equivalent to 1.8 football fields. Furthermore, because shorter surgical drapes cost less, they also provide a financial benefit.

Given that three-quarter-size surgical drapes did not adversely affect patient outcomes, reduced material waste, and were associated with lower costs, their use during cataract surgery appears justified. Even shorter surgical drapes are available on the market and use up to 70% less material than full-size drapes; however, further research is needed to determine their role in cataract surgery.

Limitations

This study is limited by its single-institution design. Additional multicenter studies with larger sample sizes would further strengthen the evidence supporting these findings.

CONCLUSIONS

The results of this study demonstrated no difference in postoperative endophthalmitis rates between drape sizes. Therefore, shorter surgical drapes may be an acceptable alternative to full-size drapes for improving the sustainability of cataract surgery.

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Comparison of AI and Manual Coding of Medical Students' Reflections: An Asynchronous Discussion Board Exploration

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ABSTRACT

Introduction: The use of generative artificial intelligence (AI) for medical education research remains controversial. Although AI has the potential to revolutionize qualitative research analysis, concerns regarding its validity and accuracy remain barriers to its use in research. We sought to compare AI-generated qualitative coding with human coding.

Methods: As part of a mandatory course, third-year medical students watched 2 health care-related videos and responded to prompts on a virtual discussion board. Students' posts were anonymized. Human coders met multiple times over a 4-month period to create a code list, generate themes, and produce an explanatory model. Generative AI also was asked to identify the main themes. Three external reviewers with expertise in qualitative research compared each pair of human-coded and AI-generated themes.

Results: Human coders required nine 60-minute meetings to code students' posts, whereas AI completed the analysis in approximately 30 seconds. Consensus among the external reviewers was that the pairs of themes were not the same or similar.

Conclusions: AI required substantially less time and effort than human coders. Although most reviewers concluded that AI-generated themes were not comparable to human-generated themes, this finding was not unanimous. Generative AI may facilitate and accelerate qualitative research in medical education; however, concerns regarding the validity and contextual interpretation of AI-generated analyses must be addressed before its widespread use in qualitative medical education research.

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INTRODUCTION

Qualitative studies involving written reflections and interviews can provide details and deeper understanding of participants' perspectives not otherwise attainable through quantitative methods. The analysis of such qualitative studies, however, is generally labor-intensive. Manually coding written posts and transcripts requires human coders and sufficient time for analysis. For most medical educators with a variety of responsibilities, finding time to meet and code qualitative data can be challenging.

Generative artificial intelligence (AI), such as ChatGPT, offers an alternative to manual coding that could change the way qualitative research is done. Generative AI is defined as "deep-learning models that can generate high-quality text, images, and other content based on the data they were trained on."[1] Research on generative AI in medicine and medical education remains limited. As an emerging area, studies on generative AI have tended to focus on patient care-related outcomes.[2-4] Studies in medical education have generally explored student evaluations rather than educational assignments.[4]

Virtual discussion boards have long been used in undergraduate education and other health professions education, such as dentistry.[5] Their use in medical education has been less common, although it increased during the COVID-19 pandemic. Posts on virtual discussion boards became a straightforward way to track and confirm student engagement with required online activities. Students' reflections contain a wealth of information, making written assignments valuable sources of data for research.[6] However,

examining reflections for research is traditionally both time- and labor-intensive.

Generative AI presents an opportunity to analyze qualitative research more efficiently with fewer personnel.[2] Integrating AI into required coursework for research and educational purposes could enhance productivity without adding to the workload. However, the extent to which AI can understand the context of data compared with human coders remains uncertain. The objectives of this study were to compare themes identified from students' reflections by AI and human coders and to evaluate how each performed the analysis.

Table 1. Video Title, Competency Domain, and Duration

Video Title	Domain	Duration
Making Mistakes	Professionalism; personal and professional development	1:37:45
Emotional Intelligence	Interpersonal and communication skills; personal and professional development; professionalism	1:04:25
Advocacy on the Frontlines: Supporting LGBTQ Patients in Combat and Beyond	Practice, interpersonal and communication skills, professionalism	0:55:00[a]
Healing in the Aftermath of Hate	Personal and professional development, professionalism	0:50:00[a]
The Art of Medicine – Patient-Centered Communication Skills	Interpersonal and communication skills; professionalism	1:00:05
Healthcare Remains the Third Leading Cause of Death: Is There Hope for the Future	Systems-based practice; practice-based learning and improvement	0:55:00
Gallows Humor	Professionalism; interpersonal and communication skills	54:58
I Am Not Your Inspiration	Practice-based learning and Improvement; professionalism, systems-based practice	0:09:02

[a]Approximate duration of video

METHODS

Participants

Third-year medical students at the Medical College of Wisconsin (MCW), a private medical school in the United States, who were enrolled in the required third- and fourth-year Continuous Professional Development (CPD) course were invited to participate. Students who volunteered were asked to complete an assignment that involved viewing 2 of 8 health care-related videos of their choice and posting a corresponding reflection on a virtual discussion board. They also were asked to respond to 2 posts by their peers. Students had 1 week to complete the assignment. Students who declined to participate received an alternative assignment. By posting on the discussion board, students consented to participate in the study. The MCW Institutional Review Board reviewed and approved the study (PRO00049191). All 224 eligible students participated and completed the assignment.

Videos

Eight videos encompassing a variety of health care-related topics were available for viewing. All videos except one were recordings of live presentations delivered between 2019 and 2021. The exception was a TED Talk. Four videos were sessions developed specifically for the CPD course, and 3 were presented as MCW or departmental grand rounds. Speakers included physicians, authors, an activist, and a lawyer. Topics, corresponding medical education competency domains, and video duration are shown in Table 1. The videos and topics focused on the art of medicine rather than knowledge-based competencies. Students were asked to address at least 1 prompt related to the videos. The prompts asked them to discuss their thoughts and reactions, the videos' themes, and the impact and value of the content on their clinical experiences and future practice.

Analysis

Four CPD course directors (KB, MG, LR, and CS) monitored the discussion board, including periodically commenting on posts. CPD coordinators anonymized all posts after the discussion boards closed. Given the exploratory nature of this study, the investigators chose to focus on the video with the greatest number of threads, titled "I am Not Your Inspiration," which focused on how individuals with disabilities are perceived. The remaining CPD course directors (CK, HP, SV, and MW) used grounded theory methodology to iteratively code the posts. Grounded theory aims to generate theory from coding patterns rather than starting with predetermined ideas.[7] Posts were categorized by student and by whether they were an original post or a response. Only original student posts were coded. Themes were generated by clustering similar sentiments and then tested and refined by the coders.[8]

The CPD course directors responsible for coding reviewed each original student post. Using a grounded theory approach, the group first performed open coding, creating preliminary codes for each post. Subsequently, axial coding was performed to identify connections and group similar codes. Iterative discussion among the coders was used to finalize the codes and organize them into themes.

Generative AI and Thematic Analysis

Microsoft Copilot for Microsoft 365, an AI-powered assistant licensed by MCW, was used for AI-based thematic analysis. Copilot operates using large language models (LLMs) in conjunction with the account user's Microsoft 365 data and internet-based information sources.[9] A PDF containing anonymized student reflections from the video with the most responses was attached to the prompt. Copilot was also provided a link to the TED Talk, the 5 discussion prompts, and instructions to identify 3 themes and 3 representative quotes for each theme.

Table 2. Themes by Human Coders and AI With Representative Student Quotes

Themes by Human Coders	Illustrative Example	Themes by AI	Illustrative Example
Emotions	"I thought about how at one point in my youth I would have been surprised by this." "I have not really thought about it the way she did and it makes me question my concepts of disabilities." "As future physicians, I believe that it can become easy for us to view the world through a 'clinical' or 'problem-base' lens. Such a lens often distorts the true reality of a situation and may alter the empathy that we feel for a particular situation or individual."	Objectification and "Inspiration Porn"	"I never realized that feeling inspired or motivated by a disabled person completing an ordinary act is objectifying them." "We often praise individuals with disabilities solely for their existence... this shouldn't be the standard." "The idea that disabled people are often seen solely as sources of inspiration or exceptional due to their disabilities... underscores a societal tendency to view disability through a narrow lens."
Future-oriented Actions	"My second half of the school year will be influence by this perspective in a positive way." "This video taught me that moving forward, whether on rotations or in the future as a practice, to be mindful of what I say...." "...impact my practice by encouraging a reevaluation of biases and a move away from viewing disability through a lens of tragedy or inspiration."	Impact on Clinical Practice and Personal Growth	"This talk will remind me that for patients with disabilities, I might need to work harder to ensure people feel safe enough to let walls down and realize they don't need to inspire, they just need to be." "I want to make sure that I continue to uplift my patients and support them without making them feel patronized." "This video really made me reflect on that experience because everyone is just learning to use their bodies to the best of their capacity."
Social construct	"Our medical system is not designed for individuals with disability....how difficult performing a physical exam on a patient would be if you are blind...." "This can be applied to other marginalized communities as well ranging from age, race, gender, socioeconomic status, sexual orientation, or other identifying features." "Perhaps our recognition of acts that should be deemed regular stems from us trying to recognize our sympathy for struggles that we cannot perceive."	The Social Model of Disability and Societal Barriers	"She is more disabled by the social world we live in compared to her body." "No amount of smiling at stairs has made it turn into a ramp." "Disability is not the result of the restrictions that someone's body or illness imposes on them but rather the effects of how society interacts with the capacity of a disabled person's body."

Comparison of Themes

Three faculty members not involved in the study compared each pair of human-coded and AI-generated themes. Two were PhD-trained qualitative researchers, and 1 was a physician with qualitative research experience. All were provided only the table of human-coded and AI-generated themes and representative quotes. They were blinded to the manuscript and study objectives. They were asked to assess each pair of themes and determine whether they were the same, similar, or different and why. This approach was chosen because of the exploratory nature of the study and the lack of validated tools for comparing themes.[10]

Reflexivity

The study idea was developed collaboratively based on several years of experience conducting the discussion board activity. All CPD directors work with medical students in clinical settings and through the CPD course. The coders are clinicians with experience in qualitative research. To engage in reflexivity, coders reflected on their experiences in medical education, interactions with patients with disabilities, and their identities and roles within medicine and society.[11] Coders acknowledged that their faculty position and experiences might influence their interpretations of students' posts. Coders openly shared their perspectives during analysis, explaining their interpretations and gaining a better understanding of one another's viewpoints.

RESULTS

The video with the most responses was "I Am Not Your Inspiration," which focused on how individuals with disabilities are viewed. There were 101 original posts for this video. Human coders identified 46 unique codes, which were categorized by consensus into 3 themes: emotions, future-oriented actions, and social construct. Human- and AI-coded themes with representative quotations for each category are shown in Table 2.

Human-Created Themes

Our 4-member group of physicians and medical educators identified 46 codes after reviewing the posts, which were developed into the following 3 themes:

Emotions: Students often reflected on their past experiences and ways of thinking, eg, "This talk made me take a look at an unconscious bias that I didn't know I had." Others thought more deeply about the video's message and how their mindset may have contributed to a larger issue, eg, "I think a common tendency, especially with strangers, is to look at others for who they are to us, rather than who they are for themselves" and "I feel it's very important to be empathetic towards someone, while also not allowing your preconceived perception of a diagnosis to define them and your expectations of their future or health."

Future-Oriented Actions: Many students looked to the future and considered how the video would influence their interactions with

patients and their practice of medicine, eg, "In my future practice, I want to create a safe space where people don't have to feel like they can't have negative feelings or thoughts." Some were specific about what they might do differently, eg, "…in the future, we can pay extra attention to their clinic experience…to see if there is any way we…can make the experience more like any other patients" and "I hope to continue to utilize this moving forward to make a conscious effort to internalize what she said and share what I learned with those around me."

Social Constructs: Students looked beyond themselves and examined society and its role in what is considered the norm, eg, "It underscores a societal tendency to view disability through a narrow lens…." They recognized their own biases and how inequities contribute to societal constructs. Students identified that certain beliefs and ideas are often reinforced for the benefit of some and to the detriment of others, eg, "True inclusivity involves addressing these challenges rather than tokenizing inspirational stories."

Generative AI-Created Themes

The PDF of anonymized posts from the video was attached to the Copilot prompt that read:

> *"Third year medical students watched the following video (https://www.ted.com/talks/stella_young_i_m_not_your_inspiration_thank_you_very_much/transcript) Anonymous I Am Not Your Inspiration- Original Posts Only 1.pdf and then were asked to respond to the following prompts: Please reflect on this video/session by answering at least one of the following questions: What themes resonated with you from this video and why? How will themes you noticed impact your practice? What was/was not meaningful about this video and why? What are your thoughts about this video? You are now at least several clerkships into your third year – how may have your experience been different if you'd seen this video earlier? Why? Please review the attached 'Anonymous I Am Not Your Inspiration- Original Posts Only. pdf' responses from the students and identify 3 themes with 3 representative quotes for each theme."*

Copilot provided the following response:

> *"After analyzing the student reflections on Stella Young's TED Talk, 'I'm Not Your Inspiration, Thank You Very Much,' 3 major themes emerged consistently across the responses. Each theme is supported by representative quotes from the students' reflections."*

(Representative quotations are shown in Table 2).

Copilot then listed the following 3 themes and a short summary of each:

Theme 1: Objectification and "Inspiration Porn." Many students reflected on how society often objectifies people with disabilities by labeling them as "inspirational" for simply living their lives, a concept Stella Young critiques as "inspiration porn."

Theme 2: The Social Model of Disability and Societal Barriers. Students resonated with Young's emphasis that societal structures, rather than individual impairments, often create the most significant barriers for people with disabilities.

Theme 3: ***Impact on Clinical Practice and Personal Growth.*** Students reflected on how the talk challenged their biases and would influence their future interactions with patients, particularly by encouraging them to avoid assumptions and foster more respectful, individualized care.

Comparison

Consensus was reached, although it was not unanimous. Both PhD faculty members concluded that all pairs of themes were different. Their explanations included a perceived lack of contextual depth and the observation that the AI-generated themes were broad and overlapping. The physician faculty reviewer concluded that all theme pairs were either the same or similar, as did the human coders.

Total Time Spent on Analyses

Total time spent by the human coders included the cumulative time devoted to coding during group meetings. This amounted to nine 60-minute meetings conducted over a 4-month period to complete coding and theme development. Total time spent on analysis using Copilot was less than 30 seconds, including the time required to enter the prompt and generate a response.

DISCUSSION

Generative AI identified themes in a fraction of the time required by human coders. Two of the 3 external reviewers did not find the AI-generated themes to be the same or similar to the human-coded themes. Coding and theme development are inherently subjective processes, which may account for the differences in how AI and human coders labeled themes and selected representative quotations. It is noteworthy that the physician reviewer and human coders, who were also physicians, considered the theme pairs comparable. This finding may illustrate differences in qualitative experience and training between qualitative research faculty and physicians who conduct research.

Qualitative research, particularly interviews and written commentary, can provide deeper insights in participants' own words that may not be attainable through other research means. While educators routinely read and review students' written responses, analyzing those responses for research purposes typically requires additional personnel and substantial time.

Generative AI provides a generalized overview of learners' input. However, evaluating and determining the quality of individual posts remains a persistent challenge.[12] At present, manual review of each learner's assignment is still needed to assess individual content and effort. This limitation remains a clear challenge for generative AI. If the purpose of reflections, discussion posts, and other written assignments is to assess learners' understand-

ing or engagement, manual review appears more appropriate than AI-assisted analysis.

Regarding time commitment, all coders had prior experience with qualitative research and coding; therefore, no additional training time was required. However, coders struggled to find times when all participants were available to code together. Like many clinical educators, each coder balanced varying administrative, educational, and clinical responsibilities, with research conducted during limited discretionary time. From an efficiency standpoint, generative AI does not require coordinating multiple schedules and can analyze qualitative responses in less than a minute. In this study, AI completed a task that took human coders more than 4 months to complete in approximately 20 seconds.

Available literature comparing generative AI with human coders in qualitative research has similarly demonstrated substantial gains in efficiency.[13] In terms of thematic accuracy, one study found fair to moderate agreement between AI-generated and human-generated themes in qualitative analysis of a text-messaging intervention for patients.[14] Nonmedical studies comparing generative AI and human coders have reported similar findings, including efficiency gains but differences in thematic development.[15,16] Others have also noted that AI may struggle to detect emotion and tone.[17] Sarcasm, for example, can be difficult for AI to detect because contextual understanding is important.[18] Cultural differences and slang further complicate these challenges. Admittedly, humans are not perfect at interpreting written tone either.[19] Additionally, some quotations identified by both the human coders and AI in our study could reasonably have fit within multiple themes, a point raised by one of the external reviewers.

The differing conclusions reached by the external PhD reviewers compared with the physician reviewer and human coders serve as an important reminder that professional background can shape qualitative interpretation. Qualitative research experts often emphasize conceptual depth and clear conceptual boundaries. In other words, they carefully consider whether each theme represents a distinct concept and avoids overlap with other themes. Consequently, the PhD reviewers viewed AI-generated themes as superficial and lacking deeper understanding and insight. In contrast, the physician coders evaluated the themes largely on the basis of practical relevance and how the themes resonated with their clinical experiences.

Many qualitative software programs, including NVivo (Lumivero), Dedoose (SocioCultural Research Consultants, LLC), and MAXQDA (VERBI Software), now incorporate AI-enabled functions.Available feature include autocoding, theme suggestion, summarization, and sentiment detection. For researchers considering AI to support qualitative analysis, software with specific AI capabilities is recommended over the use of general AI tools such as ChatGPT and Copilot so that the analysis is integrated and supported by qualitative methodological rigor.

It is also important to recognize that the appropriateness of either by hand or AI coding depends on the purpose of research. For studies requiring deep interpretive analysis, systematic and consistent procedures, clear analytic coherence, and transparent decision-making, human coders remain essential. When the primary goals are efficiency, rapid summarization, content analysis, or preliminary pattern identification, AI may be a useful analytic tool.

Limitations

This was a single-site study; therefore, the generalizability of the findings is uncertain. Additionally, allowing students to select which videos to watch may have introduced selection bias. Social desirability bias also may have been present, as students may post certain responses to create favorable impressions. Theme comparisons were performed only for the video with the largest number of posts. Whether similar results would have been observed for the remaining videos is unknown. Additionally, students may have used generative AI to help create their discussion posts. Finally, comparison of human- and AI-generated themes could have been strengthened by the inclusion of additional external reviewers.

CONCLUSIONS

Our findings suggest that AI-powered assistants can provide unmatched efficiency for qualitative data analysis. However, limitations remain regarding the validity of AI-generated interpretations and the ability to appreciate context, tone, and nuance. Addressing these limitations could transform how qualitative analysis is conducted in medical education research.

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Use of Telemedicine to Provide Linkages From Jail to Primary Care for Persons With Opioid Use Disorder

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ABSTRACT

Background: This pilot primary care transition program evaluated the impact of a prerelease intervention for incarcerated individuals with opioid use disorder (OUD) on linkage to care and treatment retention.

Methods: Participants with opioid use disorder who were incarcerated for an opioid-use offense, had a diagnosis of OUD, or were receiving medications for OUD were recruited from local county jails. Using peer support specialists, participants completed prerelease telemedicine visits with a primary care physician were scheduled for follow-up with 1 week of release.

Results: High rates of treatment retention were observed at 1 week (28/30; 93%), 3 months (24/30, 80%), and 15 months (16/30, 53%), despite 45% of participants (13/29) being unhoused.

Discussion: Integrating primary care physicians and peer support specialists into jail reentry programs for individuals with OUD may improve continuity of care and linkage to treatment following release from incarceration.

BACKGROUND

Approximately 30% to 50% of individuals incarcerated in the United States have a substance use disorder, a percentage significantly higher than that in the general population.[1]

In addition to behavioral health services and peer support, medications for opioid use disorder (MOUD), including naltrexone, buprenorphine, and methadone, have been shown to reduce overdose deaths and recidivism.[2-5] Despite the availability of these effective interventions, more than 80% of individuals with opioid use disorder (OUD) never receive treatment during incarceration, and most receiving MOUD have their medication discontinued, leading to forced withdrawal.[2-5]

As of 2021, only 25 of 61 (41%) Wisconsin jails and 5 of 25 (14%) prisons offer any form of MOUD, most commonly intramuscular (IM) naltrexone. Only 8 county jails and 1 prison offer buprenorphine continuation. Three jails and no prisons offer methadone continuation.[6]

Providing MOUD and reentry support is vital, as individuals released from incarceration are 40 times more likely to die of an overdose and face barriers such as lack of housing, access to health care, employment, and transportation.[7] Little is known about the impact of linking individuals with OUD to primary care after incarceration. This report presents the effects of a pilot program that integrated a community-based primary care team, peer support, and an initial prerelease telemedicine visit on linkage to care and OUD treatment retention.

METHODS

Program Development and Design

A real-world pilot program was developed through a collaboration among an academic family medicine clinic at the University of Wisconsin (UW) School of Medicine and Public Health Department of Family Medicine and Community Health, UW Health, and leadership at Wisconsin's Dane and Columbia County jails to create new service delivery linkages for incarcerated individuals. The 18-month enrollment period (April 2021 to September 2022) was based on the duration of grant funding. With assistance from a longitudinal nurse care coordinator, par-

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ticipants were offered a prerelease telemedicine appointment with a family medicine physician; an in-person follow-up visit with the same physician was scheduled within 1 week of release from jail, and an application for insurance was completed. Cab vouchers were provided for the initial follow-up visit and subsequent visits. A certified peer support specialist also met with participants in person at the initial follow-up visit and provided ongoing telephone support. Patients could select telemedicine or in-person follow-up visits based on their preference.

Most participants relied on Medicaid coverage, which was suspended within 30 days of incarceration and not reinstated until participants reapplied after release. Grant funds covered visits and medication during this coverage gap. At the time of this study, buprenorphine and methadone could not be initiated or continued in either participating jail.

Before study initiation, a UW-Madison Quality Improvement/Program Evaluation Self-Certification Tool was completed, and the project was deemed exempt by the institutional review board.

Participant Recruitment

Twenty-six participants from the Dane County jail and 4 from the Columbia County jail were enrolled. Participants were identified by reentry coordinators employed by the jails during reentry assessments. The number of individuals who were approached but declined to participate was not collected.

Participants met inclusion criteria if they were aged 18 years or older, agreed to participate, and met at least 1 of the following criteria: incarcerated with a diagnosis of OUD; incarcerated for an opioid-use offense with OUD confirmed at initial visit; or previously treated with MOUD and seeking to continue treatment.

Data Collection and Outcome Measures

Demographic data, including age, gender, race, ethnicity, postincarceration housing status, and mental health diagnoses, were collected at the initial telemedicine visit.

Participant retention was selected as the primary outcome because the program sought to understand how an enhanced support services can improve patient engagement. Participant retention is an accepted surrogate measure for both treatment engagement and treatment success in the addiction medicine literature.[4]

Outcomes included attendance at the 1-week postincarceration follow-up appointment; retention at 3, 6, 12, and 15 months, defined as at least 2 follow-up visits; housing status, mental health diagnoses and psychiatric medication use; preventive health measures; and type of MOUD treatment.

Care was provided longitudinally in accordance with accepted evidence-based addiction medicine practices, including periodic urine drug screening based on individualized patient needs. Participants were not removed from the study because of gaps in follow-up, urine drug screen results, or medication nonadherence during the study period. Participant retention was defined as the interval between program enrollment and the last documented contact with the treatment team.

Table 1. Outcome Measures

	n	%
Telemedicine visit occurred while incarcerated	30	
Yes	22	73
No, referred by jail staff but initial visit occurred after release	8	27
Attendance at first appointment after release	30	
Attended	28	93
No show	2	7
Medication for OUD prescribed at first appointment after release	28	
Buprenorphine (sublingual)	14	50
Intramuscular naltrexone	12	43
Buprenorphine (long-acting injectable)	2	7
Preventive health care including immunization and routine screenings accepted by patient	28	
Yes	24	86
No	4	14
Retention	30	
>3 months	24	80
>6 months	20	67
>12 months	17	57
>15 months	16	53
Prescribed a mental health medication	29	
Yes	27	93
No	2	7

Abbreviation: OUD, opioid use disorder.

Data Analysis

Chi-square tests were used to determine associations between categorical variables and 15-month retention. The Mann-Whitney-Wilcoxon test was used to assess associations between 15-month retention and both age and the percentage of visits conducted via telemedicine. No adjustment for multiple comparisons was performed despite the potential for inflation of type I error. Statistical significance was assessed at $\alpha = 0.05$.

RESULTS

Participant Characteristics

The study population was predominantly male (63%), aged 26 to 44 years (80%), and predominantly White (90%). This contrasts with the Dane County jail population, of which 49% is Black. Demographic data for the Columbia County jail population could not be obtained. Nearly half of participants(45%) were unhoused, and nearly all (97%) had a diagnosed mental health condition.

Follow-up Duration and Additional Outcome Measures

Twenty-eight of 30 participants (93%) attended their initial postrelease follow-up visit within 1 week. Medications used during the study are displayed in Table 1. The primary care physician also prescribed psychiatric medications for 93% of participants and provided preventive care to 83%.

Treatment retention was 80% (24/30) at 3 months, 67% (19/30) at 6 months, 57% (17/30) at 12 months, and 53% (16/30) at 15 months.

Older age ($P = .028$), male gender ($P = .023$), and a diagnosis of depression ($P = .024$) were associated with higher rates of follow-up at 15 months (Table 2). Although telemedicine visits comprised a lower median percentage of total visits among participants retained in treatment at 15 months (25%) than those lost to follow-up before 15 months (50%), the association between percentage of telemedicine visits and duration of follow-up was not statistically significant ($P = .344$).

Table 2. Follow-up Duration of at Least 15 months by Participant Characteristics

Variable/Category	15-month follow-up n (%)	*P* value
Visit type		
All in-person	3/5 (60)	.389
All telemedicine	1/4 (25)	
Mixed	13/21 (62)	
Age (years)		
21 to 29	2/7 (29)	**.028**
30 to 39	9/16 (56)	
40 to 55	6/7 (86)	
Gender		
Female	3/10 (30)	**.023**
Male	14/19 (74)	
Transgender male	0/1 (0)	
Race		
Black	2/3 (67)	.93
White	15/17 (88)	
Ethnicity		
Non-Hispanic Black	2/3 (67)	.672
Non-Hispanic White	14/26 (54)	
Hispanic/Latino	1/1 (100)	
Family	7/10 (70)	.166
Housing after release		
Family	7/10 (70)	.166
Homeless	8/13 (62)	
Missing	0/1 (0)	
Residential	1/5 (20)	
Sober living	1/1 (100)	
Attention-deficit hyperactivity disorder		
Yes	5/11 (45)	.346
No	12/19 (63)	
Bipolar disorder		
Yes	2/5 (40)	.410
No	15/25 (60)	
Depression		
Yes	11/14 (79)	**.024**
No	6/16 (38)	
Generalized anxiety disorder		
Yes	11/21 (52)	.469
No	6/9 (67)	
Posttraumatic stress disorder		
Yes	4/9 (44)	.376
No	13/21 (62)	

Bold *P* values indicate statistical significance (<.05).

DISCUSSION

Although MOUD in jail settings can reduce recidivism rates,[2] few studies have evaluated the role of prerelease linkage to a primary care clinician in OUD treatment retention.[8] This real-world pilot project demonstrated high rates of initial follow-up (93%), short-term retention (80% at 3 months), and long-term retention (57% at 12 months and 53% at 15 months). These findings contrast with those of Lee et al, who reported an approximately 37% retention rate 12 months after release.[8]

Retention in the present study was also comparable to or higher than rates reported in the general population with OUD, for whom retention varies widely, with average retention rates of 59% for buprenorphine and 20% to 50% for naltrexone after at least 1 month of treatment.[4] These findings are notable given that 45% of participants were unhoused.

A 2022 meta-analysis investigated factors associated with treatment retention, including recruitment methods, study duration, required psychosocial interventions, and requirements for remaining in the study.[4] Although the results should be interpreted cautiously because of high heterogeneity among studies, retention was positively associated with recruitment and negatively associated with study duration and required psychosocial intervention; however, the effect size for study duration was small. Study participation requirements were not significantly associated with retention.[4] Therefore, the high retention rates observed in the present study may be related to effective participant recruitment and the absence of required psychosocial interventions.

We also hypothesize that the favorable retention rates were influenced by several key program components, including strong partnerships between jail staff and community treatment providers, intensive follow-up immediately after release, and the involvement of nurse care coordinators and peer support specialists.

Although prerelease telemedicine visits were discontinued after the grant period, referrals to the clinicians involved in the program continued and anecdotally appeared to contribute to increased stakeholder engagement. An additional advantage of involving primary care clinicians was the ability to offer medical care beyond MOUD treatment, including mental health care, preventive health services, chronic disease management, immunizations, and routine screenings. This is particularly relevant given the high prevalence of comorbid mental health conditions (97%) among study participants.

Limitations

There program faced several implementation challenges. Providing follow-up appointments within 1 week of release required rapid appointment availability, which can be difficult to achieve in primary care settings. Additional challenges included lack of insurance coverage and uncertainty regarding release dates, which contributed to coverage gaps.

Grant funding covered the costs of medications and visits during these coverage gaps, and future programs should consider these expenses essential for long-term sustainability. Importantly, this model may face fewer barriers in states where Medicaid coverage remains active for 90 days after release or is suspended rather than terminated during incarceration.

An additional limitation was the small sample size.

At the time of this study, buprenorphine and methadone could not be initiated or continued in either participating jail. County jails commonly cite medication costs, inadequate staffing, the time required to administer medications, and concerns about diversion as barriers to offering MOUD. Continued partnerships with county jails are critical to addressing these barriers and expanding access to MOUD.

White incarcerated individuals were disproportionately represented among participants enrolled in the program, a finding that has been observed in other studies.[2] The reasons for these racial disparities are unclear but may relate to structural racism and medical mistrust. Recent literature demonstrates stark disparities in access to MOUD among racial groups despite a 7-fold rise in opioid overdose deaths among Black Americans during the past decade.[9]

CONCLUSIONS

Our pilot study demonstrated that integrating multidisciplinary support services and primary care clinicians into prerelease and reentry programs can improve treatment engagement and retention among individuals with OUD. Although retention measures differ across studies, the retention rates observed in this program were higher than those reported in several previous studies, suggesting that a primary care-based model incorporating prerelease telemedicine may improve continuity of care and linkage to treatment following release from incarceration.

The use of telemedicine during ongoing follow-up was not significantly associated with treatment retention. Primary care clinicians may also play an important role in recovery by addressing acute, chronic, and preventive health care needs while providing continuity of care and facilitating connections to community-based resources that support long-term recovery.

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Smartphone-Delivered Animated Videos to Train Neonatal Intensive Care Unit Physicians in Communication Skills: A Feasibility Study

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ABSTRACT

Background: Physician training in the neonatal intensive care unit (NICU) emphasizes diagnosis and procedures, whereas communication training is often sporadic.

Objective: We sought to assess the feasibility of smartphone-based animated videos to teach communication skills to physicians in the NICU.

Methods: Eight videos modeling communication best practices were delivered twice weekly via text messages. Software tracked video use, and participants provided feedback through surveys.

Results: Of the 29 participants, 19 (66%) viewed some or all the videos. Participants reported implementing the communication techniques and making changes to their communication style. Two months postintervention, the 7 physicians who completed follow-up surveys reported sustained use of learned skills.

Conclusions: Communication training delivered via smartphone through short, animated videos is a feasible and well-received approach for physicians in the NICU.

BACKGROUND

Effective communication between neonatal intensive care unit (NICU) parents and physicians is essential for building trust and optimizing health outcomes. However, the most frequent complaints by parents are that physicians do not listen to their concerns, care about their problems, or provide sufficient information about treatments.[1] Ineffective communication is associated with parental stress and dissatisfaction with care, inappropriate use of therapeutic modalities, and malpractice lawsuits.[2-4]

Physicians are introduced to communication skills during medical school. During clinical rotations, including those in the NICU, medical training focuses on diagnoses, treatments, and procedures, whereas communication training is sporadic. A survey of pediatric residency program directors found that, when communication training is offered, it typically occurs 1 to 3 times per year and consists of formal didactics, role-playing, workshops, and simulated cases. Fourteen percent of programs offer no formal training.[5] Furthermore, in a national survey of graduating neonatology fellows, 41% reported no formal communication training during fellowship.[6] Training programs struggle to teach communication skills because of limited time and shortage of trained faculty. To our knowledge, no existing program formally reaches NICU physicians within the clinical setting to reinforce and facilitate practice of communication skills learned in classrooms.

This lack of preparation for effective communication is especially concerning in the NICU, where prolonged NICU stays provide abundant opportunities to build trust between parents and health care providers but may also foster distrust when communication is ineffective. Smartphones offer opportunities for situational, in-context communication training, bridging gaps that traditional didactics cannot address. We aimed to address challenges in NICU communication skills training in the NICU by developing an animated video training program delivered to physicians via smartphone.

METHODS

Study Site and Ethics Approval

The study was conducted at an academic, level IV NICU within a freestanding children's hospital. Institutional Review Board approval was obtained with a waiver for documentation of con-

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sent. Participants were provided with an informational letter, and agreement to participate was indicated by completion of the enrollment survey.

Participants

Eligible participants included pediatric residents, fellows, and attending physicians rotating in the NICU during the study period. Physician enrollment was completed through a REDCap (Research Electronic Data Capture; Vanderbilt University) survey sent via email before the start of each participant's rotation. Enrollment took place between October 2022 and May 2023. As this was a feasibility study, no power analysis was conducted to determine the sample size.

Intervention

Content identification: A literature review identified evidence-based communication techniques for physicians. These techniques were packaged into tasks commonly performed by physicians in the NICU, including communicating with families during a code event and using the SPIKES framework[7] to guide a family meeting (Figure 1A and 1B).

Animated video development: Considerations in developing the video curriculum included clinicians' rotation schedules, the goal of delivering 2 videos each week, and the need to achieve learning objectives while limiting each video's duration to 2 to 3 minutes. These considerations resulted in the creation of 8 training videos. To create each video, a script was developed to address the learning objectives. A team that included pediatric residents, neonatal fellows, and NICU parent representatives reviewed each script and provided feedback to refine the content and style. Animations were produced using PowToon (Powtoon Limited) and Vyond (GoAnimate, Inc), and narration was provided by professional voice actors. Video production involved an iterative refinement process to improve representation, ensure that the communication techniques were accurately modeled, and adjust visuals to better reflect the NICU environment. The Figure contains links for the videos.

Text-message video delivery platform: A technical platform was developed that included a website to host the videos, programming to automatically deliver text messages, and software to track participant-specific usage. Each video was delivered via a link embedded in a text message. Participants received 4 to 8 videos over 2 to 4 weeks, depending on the length of their NICU rotation. Compatibility of the delivery platform was tested across various mobile devices and phone carriers.

Figure 1A. Neonatal Intensive Care Unit Scenarios and Communication Objectives for Physician Videos 1-4

PHYSICIAN COMMUNICATION VIDEO	LEARNING OBJECTIVES
Meeting a new family  https://mcw.box.com/s/wir18tjpqtib4gh5s0eidthbavbz2or1	Acknowledge the child apart from their medical status. Sit down with parents when talking with the parents and listen without interrupting. Use names and person-first language.
Empowering families to participate in infant's care  https://mcw.box.com/s/ek2vhtg71r9vzfdl51eclfftbe3i7jop	Explain to parents what is happening to their child. Ask parents what is most important to them. Encourage parents to participate in caring for their child.
Explaining lab results using emotion words  https://mcw.box.com/s/xb6r5fl3id3c6mh4o6a0qtidun7yqsg5	Frame results with emotion words, such as happy or worrisome, to communicate what the results mean. Avoid use of the words "positive" or "negative," which may cause confusion.
Creating opportunities for empathy  https://mcw.box.com/s/ueyxxq9ievvt3kme1cyfsy7c1nald2we	Respond to cues for empathy as a human first - responding with data first only addresses part of parents' needs. Display empathy with the SAVE framework: Support, Acknowledge, Validate, Emotion name.[8]

Outcomes

Enrollment surveys (Appendix, Survey 1) collected information on demographics, previous communication experiences and training, and mobile device usage. Weekly assessments (Appendix, Survey 2) evaluated engagement, adoption of communication techniques, and discussions about these techniques with others. End-of-curriculum evaluations (Appendix, Survey 3) included feedback on video quality, perceived impact on communica-

tion, and the overall learning experience. Two months after completion of the curriculum, participants were sent follow-up surveys (Appendix, Survey 4) to assess sustained effects. Assessments were automatically delivered to participants via email through REDCap. As compensation for time completing evaluations, participants received a $4 gift card for each evaluation completed (up to $24 for completion of all evaluations).

RESULTS

Seventy-nine physicians were eligible to participate, including 58 residents, 6 fellows, and 15 attending physicians. Invitations were sent via email, and 29 physicians (37%) enrolled, including 19 residents, 5 fellows, and 5 attending physicians. Most (69%) identified as non-Hispanic White, 17% identified as Asian, 14% as Black, and 7% as Hispanic. Thirteen participants (45%) reported no prior communication skills training. Among those with prior training, common methods included role playing, simulations, small-group discussions, and lectures.

Nineteen physicians (66%) watched 1 or more videos. Due to varying NICU rotation lengths, 77 total weekly impact assessments were sent, of which 28 (36%) were completed. Among these, 15 (54%) indicated that they had discussed the video content with colleagues. In 16 (57%) assessments, participants reported practicing techniques presented in the videos during family interactions in the NICU, and 21 (75%) reported that viewing the videos caused a change in their communication style. Open-ended feedback highlighted techniques physicians implemented, such as using lay language and active listening.

At the end of the curriculum, 88% of the respondents rated their learning experience as good or excellent. Two months postintervention, 7 physicians completed the follow-up survey, reporting a median score of 8/10 for content retention and 7/10 for application of the techniques in clinical practice. All respondents expressed interest in receiving similar videos in the future.

Figure 1B. Neonatal Intensive Care Unit Scenarios and Communication Objectives for Physician Videos 5-8

PHYSICIAN COMMUNICATION VIDEO	LEARNING OBJECTIVES
Using teach-back to confirm understanding	
	Prepare parents to make a phone call about the information to their loved ones. Invite teach-back using language that places responsibility for clarity on the physician.
https://mcw.box.com/s/8pv68l5m5lcftxoom1rkwmlkukk6w04j	
Communicating with families in the delivery room	
	Ask about the child's name and use pronouns matching the baby's sex. Prepare parents based on the level of infant risk. Tell parents that while treating the child, the physician may not have the time to talk to them.
https://mcw.box.com/s/slktzf6r5uiylowo7h1pqomsygyi1e33	
Leading a family meeting	
	Structure a family meeting with the SPIKES framework: Set up the meeting time and place, assess the family's Perception of the situation, obtain the family's Invitation to proceed the discussion, share the new Knowledge, address the family's Emotion and respond with Empathy, then briefly Summarize the meeting and create a Strategy for moving forward.[7]
https://mcw.box.com/s/kyg9hvyofe2669x47fs2zs108n5po1xe	
Communicating with families during a code blue	
	Designate someone on the medical team to talk to and support the parents. Remind parents the situation is not their fault. If the infant is not improving, prepare parents for a possible bad outcome in a stepwise fashion. Avoid asking the family for permission to stop interventions. Avoid euphemisms like "passed away."[10]
https://mcw.box.com/s/8vnmh9x28ise2pv4mju21vzs27zb71nk	

DISCUSSION

Our innovative animated videos harness ubiquitous mobile technology to teach communication skills, making them easily accessible to physicians in the fast-paced NICU environment. Most enrolled physicians watched the videos sent to them, demonstrating the convenience and effectiveness of this delivery method. Participant feedback suggested that the program positively influenced communication behaviors.

Our results are consistent with previous research, reinforcing the idea that smartphones are a practical platform for delivering educational content to physicians. A 2014 survey found that 77% of medical students and resident physicians used their smartphones multiple times daily to access medical resources.[9] Additionally, our findings supports prior research demonstrating that mobile learning, particularly through text messages, is an effective and efficient

educational strategy in medicine.[11] Beyond their widespread availability, smartphones offer the advantage of tracking curriculum engagement while allowing physicians to learn at their convenience.

By integrating communication skills training into the clinical setting, our curriculum enabled physicians to immediately apply newly learned techniques during interactions with parents. Trainees have reported that practicing communication skills in real clinical scenarios enhances the effectiveness of communication training.[12] Additionally, communication skills are best developed through continuous professional education.[12] To support this approach, we included residents, fellows, and attending physicians, fostering team-based learning that reinforces communication skills across all levels of experience.

Limitations

Our study is limited by its sample size. Recruiting physicians and integrating a new curriculum into an already busy NICU rotation proved challenging. The enrollment survey and weekly evaluations were distributed via email and were often overlooked; delivering these assessments by text message may improve response rates. Additionally, the communication skills taught in the curriculum are relevant beyond the NICU, and the program could be expanded to physicians in outpatient settings or other inpatient units where greater flexibility for education may exist.

Another limitation is reliance on survey data alone to assess impact. Future studies incorporating additional forms of feedback, such as qualitative interviews or assessments of actual communication behaviors, could provide further insight. Finally, the absence of a comparison group limited our ability to evaluate changes beyond participants' self-reported perceptions.

CONCLUSIONS

This study demonstrates that smartphone-delivered animated videos modeling evidence-based physician communication skills are a feasible and well-received method for improving parent-physician communication in the NICU.

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Appendix: Available at www.wmjonline.org

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Diabetes Health Care Transition Assessment at School: Collaborating with School Nurses for Success

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ABSTRACT

Background: The transition from pediatric to adult care is particularly complex for adolescents with type 1 diabetes because of the demands of diabetes self-management. Transition readiness assessments can provide education, support autonomy, and individualize care; however, limited time and resources may hinder implementation of an optimal transition process. Partnerships between health care and education systems may extend the multidisciplinary transition team into the school setting.

Methods: This study assessed the feasibility of implementing a school-based diabetes transition readiness assessment using a diabetes-specific tool and evaluated changes in student participation over a 2-year period.

Results: Integrating school nurses into the diabetes transition team was feasible. With targeted promotion and program refinements, student participation increased by 68% in Year 2 compared with Year 1.

Conclusions: A school-based diabetes transition readiness assessment using the Readiness of Emerging Adults with Diabetes Diagnosed in Youth (READDY) tool was feasible and associated with increased student participation over time. This model may represent a promising community-based approach to support transition readiness among adolescents with type 1 diabetes.

BACKGROUND

Health care transition, during which adolescents move from pediatric, family-based care to an adult, self-directed model of care, is exceptionally complex for adolescents with type 1 diabetes.[1] Optimally, diabetes health care transition ensures that adolescents have the skills needed to manage diabetes independently and effectively in adulthood. Adolescents with type 1 diabetes are a vulnerable population who experience frequent lapses in care due to adherence challenges, gaps in health care contact, and other life stressors. Despite improvements in glycemic control associated with advancements in diabetes technology, adolescents continue to have higher A1c levels than both younger children and adults.[2,3]

Successful diabetes transition requires a structured, multidisciplinary approach that fosters self-management and health care navigation skills, as recommended by the American Academy of Pediatrics and American Diabetes Association.[3] This process should start in early adolescence to allow for a gradual transition of diabetes responsibilities. Assessing readiness for transition provides opportunities to deliver education, individualize care, and support autonomy.[4] The Readiness of Emerging Adults with Diabetes Diagnosed in Youth (READDY) tool, designed for adolescents with type 1 diabetes aged 15 years and older, is a well-studied 44-item questionnaire that assesses self-confidence in 4 areas: Diabetes Knowledge, Health System Navigation, Insulin Self-Management, and Health Behaviors.[1,5,6] Unfortunately, current health care systems often lack sufficient resources to support the transition process for adolescents with chronic disease during this critical period.

One innovative solution is to partner with school nurses as members of the transition team. School nurses have unique access to students during school hours, a practical time when adolescents use diabetes self-management skills more independently. Despite the National Association of School Nurses noting that school nurses are well positioned to support health care transition,[7] to our knowledge, no prior studies have evaluated the use of a school

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nurse as part of a multidisciplinary transition team. This partnership offers a novel opportunity to integrate transition readiness assessments into the school setting.

This study assessed the feasibility of implementing a school-based diabetes transition readiness assessment using the READDY tool and evaluated student participation over a 2-year period.

METHODS

This study was conducted in middle schools (grades 6-8) and high schools (grades 9-12) in a single public school district. This study was approved by the school system's external research committee and was deemed not to constitute human subjects research by the University of Wisconsin Minimal Risk Institutional Review Board. The study team consisted of diabetes care providers from an academic medical center (2 physicians, 1 clinical nurse specialist, and 1 advanced practice provider [APP]) and public school nurse leaders (1 nurse coach/APP and 1 registered nurse), who met regularly to develop and implement this project. The READDY tool was distributed to middle school and high school students with type 1 diabetes by school nurses at their respective schools. Participation by school nurses and students was voluntary.

Because of concerns related to the length of the READDY tool, in Year 1 the study team abridged the instrument to 5 questions focusing on insulin dosing and blood glucose management. The lead school nurse emailed all middle and high school nurses within the district to describe the project and invite participation. Participating school nurses distributed printed versions of the abridged READDY tool to English-speaking students with type 1 diabetes during the fall and spring semesters. In the spring, a second survey was distributed to both students and nurses to collect feedback and guide changes for the second year. Data collected included (1) the number of students who completed the READDY tool, (2) the number who completed the spring survey, and (3) feedback from participating students and nurses obtained through Likert scales and open-ended questions. Students who completed surveys in both semesters received a $25 gift card.

In Year 2, the complete READDY tool was administered to high school students, while middle school students received a 23-item version that excluded less age-appropriate items (eg, driving). Both English- and Spanish-language versions were distributed during the fall semester. In addition, students were asked to select a learning topic from the tool to review with school nurses, as opportunities allowed, utilizing resources organized by the academic diabetes team, including PowerPoint presentations, handouts, and website links.

Participating students completed a follow-up survey in the spring semester focused on their self-identified learning topic and project feedback. Participating school nurses completed a spring survey assessing time commitment, available resources, utility of completing the READDY tool, and the process of identifying learning goals with students.

Table 1. Participation Year 1 vs Year 2

	2023-2024 n	2024-2025 n
Schools		
Middle schools	5	7
High schools	3	6
Students		
Middle schoolers – total	11	12
Middle schoolers who picked learning topic	–	12
High schoolers – total	8	20
High schoolers who picked learning topic	–	16
Nurses		
Total	9	15

Table 2. Student Feedback Year 2

	Middle School (N = 12)	High School (N = 18)
I found it helpful to complete the transition readiness survey.	92%	66%
I found that completing the transition readiness survey helped me communicate with my school nurse better.	83%	66%
I found that completing the transition readiness survey gave me more confidence in my diabetes skills.	92%	56%

During Year 2, all project materials were made available on the school district website. The lead school APP tracked and collected all data in a shared, anonymized spreadsheet. Data collected included (1) the number of students who completed the READDY tool, (2) the number of students who identified a learning topic, (3) the number of students who completed the spring survey, and (4) feedback from participating students and nurses. Participating nurses and students received gift cards. The 2 school nurse leaders received consultation fees.

RESULTS

Five of 8 middle schools and 3 of 5 high schools with students with type 1 diabetes participated in Year 1, with a total of 23 eligible students (11 middle school and 12 high school). All middle school students and 67% (n = 8) of high school students completed the READDY tool. Feedback from 18 students and 9 nurses, as well as input from a high school student advisory group, indicated that this project was feasible. Recommendations included expanding the READDY tool and incorporating an educational intervention.

In Year 2, increases were seen in the number of schools participating (13 vs 8), the number of eligible students (43 vs 23), and the number of students completing the READDY tool (32 vs 19). Most participating students selected a learning topic (middle school, n = 12; high school, n = 16) (Table 1).

The Year 2 spring survey was completed by 12 middle school and 18 high school students. The majority (92% of middle

school students and 72% of high school students) provided clear responses to the question, "What did you learn about this topic?" Many identified the school nurse as their primary learning resource (85% of middle school participants and 67% of high school participants). Most of the middle school students and over half of the high school students strongly or somewhat agreed that completing the READDY tool was beneficial (Table 2).

Thirteen nurses provided feedback, and 85% agreed that participation in this process increased engagement with their students, while 38% found it difficult to find time to meet with students. Nurse engagement with students varied, with most nurses meeting with students twice (range, 1–7 times). Most nurses (77%) found the education materials helpful and reported benefits from establishing relationships with students and observing growth in their diabetes knowledge and confidence. Areas for improvement included additional educational resources for younger and Spanish-speaking students.

DISCUSSION

This study evaluated a novel collaboration between a diabetes health care team and a public school system, representing an important intersection in the management of chronic disease among adolescents. This 2-year study demonstrated that partnering a diabetes health care team with school nurses, who have direct access to students, provided a feasible and well-received model for diabetes transition readiness assessment in the school setting.

Leveraging schools' to students and utilizing school-based resources, particularly school nurses, can expand the multidisciplinary health care team, facilitate type 1 diabetes transition readiness assessment, and potentially reduce lapses in care and diabetes-related complications associated with a poor transition to adult diabetes care.[2,3,8] However, this approach, in which school nurses serve as key facilitators of diabetes education, must be balanced with their existing responsibilities, including acute and chronic disease management, medication administration, and health screening.[9] Indeed, early adoption and engagement among lead school nurses may be the most important determinant of successful implementation of transition readiness assessment within school systems and potentially for other chronic diseases.

Despite the success of this initiative, barriers such as limited time for school nurses, competing academic priorities for students, and the need for greater student engagement impeded full implementation. Strategies to increase student participation and provide additional resources for nurses are needed to address these obstacles. The lack of a tool specifically designed to assess diabetes transition readiness remains a challenge, as the READDY tool, which relies on the self-reported confidence in diabetes-specific skills among high school-aged adolescents, is not linked to objective assessment of those skills.

Ongoing collaboration between health care and education systems is needed to further refine transition programs that are not only school-based but also scalable and adaptable to a variety of chronic conditions. Future phases of this project will focus on overcoming barriers related to resource limitations, time commitment, and student participation, as well as formalizing targeted diabetes education based on identified knowledge gaps.

CONCLUSIONS

The implementation of a collaborative, school-based diabetes transition readiness assessment using the READDY tool is novel, feasible, and, with buy-in from key stakeholders within the school setting, capable of serving increasing numbers of students. This collaboration represents a promising model for community-based approaches that complement and extend the reach of traditional health care settings to enhance chronic disease management.

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Prevalence and Incidental Detection Rates of Thoracic Aortic Dilation and Aneurysm Across Computed Tomography Imaging Modalities in a Veteran Population

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ABSTRACT

Background: The prevalence and incidental detection rates of thoracic aortic dilation (TAD) and thoracic aortic aneurysm (TAA) in computed tomography (CT)-based screening programs (eg, low-dose CT for lung cancer screening) are poorly characterized but could inform opportunistic screening strategies.

Methods: In this single-center retrospective cohort analysis, 9409 consecutive chest CT studies for 6795 unique patients at the Milwaukee Veterans Affairs Medical Center in Milwaukee, Wisconsin, were evaluated between January 2023 and January 2025. Radiology reports were reviewed manually. Incidental cases were defined as findings not previously documented in clinical notes or prior imaging. Point prevalence and incidental rates were calculated.

Results: The overall prevalence of TAD and TAA across CT cohorts was 6.1% (95% CI, 5.5%–6.6%) and 1.2% (95% CI, 0.95%–1.5%), respectively. The prevalence of TAD was 8.1% for low-dose CT (95% CI, 7.1%–9.1%), 8.3% for CT without contrast (95% CI, 6.5%–10.1%), and 3.2% for CT with contrast (95% CI, 2.6%–3.9%). The incidental detection rate of TAD was higher for low-dose CT (3.7%) than for CT without contrast (1.9%) and CT with contrast (1.2%).

Conclusions: Thoracic aortic dilation and thoracic aortic aneurysm are common among veterans undergoing clinically indicated chest CT imaging. Integrating opportunistic aortic assessment into existing CT screening programs deserves prospective evaluation to determine its clinical relevance and impact on downstream management.

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BACKGROUND

Thoracic aortic aneurysms (TAAs) are associated with significant morbidity and mortality.[1] The prevalence of thoracic aortic dilation (TAD; aortic diameter > 4.0 cm) and TAA (> 4.5 cm) varies based on the population studied and the presence of risk factors, including advanced age, hypertension, and smoking.[1] Unlike abdominal aortic aneurysms, available evidence does not support population-based screening except in patients with hereditary conditions.[1] There are few reports of the prevalence of TAD/TAA in clinically relevant populations at elevated risk, such as patients undergoing low-dose computed tomography (LDCT) for lung cancer screening.

Integrated dual screening for both lung cancer and TAD/TAA was recently explored in the United Kingdom National Health Service Targeted Lung Health Check (TLHC) program.[2] Among more than 10 000 patients in the TLHC program who underwent LDCT for lung cancer screening, referrals for TAD/TAA were made in 153 patients (1.5%), of whom 136 (1.3%) had findings confirmed by dedicated CT angiography. In another study of more than 36 000 patients undergoing coronary artery calcification (CAC) screening, the prevalence of TAD and TAA was 8.6% and 0.7%, respectively.[3] These studies highlight the potential yield of opportunistic screening for TAD/TAA. We therefore performed a single-center retrospective analysis to determine the prevalence and incidental detection rates of TAD/TAA among veterans undergoing clinically indicated CT imaging for purposes other than aortic evaluation at our institution.

METHODS

This single-center retrospective cohort analysis included consecutive patients undergoing clinically indicated LDCT for lung cancer screening, chest CT without contrast, or chest CT with contrast at the Milwaukee VA Medical Center in Milwaukee, Wisconsin. Indications for CT without contrast (n = 925 scans) included evaluation of pulmonary nodules, pleural plaques, granulomas, and ground-glass opacities (Table 1). Indications for CT with contrast (n = 2745 scans) included evaluation for malignancy, cancer surveillance or staging, or infection (eg, lung abscess or empyema), and CT pulmonary angiography (n = 1664) for suspected pulmonary embolism (Table 1). CT scans ordered for TAD/TAA surveillance and CT angiography of the chest (eg, for suspected aortic dissection) were excluded.

CT imaging reports from January 2023 to January 2025 were analyzed. Radiology reports were reviewed manually for the presence of TAD/TAA. TAD was defined as a maximal thoracic aortic diameter of ≥ 4.0 cm, and TAA was defined as ≥ 4.5 cm, consistent with prior studies and guidelines.[1,3] We manually reviewed the medical records of patients with reported TAD/TAA to determine whether findings were incidental, defined as not previously documented in imaging studies or clinical notes.

Point prevalence was calculated for each CT imaging modality as the number of TAD/TAA cases divided by the total number of unique patients during the study period. If multiple CT scans were obtained from the same patient, only the first CT scan during the study period was used to estimate prevalence. The incidental detection rate was calculated as the number of patients with incidental TAD/TAA divided by the number of unique patients. Three authors (TAJ, WB, JW) performed dual abstraction on a random subset of 101 positive and 102 negative TAD/TAA cases to determine interrater reliability. Interrater agreement was 98% ($\kappa = 0.96$) for the presence or absence of TAD/TAA.

This analysis was performed as part of a larger project assessing the completeness of International Classification of Diseases coding and clinical follow-up of TAD/TAA at our institution and therefore was deemed not to constitute human subjects research by the Institutional Review Board.

Statistical Analysis

We calculated descriptive statistics and performed univariate comparisons across CT imaging modalities using chi square test and 1-way analysis of variance (ANOVA) with Tukey post hoc testing. We report 95% binomial confidence intervals for prevalence and incidental detection rates for each CT imaging modality. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc).

RESULTS

TAD Cohort Descriptions

Across the entire cohort, 439 veterans had TAD (mean [SD] age, 72.0 [7.8] years; 98% male), including 84 with TAAs (Table 2). Most TADs (96.1%) involved the ascending aorta. The mean [SD] diameter was 4.27 cm [0.26 cm]. Patients with TAD identified on LDCT were significantly younger than those with TAD identified on other CT imaging modalities (69.4 vs 75.8 years; $P < .0001$). Patient sex and aortic diameter did not vary by CT modality.

Table 1. Summary of Total CT Cohort by Index Imaging Modality

	All CT Modalities	LDCT	CT Chest w/out Contrast	CT Chest with Contrast
Total scans	9409	3875	1125	4409
Unique patients	6795	2996	925	2874
Age, mean [SD], years[a]	69 [10.2]	67.6 [7.3]	71.4 [0.6]	69.8 [12.3]
Percent male[a]	93.0%	92.9%	94.2%	92.6%

Abbreviations: CT, computed tomography; LDCT, low-dose computed tomography.
[a]Using only first CT scans during the study period.

Prevalence

The prevalence of TAD and TAA was 6.1% (95% CI, 5.5%–6.6%) and 1.2% (95% CI, 0.95%–1.5%), respectively, across the combined CT cohorts (Table 2). The prevalence of TAD was approximately 8% in both the LDCT (8.1%; 95% CI, 7.1%–9.1%) and CT without contrast (8.3%; 95% CI, 6.5%–10.1%) groups and was significantly higher than in the CT with contrast group (3.2%; 95% CI, 2.6%–3.9%, $P < .05$). The prevalence of TAA was similar across LDCT (1.4%), CT without contrast (1.7%), and CT with contrast (0.8%) (Table 2).

Incidental Detection Rates

The overall incidental detection rates of TAD and TAA across all CT cohorts were 2.4% (95% CI, 2.0%–2.8%) and 0.4% (95% CI, 0.3%–0.6%), respectively (Table 2). The incidental detection rate for TAD on LDCT was significantly higher than those for CT without contrast and CT with contrast (3.7% vs 1.9% and 1.2%, respectively; $P < .05$). The incidental detection rate for TAA on LDCT was similar to that for CT without contrast (0.7% vs 0.5%) and significantly higher than that for CT with contrast (0.14%; $P < .05$).

DISCUSSION

We found a high prevalence of TAD/TAA in veterans undergoing annual LDCT for lung cancer screening (8.1% with TAD, including 1.4% with TAA) and chest CT without contrast (8.3% with TAD, including 1.7% with TAA). We also found that these CT modalities identified small but potentially important numbers of previously unrecognized TAD/TAA. These findings provide estimates of the potential yield of opportunistic screening programs that leverage existing CT imaging. Incidental detection rates for TAD were higher with LDCT for lung cancer screening (3.7%) than with other CT imaging modalities (1%–2%). The higher rate observed with LDCT likely reflects the fact that many

of these studies represented patients' first chest CT examination. It may also reflect a higher risk of aortic aneurysm among smokers,[1] although some recent cohort studies have found no association between smoking status and TAD/TAA.[4,5]

Overall, our prevalence estimates for LDCT and chest CT without contrast are similar to those reported by Khawaja et al, who reported TAD and TAA prevalences of 8.6% and 0.7%, respectively, in more than 36 000 patients (mean age, approximately 60 years) referred for clinically indicated CAC screening in Ohio.[3] The TLHC lung cancer screening program in the United Kingdom included more than 10000 participants who underwent LDCT (median age, 69 years; 34% female; 84% White British) and referred 1.5% of patients for dedicated aortic imaging to evaluate suspected thoracic aortic dilation,[2] a rate that was slightly lower than the incidental detection rate observed in our LDCT cohort (3.7%).

Table 2. Thoracic Aortic Dilation (TAD) and Thoracic Aortic Aneurysms (TAA) by Index Imaging Modality

	All CT Modalities	LDCT	CT Chest w/out Contrast	CT Chest with Contrast
Total no. of patients with TAD[a]	439	260	81	98
Total no. of patients with TAA[a]	84	43	18	23
Age, mean [SD], years[a]	72.0 [7.8]	69.4 [6.5][c]	76.0 [7.5]	75.7 [8.8]
Percent male[a]	98.2	98.1	97.5	99.0
Percent involving ascending aorta[a]	96.1	98.5	90.1	93.2
Aortic diameter, mean [SD], cm[a]	4.27 [0.6]	4.25 [0.24]	4.32 [0.30]	4.29 [0.32]
No. patients with TAD[b]	412	242	77	93
TAD prevalence estimate (95% CI)	6.06% (5.49%–6.63%)	8.08% (7.1%–9.05%)	8.32% (6.54%–10.10%)	3.24% (2.59%–3.88%)[c]
No. of patients with TAA[b]	82	43	16	23
TAA prevalence estimate	1.21% (0.95%-1.47%)	1.44% (1.01%-1.86%)	1.73% (0.89%-2.57%)	0.80% (0.48%-1.13%)
No. of patients with incidental TAD[a]	162	110	18	34
Incidental detection rate TAD[a]	2.38%) (2.02%-2.75%)	3.67%[c] (3.00%-4.34%)	1.95% (1.06%-2.84%)	1.18% (0.79%-1.58%)
No. of patients with incidental TAA[a]	30	21	5	4
Incidental detection rate TAA[a]	0.41% (0.28%-0.60%)	0.70%[d] (0.40%-1.00%)	0.54% (0.07%-1.01%)	0.14% (0.00%-0.28%)

Abbreviations: CT, computed tomography; LDCT, low-dose computed tomography.

[a]TAD/TAA not limited to the first CT scan during the study period.

[b]Using only first CT scans during the study period.

[c]Significant differences ($P < .05$) between CT modalities on analysis of variance (ANOVA).

[d]Significant difference ($P < .05$) between LDCT and CT chest with contrast only.

If opportunistic screening for TAD/TAA were implemented across the entire Veterans Affairs health system, substantial numbers of previously unrecognized cases could potentially be identified. Khawaja et al reported that the risk of TAD/TAA was increased in patients with higher 10-year atherosclerotic cardiovascular disease risk and CAC scores, suggesting a potential benefit of integrating TAD/TAA assessment into CAC screening programs.[3] Prospective studies are needed to determine the clinical relevance and downstream health care utilization associated with integrating opportunistic screening for TAD/TAA into existing CT-based screening programs. Future investigations could also explore the integration of artificial intelligence-based pipelines for automated measurement of thoracic aortic diameter into LDCT for lung cancer screening and other CT-based screening programs.[6,7]

Limitations

This analysis has several limitations. First, it is a single-center cohort, which may limit the generalizability of the findings. Second, we used radiology reports rather than manually reviewing CT images. This approach may have led to underascertainment of TAD/TAA if findings were not documented by the reporting radiologist. Third, although LDCT generally has strong correlation with CT angiography, Ahmed et al found that absolute differences in aortic measurements ranged from -3 to +3 mm.[2] Our findings therefore reflect real-world assessment of thoracic aortic diameter and the prevalence of TAD/TAA in clinically indicated CT imaging performed without electrocardiographically (ECG) gated acquisition and subject to variation in aortic diameter across the cardiac cycle.

CONCLUSIONS

Thoracic aortic dilation and thoracic aortic aneurysm are common among veterans undergoing clinically indicated chest CT imaging. Our findings highlight the potential utility of integrating thoracic aortic diameter measurement and reporting into existing CT screening programs, such as LDCT for lung cancer screening, to improve detection of TAD/TAA. The clinical impact of opportunistic screening for thoracic aortic disease warrants future investigation in larger studies, including prospective cohorts.

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Catastrophic Antiphospholipid Syndrome in a Young Adult: A Case Report and Literature Review

Thomas Szewczyk, BS; Farzana Hoque, MD, MRCP, FRCP

ABSTRACT

Introduction: Catastrophic antiphospholipid syndrome (CAPS) is a rare, life-threatening variant of antiphospholipid syndrome marked by rapid multiorgan thrombosis. Early diagnosis remains challenging, especially in young adults.

Case Presentation: A 22-year-old woman with immune thrombocytopenia, Raynaud's phenomenon, and a recent cholecystectomy presented with headache, abdominal pain, and systemic symptoms. She developed thrombotic events in the brain, spleen, and kidneys. Laboratory testing demonstrated positive antiphospholipid antibodies, and renal biopsy confirmed thrombotic microangiopathy.

Discussion: CAPS was diagnosed in the context of evolving systemic lupus erythematosus. Treatment included corticosteroids, plasma exchange, anticoagulation, hydroxychloroquine, and rituximab. Despite delayed recognition due to overlapping autoimmune conditions, multidisciplinary management led to clinical stabilization.

Conclusions: This case highlights the diagnostic complexity of CAPS in young patients with autoimmune comorbidities. Early recognition and aggressive multidisciplinary treatment are essential for favorable outcomes.

INTRODUCTION

Catastrophic antiphospholipid syndrome (CAPS) is a rare, life-threatening variant of antiphospholipid syndrome (APS) characterized by widespread small-vessel thrombosis leading to multiorgan failure. First formally described in the early 1990s, CAPS affects fewer than 1% of patients with APS and carries a high mortality rate, historically ranging from 30% to greater than 50% despite advances in treatment.[1,2] The condition evolves rapidly, often within days, distinguishing it from classic APS, which typically involves thrombosis at a single site. The pathophysiology of CAPS is multifactorial and involves the pathogenic antiphospholipid antibodies (aPLs), including lupus anticoagulant, anticardiolipin, and anti-β2 glycoprotein I antibodies. These antibodies promote a prothrombotic state through endothelial activation, complement activation, and inflammatory cytokine release, culminating in systemic microvascular occlusion.[2,3] A widely accepted "two-hit" hypothesis suggests that an external trigger, most commonly infection, surgery, malignancy, or anticoagulation withdrawal, precipitates the catastrophic cascade in individuals with underlying aPL positivity.[2,4]

CAPS is frequently associated with autoimmune disorders, particularly systemic lupus erythematosus (SLE), which coexists in approximately 30% to 40% of cases.[5] The neurologic, renal, pulmonary, and cardiac systems are most commonly affected. Diagnostic criteria for CAPS include multiorgan involvement, acute symptom onset within 1 week, histopathologic confirmation of small-vessel thrombosis, and laboratory detection of aPLs.[3] Empiric treatment consists of "triple therapy": therapeutic anticoagulation, high-dose corticosteroids, and either plasma exchange or intravenous immunoglobulin (IVIG). In refractory cases, immunomodulatory agents such as rituximab and eculizumab have shown positive results.[2,6] Despite these interventions, prognosis typically remains unclear, underscoring the importance of early recognition and aggressive multidisciplinary management.[4,6]

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CASE PRESENTATION

A 22-year-old woman with a complex medical history notable for immune thrombocytopenic purpura (ITP), Raynaud's phenomenon, rheumatic mitral valve disease, myopericarditis, and recent cholecystectomy (2 weeks before admission) was transferred to our institution for further evaluation of abdominal pain, intractable headache, nausea, and vomiting. She had previously been scheduled for an outpatient renal biopsy because of hematuria and proteinuria identified during a prior admission; however, she presented to the emergency department before the biopsy could be performed.

On initial presentation, the patient was found to have a malar rash, joint pain, easy bruising, and chronic headaches, a constellation of findings suggestive of an autoimmune disorder, in addition to abdominal pain, nausea, and vomiting. Physical examination revealed a murmur and right lower quadrant abdominal tenderness. She was hemodynamically stable and afebrile. Initial imaging revealed a right middle cerebral artery infarct on brain magnetic resonance imaging (MRI) (Figure 1) and a splenic infarct on abdominal computed tomography (CT) (Figure 2). Urinalysis demonstrated 2+ protein and 2+ blood, suggestive of a nephritic syndrome. Collectively, these findings, along with a new-onset rash, raised concern for a systemic autoimmune or thrombotic process.

Further serologic testing revealed positive lupus anticoagulant and elevated IgM anticardiolipin and IgM β2-glycoprotein I antibodies. Although her antinuclear antibody (ANA) and extractable nuclear antigen (ENA) profiles initially were negative, an ANA titer of 1:160 was later confirmed by immunofluorescence. Given the multiorgan involvement, including the central nervous system, spleen, kidneys, and heart, together with the serologic findings, a working diagnosis of CAPS was made. The rheumatology service also considered underlying SLE as a contributing autoimmune condition, although the patient did not meet full classification criteria at the time of diagnosis.

The patient's vital signs remained relatively stable throughout hospitalization. Blood pressure fluctuated between hypertensive and normotensive ranges during the first 10 days, with a peak measurement of 159/111 mm Hg on the hospital day 2. She never developed hypotension requiring vasopressor support. The patient remained afebrile throughout hospitalization, and no supplemental oxygen was required.

During admission, the patient experienced worsening cardiopulmonary symptoms, including pleuritic chest pain and elevated troponin levels. Serial echocardiograms and cardiac MRI demonstrated an ejection fraction of 47%, classified as mildly reduced according to contemporary cardiology guidelines, as well as new regional wall motion abnormalities consistent with recurrent myopericarditis. Cardiology attributed myopericarditis to underlying inflammatory activity rather than ischemic heart disease. Coronary angiography showed no evidence of thrombotic lesions.

Figure 1. Brain Magnetic Resonance Imaging of Patient Consistent With Right Middle Cerebral Artery Infarct

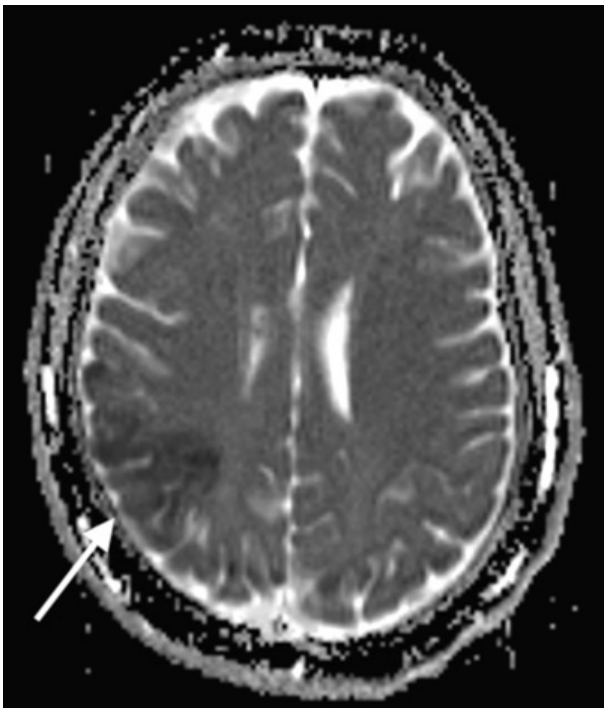
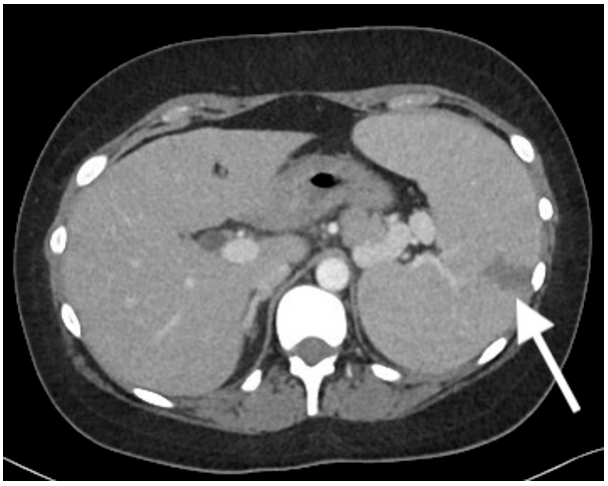


Figure 2. Abdominal Computed Tomography of Patient Consistent With Splenic Infarct



Colchicine and corticosteroids were administered for symptom control, and guideline-directed medical therapy for heart failure, including carvedilol and empagliflozin, was initiated. Renal biopsy demonstrated thrombotic microangiopathy with features of acute interstitial nephritis and acute tubular injury, findings consistent with renal involvement in CAPS. Unlike cerebral and splenic infarcts, no renal infarction or other renal abnormality was identi-

fied on imaging. Evidence of renal thrombosis was demonstrated only on biopsy. Significant laboratory findings are summarized in the Table.

Initial attempts at biopsy were delayed because of concerns regarding bleeding in the setting of chronic ITP and thrombocytopenia. A skin biopsy performed to evaluate a faint malar and reticulated rash demonstrated leukocytoclastic vasculitis. The cumulative clinical, radiographic, and histopathologic findings supported the diagnosis of CAPS. Anticoagulation was initiated with a heparin drip and later transitioned to therapeutic enoxaparin bridging to warfarin. Because of the known limitations of international normalized ratio (INR) monitoring in APS, the hematology and pharmacy teams recommended chromogenic factor X activity testing to guide anticoagulation therapy. The patient was discharged with a target factor X activity level of 20% to 30%, with outpatient INR correlation planned.

For immunosuppression, she received pulse-dose methylprednisolone (1 g intravenously daily for 3 days), followed by high-dose maintenance methylprednisolone and transition to oral prednisone, 60 mg daily, at discharge. Hydroxychloroquine was initiated, and the patient completed 5 plasma exchange (PLEX) sessions. She also received 2 doses of rituximab, 1000 mg each, administered 2 weeks apart. Trimethoprim-sulfamethoxazole (Bactrim) prophylaxis was initiated to prevent opportunistic infections during immunosuppressive therapy, with plans to consider alternative agents such as atovaquone or dapsone if needed.

Neurology remained involved because of persistent intractable headaches and for ongoing stroke management. Despite multiple therapeutic interventions, The headaches remained partially refractory, with only mild improvement following treatment with topiramate and gabapentin. Opioids gradually tapered during hospitalization. The patient's hospital course was further complicated by profound fatigue, anorexia, and weight loss, with clinical evidence of severe protein-calorie malnutrition. Nutritional supplementation and a gradual diet reintroduction were implemented under the supervision of the internal medicine team.

Following stabilization of her condition, improvement of symptoms, and completion of planned immunosuppressive and anticoagulation therapies, the patient was discharged home in stable condition on hospital day 30. She was instructed to follow closely with outpatient specialists in rheumatology, hematology, nephrology, neurology, cardiology, and gynecology. Follow-up appointments and laboratory monitoring, including repeat antiphospholipid antibody testing and chromogenic factor X assays, were arranged to ensure continuity of care.

Table. Significant Lab Results During Hospitalization

Lab Test	Days Collected	Peak/Key Value
Platelet count	Days 2–30	Lowest: 47 (day 3); improved to 161
White blood cell count	Days 2–30	Peak: 46.5 (day 22); improved to 16.4
Creatinine	Days 2–30	Peak: 1.29 (day 20); normalized to 0.89
Troponin I	Days 12, 13, 14, 23	Peak: 52,695 (day 14); elevated on days 12, 13, 14, 23
Urinalysis	Days 2, 10	Protein 2+, Blood 2+; Protein 2+, Blood 2+
Antinuclear antibody titer	Day 3	1:160
Lupus anticoagulant	Day 3	Positive
aCL IgM	Day 3	Positive
β2GPI IgM	Day 3	Positive

DISCUSSION

CAPS is a rare but life-threatening variant of APS, defined by rapid multiorgan failure due to widespread small-vessel thrombosis. This case of a 22-year-old woman demonstrates a diagnostically and therapeutically complex presentation of CAPS, made more challenging by comorbidities, including refractory ITP, nephritic syndrome, myopericarditis, and possible SLE. The patient's admission was initially prompted by gastrointestinal symptoms and severe headache but rapidly escalated into a systemic evaluation when imaging revealed infarctions in the brain and spleen. Renal biopsy showed thrombotic microangiopathy, with additional findings of acute interstitial nephritis and tubular injury. The diagnosis of CAPS was ultimately supported by the involvement of 3 major organ systems (brain, kidney, spleen), along with laboratory evidence of antiphospholipid antibodies (lupus anticoagulant positive, anticardiolipin IgM positive, β2-glycoprotein I IgM positive) and biopsy-proven microthrombosis. This constellation satisfies the international consensus criteria for definitive CAPS, which require evidence of small-vessel thrombosis in at least 3 organs occurring over a short period and the presence of antiphospholipid antibodies.[7] The lack of hypotension further supports thrombosis, rather than hypoperfusion, as the cause of organ injury. CAPS occurs in less than 1% of patients with APS, with a female predominance and an average age in the mid-30s, making this patient's diagnosis at age 22 relatively early.[8]

Neurological involvement is common in CAPS, with stroke being the most frequent manifestation, followed by seizures and cognitive dysfunction.[9] The patient's right middle cerebral artery infarct aligns with the neurologic manifestations commonly seen in CAPS. Though her persistent headaches were initially attributed to migraine, there was consideration of underlying cerebrovascular inflammation or vasculitis. However, repeat neuroimaging did not show progression of vessel irregularities, making progressive large-vessel vasculitis unlikely. Thus, microvascular thrombosis, a hallmark feature of CAPS, remains the most likely mechanism behind her infarct. Renal involvement in CAPS commonly presents as thrombotic microangiopathy or APS nephropathy,[10] and in this patient, the renal biopsy revealed hallmark features consistent with this pathology, including glomerular microthrombi. Her urine

protein-creatinine ratio improved from 0.88 to 0.57, and stable creatinine levels suggest partial response to therapy, although long-term outcomes remain uncertain. Cardiac complications in CAPS range from valvular abnormalities (including Libman-Sacks endocarditis) to myocardial infarction secondary to coronary thrombosis or microvascular disease.[11] The patient had prior mitral valve abnormalities suspected to be congenital, but worsening left ventricular function and wall motion abnormalities during the hospital course likely reflected CAPS-related myocardial involvement. Serial echocardiograms and cardiac MRI findings of hypomobility without fibrosis support this interpretation.

One of the significant hurdles in this case was distinguishing CAPS from other overlapping autoimmune syndromes. Despite systemic features consistent with SLE (including malar rash, photosensitivity, pericarditis, nephritic syndrome, and cytopenias), her initial autoimmune panel was largely negative. However, ANA later returned at a titer of 1:160 by indirect immunofluorescence assay, and skin biopsy confirmed leukocytoclastic vasculitis, raising strong suspicion for SLE. Whether the initially negative serologies reflected evolving disease or the effects of acute illness remain uncertain.[12] The literature recognizes that CAPS can either be primary or secondary to conditions such as SLE, and in up to 40% of cases, CAPS may be the first manifestation of APS or lupus.[13]

The coexisting diagnosis of ITP further complicated management. While thrombocytopenia is a paradoxical feature of a prothrombotic syndrome, it is frequently seen in APS and especially in CAPS, where platelet consumption is accelerated by ongoing microthrombosis.[4] This also delayed the renal biopsy and complicated anticoagulation decisions. Treatment of CAPS is multifaceted and often referred to as "triple therapy," consisting of anticoagulation, high-dose corticosteroids, and PLEX, with or without IVIG.[5] The patient received all three, plus rituximab, an anti-CD20 monoclonal antibody increasingly employed in refractory or overlapping CAPS/SLE cases.[14] The decision to escalate to rituximab was supported by the patient's poor response to thrombopoietin receptor agonists for ITP, suspected lupus activity, and evolving CAPS. The use of hydroxychloroquine further aligns with SLE management guidelines, and its potential antithrombotic benefit may aid in preventing recurrent thrombosis.[6] The patient's condition gradually stabilized following 5 sessions of PLEX, 2 doses of rituximab, and transition to warfarin with enoxaparin bridging. Given the complexity of CAPS management, shared decision-making with patients and families is critical to ensure understanding of the treatment goals, risks, and alternatives.[15] Discharge on prednisone 60 mg, hydroxychloroquine, aspirin, and a carefully titrated anticoagulation plan (monitored using chromogenic factor X activity assays because of potential lupus anticoagulant interference with standard coagulation testing), demonstrates adherence to tailored therapy recommendations in complex APS.[16]

At discharge, the patient was clinically stable but remained on substantial immunosuppressive and anticoagulation regimens. Her renal function had improved slightly, and her platelet counts were monitored without requiring platelet transfusions. Her headaches were managed with topiramate and gabapentin, and she was counseled on medication adverse effects and contraception due to potential teratogenic risk. Follow-up with hematology, rheumatology, nephrology, cardiology, and neurology was arranged.

CONCLUSIONS

This case demonstrates the diagnostic and therapeutic complexity of CAPS, particularly in young adults with overlapping autoimmune and hematologic conditions. The patient's rapid multiorgan involvement, including cerebral, renal, splenic, and cardiac manifestations, highlighted the importance of considering CAPS even in younger patients who fall outside the typical age range at presentation. Despite initially confounding features and negative serologies, the evolving clinical picture, supported by serologic and histopathologic findings, met diagnostic criteria for CAPS likely associated with evolving SLE. Early multidisciplinary collaboration and prompt treatment with high-dose corticosteroids, anticoagulation, plasma exchange, and rituximab were critical to disease stabilization and the patient's favorable condition at discharge.

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Breakthrough Cutaneous Crohn's Disease Healed With Risankizumab

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ABSTRACT

Introduction: Extraintestinal manifestations of Crohn's disease are associated with substantial morbidity and commonly present as arthropathies or painful lesions involving the skin, eyes, and mouth. However, they can involve nearly any organ system and do not correlate directly with intestinal inflammation, complicating diagnosis and treatment. As treatment options expand, this article explores the potential role of risankizumab in the treatment of cutaneous Crohn's disease.

Case Presentation: A 75-year-old man developed a gluteal fissure consistent with cutaneous Crohn's disease despite longstanding maintenance with adalimumab, an anti-tumor necrosis factor-α (TNF-α) monoclonal antibody. He transitioned to risankizumab, an interleukin-23 (IL-23) inhibitor, with resolution of cutaneous disease involving the gluteal cleft and continued luminal remission.

Discussion: This case report is the first to demonstrate successful treatment of anti-TNF-resistant cutaneous Crohn's disease with an IL-23 inhibitor. No other published cases were found.

Conclusions: While TNF-α inhibitors remain the standard of care for extraintestinal manifestations of Crohn's, IL-23 inhibitors are a promising therapy option.

INTRODUCTION

Extraintestinal manifestations (EIM) are known to affect up to 50% of individuals diagnosed with inflammatory bowel disease (IBD) and burden patients with Crohn's disease more than those with ulcerative colitis.[1-3] These symptoms increase the morbidity associated with IBD and often have a greater negative impact on quality of life than the underlying intestinal disease itself.[4] Metastatic Crohn's disease is a rare EIM in which inflammatory skin lesions occur at sites that are not contiguous with active luminal disease and often develop independently of intestinal disease activity. The limited nature of these lesions and poor understanding of their etiology have contributed to a lack of consensus regarding management.[5,6] Classic cutaneous Crohn's disease findings include linear gluteal cleft ulcers and fissures with sharply demarcated borders resembling knife cuts, perianal and peristomal skin tags, fistulae, and abscesses. Patients with ileocolonic Crohn's disease and EIMs are more challenging to manage, statistically requiring a greater number of biologic therapies over time than those with ileal Crohn's disease and associated EIMs.[7] Anti-tumor necrosis factor α (TNF-α) monoclonal antibodies are often first-line therapies for patients with IBD and EIMs, as they have demonstrated substantial efficacy in treating both luminal disease and many identified EIMs.[4,8] This case demonstrates successful resolution of cutaneous Crohn's disease with continued luminal remission upon transitioning from adalimumab to riskanizumab.

CASE PRESENTATION

A 75-year-old man with a history of severe ileocolonic Crohn's disease, maintained on adalimumab, presented for gastroenterology follow-up with complaints of new intergluteal irritation and gluteal cleft fissuring over the past few months. His symptoms began with discomfort in the perianal region and progressed to scant intermittent blood streaking with wiping and the development of gluteal cleft splitting. He reported variable consistency and frequency of bowel movements unchanged from baseline, typically ranging from 3 to 6 episodes per day. He denied purulence or fecal discharge from the area. On examination, he was

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found to have pathognomonic knife-like fissuring along the gluteal cleft overlying an erythematous base, separate from the anal mucosa.

In 1975, the patient was diagnosed with stricturing and fistulizing ileocolonic Crohn's disease with perianal involvement and abscess formation requiring incision and drainage. He underwent 2 small bowel resections in 1986 and 1996. Biologic therapy with infliximab was initiated in 2006 and discontinued after 18 months because of an infusion reaction. He subsequently transitioned to maintenance therapy with adalimumab in 2008. A 2020 restaging colonoscopy was complicated by a transverse colon perforation requiring emergent laparotomy and intensive care unit admission. Because of infectious complications during recovery, his immunosuppression was held for approximately 18 months. Adalimumab was reinitiated in November 2021 with induction dosing.

Given his lapse in biologic therapy, quantitative drug levels and antibody testing were ordered following induction and demonstrated therapeutic adalimumab levels of 9.8 ug/mL without antibodies. Posterior gluteal cleft fissuring was noted during an office visit on April 19, 2023. He was evaluated by dermatology, which affirmed the diagnosis of cutaneous Crohn's disease and jointly monitored his disease. Biopsy was not obtained because of his clinical history and pathognomonic fissuring on examination.

Despite adequate adalimumab levels and stable intestinal symptoms, the patient was counseled regarding breakthrough cutaneous Crohn's disease and was transitioned to riskanizumab. His intergluteal fissure demonstrated marked improvement at a routine 6-month follow-up. Restaging colonoscopy performed 1 year later demonstrated complete resolution of the fissure and continued luminal remission on riskanizumab. The patient reported substantial improvement in quality of life due to pain relief, fissure healing, and peace of mind associated with disease control.

DISCUSSION

The proinflammatory cytokine TNF-α has been identified as a major contributor in the recruitment and perpetuation of the inflammatory cascade responsible for a variety of EIMs in Crohn's disease, especially cutaneous eruptions.[9,10] Given this mechanism, anti-TNF-α therapies (infliximab and adalimumab) have been well studied and demonstrate significant efficacy in treating both luminal and extraintestinal disease.[11,12] TNF- α inhibitors may be considered preventive, as patients with Crohn's disease maintained on this class have demonstrated an overall reduction in the development of EIMs.[12] However, their efficacy is not absolute, as clinical data continue to demonstrate substantial variability in individual responsiveness, dosing requirements, and adverse effects. Despite this patient's therapeutic adalimumab level of 9.8 ug/mL and absence of anti-drug antibodies, he developed breakthrough intergluteal Crohn's development.

This case raises questions regarding optimal management, as dose escalation, trialing another anti-TNF agent, introduction of concomitant immunomodulators, or a change in therapeutic class are all reasonable options. The incidence of breakthrough EIMs despite quantitatively adequate drug levels is not well documented.

The US Food and Drug Administration has approved risankizumab, an interleukin-23 (IL-23) inhibitor, for the treatment of moderate-to-severe Crohn's disease. The drug is traditionally used in patients with plaque psoriasis and psoriatic arthritis. The pathophysiology of psoriasis and spondyloarthritis has highlighted the role of IL-23 signaling in the maturation and stabilization of the inflammatory cascade.[13,14] Specifically, IL-23 is a fundamental component of barrier tissue defense and is secreted by respiratory, gastrointestinal, epithelial, and secretory cells to maintain mucosal integrity and homeostasis.[14] When dysregulated, IL-23 promotes heightened local inflammation, making it an ideal target for cutaneous autoimmune sequelae such as the cutaneous Crohn's disease observed in this patient. A multicenter European case series identified 10 patients with anti-TNF-refractory cutaneous Crohn's disease, among whom ustekinumab, an IL-12/IL-23 inhibitor, induced remission in 5 cases and partial remission in 4 cases.[15] Risankizumab was chosen in this case instead of ustekinumab because of evidence demonstrating the superiority of risankizumab over ustekinumab for moderate-to-severe Crohn's disease in patients with previous failure of anti-TNF treatment.[16]

CONCLUSIONS

To our knowledge, this is the first case report documenting resolution of cutaneous Crohn's disease with risankizumab. IL-23 inhibitors represent a promising therapeutic option for patients with cutaneous Crohn's disease. Future large-scale clinical studies comparing EIM responsiveness to different biologic and systemic therapies, along with continued phenotypic correlation, are needed to further optimize treatment strategies.

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Eosinophilic Gastrointestinal Disease Masquerading Radiographically as Peritoneal Carcinomatosis

Kyle A. Burton, MD; Jack Koueik, MD; Mark D. Oliver, DO; Daniel L. Rosenberg, MD; Melissa MacDonald, MD

ABSTRACT

Introduction: Eosinophilic gastrointestinal disease (EGID) is a rare disorder characterized by gastrointestinal symptoms and eosinophilic infiltration of the gastrointestinal tract in the absence of secondary causes of eosinophilia.

Case Presentation: A 76-year-old man presented with abdominal pain, early satiety, and ascites. Imaging and laparoscopy were concerning for peritoneal carcinomatosis. Laboratory evaluation revealed peripheral eosinophilia. Extensive infectious, autoimmune, and neoplastic evaluations were negative. Biopsies and cytology revealed no evidence of malignancy but demonstrated eosinophilic tissue infiltration supporting a diagnosis of EGID. Corticosteroid treatment led to rapid resolution of eosinophilia. The patient was diagnosed with serosal EGID and subsequently transitioned to mepolizumab, with sustained disease control.

Discussion: Hypereosinophilia often requires extensive evaluation. This case highlights the diagnostic complexity of EGID, particularly when it mimics advanced malignancy.

Conclusions: EGID should be considered in patients with unexplained eosinophilia and radiographic findings suggestive of malignancy, particularly within the abdomen or gastrointestinal tract. Early recognition may prevent unnecessary interventions and allow timely initiation of effective therapy.

INTRODUCTION

Eosinophilia is defined as an elevated level of eosinophils in the serum or tissues.[1] It may arise from a broad spectrum of underlying conditions, including allergic, infectious, neoplastic, genetic, and immune-mediated disorders.[2]

Hypereosinophilic syndromes (HES) comprise a group of rare disorders characterized by an absolute eosinophil count greater than 1500/ μL and eosinophil-associated organ damage.[3] Idiopathic HES, a subset of HES with no identifiable underlying cause, is a rare clinical entity that can present with diverse manifestations affecting multiple organ systems. Eosinophilic gastrointestinal diseases (EGID) are rare disorders characterized by gastrointestinal symptoms and eosinophilic infiltration of the gastrointestinal tract in the absence of secondary causes of eosinophilia.[4] EGID and idiopathic HES share significant clinical overlap. Interleukin-5 (IL-5) inhibitors, including mepolizumab, reslizumab, and benralizumab, have shown promising efficacy in the treatment of eosinophil-mediated diseases.[5]

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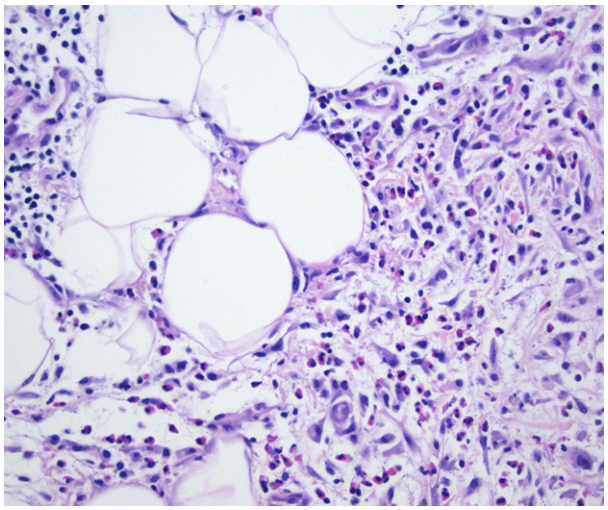
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CASE PRESENTATION

A 76-year-old man with a medical history of hypertension, hyperlipidemia, gastroesophageal reflux disease, Raynaud's disease, eczema, transient ischemic attack, and recurrent *Clostridioides difficile* infection presented with a 2-month history of progressive right upper quadrant abdominal pain.

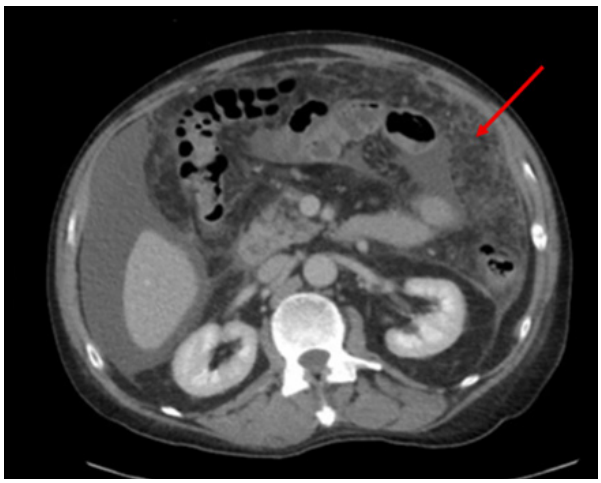
The patient initially presented to the emergency department reporting a progressive sensation of abdominal fullness, early satiety, and worsening right upper quadrant pain over the preceding week. Physical examination revealed significant distension concerning for ascites. Notably, no cutaneous rash was present. Laboratory examination on admission showed hypoalbuminemia (2.8 g/dL), low total protein (6.2 g/dL), normal liver function test results, elevated C-reactive protein (13.6 mg/dL), elevated erythrocyte sedimentation rate (38 mm/h), a white blood cell count of 10.7 K/μL), normal hemoglobin, elevated

Figure 1. Histologic Image of Omentum Biopsy



Hematoxylin and eosin-stained section at 400X magnification showing eosinophil-rich chronic inflammation in a background of abundant reactive myofibroblasts.

Figure 2. Representative Slice From Computed Tomography Abdomen/Pelvis With Intravenous Contrast



CT was notable for diffuse nodular infiltration of the omentum along with interloop mesenteric fluid. There was also medium volume ascites and small bilateral (right greater than left) pleural effusions.

platelet count (427 K/μL), a normal absolute neutrophil count (7270/μL), lymphopenia (970/μL), monocytosis (1480/μL), eosinophilia (800/μL), a normal absolute basophil count (20/μL), and an elevated absolute immature granulocyte count (120/μL).

Computed tomography (CT) of the abdomen and pelvis revealed a new moderate volume ascites and mesenteric edema. Chest CT showed a small right pleural effusion without evidence of malignancy. Right upper quadrant ultrasonography demonstrated omental infiltration and stranding, as well as moderate ascites. Liver morphology and Doppler studies were normal. Magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography showed gallbladder wall lesions, periportal lymphadenopathy, and peritoneal enhancement and nodularity concerning for carcinomatosis, although findings were nonspecific. Tissue sampling was recommended. Electrocardiography revealed a new left bundle branch block. Transthoracic echocardiogram demonstrated a normal left ventricular ejection fraction (55%) and normal right ventricular function.

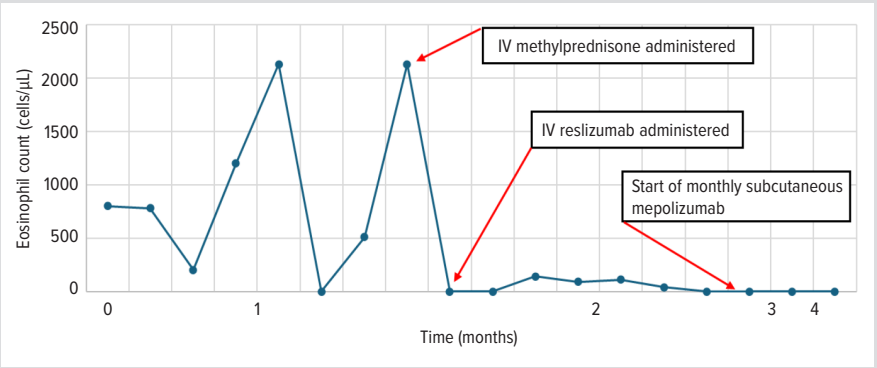
The patient underwent paracentesis, with removal of 2.5 L of ascitic fluid. Acid-fast bacilli smear results were negative, and fluid was sent for culture. Surgical oncology was consulted, and the patient underwent exploratory laparoscopy, which demonstrated diffuse omental caking with abundant brown ascitic fluids. Omental biopsy specimens and additional ascitic fluid samples were obtained. Frozen sections demonstrated abundant inflammation and atypical cells without definitive evidence of carcinoma. Further classification was deferred pending permanent sections, and portions of the specimen were sent for flow cytometry and chromosome analysis. The patient was discharged while pathology results were pending. Ascitic fluid cytology was negative for malignancy but showed eosinophilic and neutrophilic leukocytes. Flow cytometry did not identify an abnormal lymphocyte population, and chromosome analysis was not completed because of insufficient metaphase cells. Permanent histology of the biopsy specimens revealed eosinophil-rich chronic inflammation (Figure 1).

One month later, the patient was readmitted with worsening shortness of breath, wheezing, and abdominal pain. Laboratory evaluation was notable for a normal white blood cell count (9.3 K/μL), elevated platelet count (551 K/μL), normal hemoglobin, normal troponin, monocytosis (1310/μL), and marked eosinophilia (2130/μL), with normal neutrophil and basophil counts.

Repeat CT of the abdomen and pelvis showed persistent infiltration concerning for peritoneal carcinomatosis, with increased ascites compared with prior imaging (Figure 2). Small bilateral pleural effusions also were present. CT pulmonary angiography showed no pulmonary emboli or pulmonary infiltrates. Hematology was consulted for evaluation of eosinophilia. Peripheral smear demonstrated only nonspecific thrombocytosis and mild monocytosis. The patient underwent a paracentesis, with removal of 700 mL of peritoneal fluid, and thoracentesis, with removal of 2200 mL of pleural fluid. Pleural fluid analysis demonstrated 2068 nucleated cells/μL and was mildly exudative according to Light criteria, with pleural fluid lactate dehydrogenase (LDH) of 131 U/L (serum LDH, 116 U/L) and pleural fluid protein of 2.8 g/dL (serum protein, 5.5 g/dL). Differential counts showed 14% neutrophils, 25% lymphocytes, 43% macrophages, and 17% eosinophils. Pleural fluid cytology was negative for malignancy, and concurrent flow cytometry showed no evidence of a lymphoproliferative disorder.

Additional evaluation of eosinophilia revealed negative *Strongyloides* IgG antibody, *Toxocara* IgG antibody, and QuantiFERON-TB Gold test results. Serum IgE levels were within normal limits. Tryptase and vitamin B12 levels were normal. Autoimmune serologic testing, including RNA polymerase III antibody, polymyositis panel, Scl-70 antibody, cyclic citrullinated peptide IgG antibody, rheumatoid factor, antinuclear antibody, extractable nuclear antigen panel, myeloperoxidase IgG antibody, and proteinase 3 IgG antibody, was negative. Stool examination for parasites, including direct preparation and trichrome staining, was unremarkable.

Figure 3. Serial Absolute Eosinophil Counts Over the Course of Hospitalization and Follow-up, Demonstrating Rapid Normalization Following Corticosteroid Initiation and Sustained Suppression With Mepolizumab



Following discharge, the patient underwent bone marrow biopsy, which demonstrated essentially normal morphologic findings, with no lymphoid abnormalities detected by concurrent flow cytometry. Molecular testing identified a mutation with a low variant allele frequency of uncertain clinical significance in the setting of otherwise unremarkable marrow findings. Platelet-derived growth factor receptor alpha rearrangement and Janus kinase 2 mutation testing were negative. Therefore, there was no evidence of a myeloid variant to explain the patient's eosinophilia. Positron emission tomography (PET) showed no evidence of malignancy. Subsequent outpatient colonoscopy likewise revealed no evidence of malignancy. Ongoing monitoring of blood counts was recommended.

Allergy consultation initially determined that the patient met diagnostic criteria for idiopathic hypereosinophilic syndrome because testing did not identify a hematologic malignancy or other apparent cause. Subsequently, serosal EGID with peripheral hypereosinophilia was considered a more specific diagnosis. The patient was treated initially with intravenous methylprednisone 60 mg. The following day, complete resolution of eosinophilia was observed (eosinophil count, 0/μL), and he received reslizumab, an IL-5 antagonist. He was discharged on a prednisone taper.

At follow-up in the outpatient allergy clinic, the patient was transitioned to mepolizumab 300 mg subcutaneously administered every 4 weeks. Serial absolute eosinophil counts were monitored every 2 weeks and remained suppressed. These trends are shown in Figure 3. Despite IL-5 inhibitor therapy and resolution of peripheral eosinophilia, the patient experienced recurrent ascites. Repeat peritoneal fluid flow cytometry obtained after paracentesis approximately 6 months later remained negative for malignancy.

Although the ascites subsequently resolved, recurrent pleural effusions persisted, necessitating placement of an indwelling pleural catheter. Pleural fluid analysis from subsequent thoracentesis remained marginally exudative, based on mild protein elevation, but persistent eosinophilia was not observed in the context of treatment with mepolizumab.

The patient was referred to a quaternary referral center for further evaluation. No underlying malignancy or alternative etiology was identified, and he was advised to continue mepolizumab indefinitely given the favorable clinical response and good tolerability. Follow-up with repeat PET imaging, pulmonary function testing, and troponin monitoring was recommended, with cardiac MRI advised if troponin levels became elevated to assess for myocardial involvement. To date, the patient has had no evidence of malignancy or another etiology for hypereosinophilia and remains on outpatient mepolizumab therapy.

DISCUSSION

Eosinophilia refers to an increased number of eosinophils in the tissues and/or blood. Absolute eosinophil counts greater than 450 to 550/μL are commonly considered elevated, although thresholds may vary depending on laboratory standards.[1] Hypereosinophilia refers to an absolute eosinophil count >1500/μL.[2] The differential diagnosis of eosinophilia is broad and encompasses allergic, infectious, neoplastic, genetic, and immune-mediated disorders.[2] Given the broad possible etiologies, an extensive diagnostic workup is often necessary. A detailed clinical history is frequently the most important clue to identifying the underlying etiology of eosinophilia.[1]

Hypereosinophilic syndromes are a rare group of disorders characterized by an absolute eosinophil count of 1500/μL or greater, evidence of end-organ involvement attributable to eosinophilia, and the absence of an alternative explanation.[2] Idiopathic hypereosinophilic syndrome (HES) is one potential cause of eosinophilia. Idiopathic HES has been reported to present with a wide variety of manifestations, including persistent diarrhea and other gastrointestinal symptoms, as well as cutaneous, pulmonary, and cardiac involvement, as summarized in the Table.[6-9]

EGID is a rare disorder characterized by gastrointestinal (GI) symptoms and eosinophilic infiltration of specific areas of the GI

Table. Representative Published Cases of Eosinophilic Gastrointestinal Disease (EGID) or Hypereosinophilic Syndrome (HES) With Gastrointestinal Involvement

Author, Year	Patient Presentation	Treatment	Outcome
Foreman et al, 2024[6]	70-year-old male presenting with generalized erythematous and pruritic cutaneous lesions and peripheral hypereosinophilia	Corticosteroids	Complete resolution of skin lesions
Wang et al, 2025[7]	73-year-old male with pulmonary hypertension and asthma presenting with persistent eosinophilia	Corticosteroids, mepolizumab	Significant response to corticosteroids and mepolizumab
Gruber et al, 2024[8]	50-year-old male presenting with diarrhea, nausea, emesis, abdominal pain, and tissue biopsies revealing mucosal eosinophilia	Corticosteroids	Significant improvement in symptoms and eosinophilia
Khalid et al, 2019[9]	83-year-old female presenting with worsening dyspnea, found to have eosinophilic myocarditis	Corticosteroids	Significant clinical improvement

tract in the absence of secondary causes of eosinophilia.[4] EGID can involve the mucosal, muscular, or serosal layers of the GI tract and is often classified accordingly. The serosal subtype is uncommon and may present with eosinophilic ascites.[10] In this case, the distinction between idiopathic HES and EGID, particularly serosal EGID, warrants consideration.

The radiographic appearance of omental infiltration often presents a diagnostic challenge because it may result from either benign or malignant processes. Distinguishing among these etiologies on imaging alone can be particularly difficult.[11] Omental biopsy is often required for definitive evaluation and has been shown to be more sensitive than peritoneal cytology for detecting malignancy.[12]

Mepolizumab and reslizumab are humanized monoclonal antibodies that target IL-5.[13] Mepolizumab is approved in the United States for treatment of severe eosinophilic asthma, eosinophilic granulomatosis with polyangiitis, and HES.[14]

We present a case of a 76-year-old man who presented with progressive abdominal swelling, early satiety, and right upper quadrant pain. Laboratory studies demonstrated persistent eosinophilia, and imaging revealed omental infiltration concerning for peritoneal carcinomatosis. An extensive evaluation for eosinophilia, including infectious, autoimmune, hematologic, and oncologic causes, was unrevealing. The patient ultimately was diagnosed with serosal EGID and treated with methylprednisone and reslizumab during hospitalization before transitioning to mepolizumab as an outpatient. Subsequent evaluation at a quaternary referral center likewise failed to identify an alternate cause of eosinophilia.

Given the negative malignancy workup, eosinophil-predominant histopathologic findings, and GI serosal involvement, serosal EGID was considered the most likely diagnosis. Although idiopathic HES remains a diagnosis of exclusion, distinguishing it from EGID may have limited clinical significance in some cases, as both conditions can present with overlapping manifestations and may respond to IL-5 targeted therapies. The patient continues to demonstrate sustained suppression of eosinophilia control and symptomatic improvement while receiving mepolizumab.

CONCLUSIONS

Our case describes a unique presentation of eosinophilic disease mimicking peritoneal carcinomatosis. Eosinophilia encompasses a broad differential diagnosis, including allergic, infectious, neoplastic, and immune-mediated disorders, and often requires a comprehensive evaluation. Although serosal EGID was diagnosed in this case, idiopathic HES remained a relevant consideration in the differential diagnosis.

This case underscores the importance of careful interpretation of the complete blood cell count and differential and highlights the need to maintain a broad differential diagnosis in patients with persistent eosinophilia and radiographic evidence of omental infiltration. Eosinophilic disorders may mimic malignancy, and although distinguishing between overlapping syndromes such as idiopathic HES and EGID may be diagnostically important, management strategies often overlap. IL-5 inhibitors, including mepolizumab, may offer an effective targeted treatment option for patients with serosal EGID and related eosinophilic disorders.

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Atypical Presentation of Intimomedial Mucoid Degeneration: Ascending Aortic Aneurysm and Dissection in a Young White Man Mimicking Multifocal Pneumonia

Solomon Ocran, DO; Mukul Sharda, BS; Charles Haynes, MD; Pinky Jha, MD, MPH

ABSTRACT

Introduction: Intimomedial mucoid degeneration (IMMD) is a rare noninflammatory arteriopathy classically affecting young Black African women with hypertension.

Case Presentation: A 34-year-old White man with chronic tobacco use presented with progressive dyspnea initially attributed to multifocal pneumonia and pulmonary edema. Computed tomography revealed bilateral pulmonary infiltrates and a 6.2-cm ascending aortic aneurysm with a pericardial effusion. Echocardiography demonstrated severe aortic regurgitation. During hospitalization, he developed chest pain and asymmetric pulses; computed tomography angiography confirmed an acute arch dissection. Emergent valve-sparing aortic root replacement, total arch repair, and descending thoracic stent graft placement were performed. Histopathologic examination confirmed IMMD.

Discussion: This case expands the demographic profile of IMMD and illustrates its potential to mimic pulmonary infection, delaying recognition of underlying cardiovascular disease. The recent COVID-19 infection in this patient raises the theoretical possibility that viral-induced endothelial injury contributed to aortic wall degeneration, although this association remains speculative and warrants further investigation.

Conclusions: Clinicians should consider structural cardiovascular disease in patients with unexplained dyspnea or presumed pneumonia unresponsive to antibiotic therapy, particularly when cardiac murmurs are present or imaging reveals mediastinal abnormalities. Early recognition, prompt surgical intervention, and histopathologic confirmation are essential for favorable outcomes in patients with IMMD.

INTRODUCTION

Intimomedial mucoid degeneration (IMMD) is a rare, noninflammatory degenerative arteriopathy characterized by pathological accumulation of mucopolysaccharides within the intima and media, resulting in fragmentation of elastic fibers and weakening of the aortic wall.[1,2] IMMD is classically described in young to middle-aged Black African women with hypertension and most often involves the aorta and its major branches, predisposing affected patients to aneurysm formation, dissection, and valvular dysfunction.[1,3,4] Extra-aortic involvement, including the coronary, brachial, renal, and peripheral arteries, has been reported but remains uncommon.[2,5]

Diagnosis is most often established histologically, either at autopsy or from surgical specimens, and reveals mucin pools in the intima and media, elastic fiber disruption, and smooth muscle cell loss.[2,6] Preoperative imaging, such as transthoracic echocardiography (TTE), computed tomography (CT), and computed tomography angiography (CTA), can detect aneurysms, dissections, and valvular regurgitation but cannot confirm IMMD without tissue analysis.[4]

We describe an atypical case of an ascending aortic aneurysm with dissection and severe aortic regurgitation due to IMMD in a young White male who initially presented with presumed multifocal pneumonia and pulmonary edema shortly after COVID-19 infection. This case expands the demographic profile of IMMD and highlights its potential to mimic infectious pulmonary disease, leading to delayed recognition of underlying structural cardiovascular pathology.

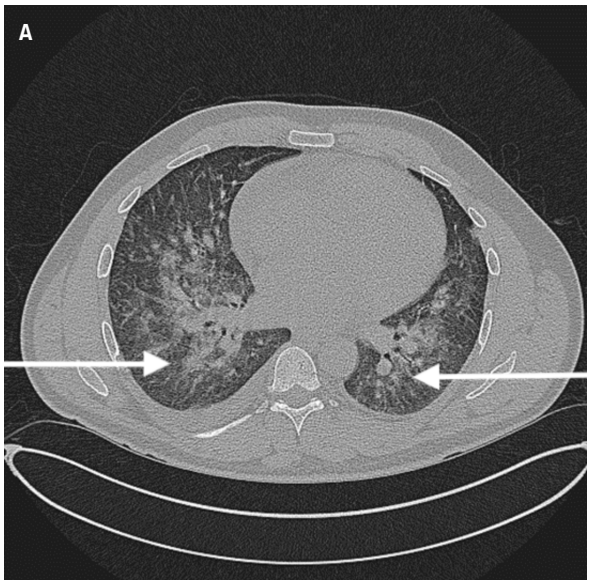
CASE PRESENTATION

A 34-year-old White man with a history of chronic tobacco use, attention-deficit/hyperactivity disorder, anxiety, and depression presented to our institution after transfer from an outside hospital with worsening shortness of breath initially attributed to multi-

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Figure 1. Computed Tomography of the Patient's Chest Demonstrating (A) Bilateral Pulmonary Infiltrates (arrows) Initially Interpreted as Multifocal Pneumonia and (B) Marked Dilation of the Ascending Aorta Consistent With Aneurysm (arrow)



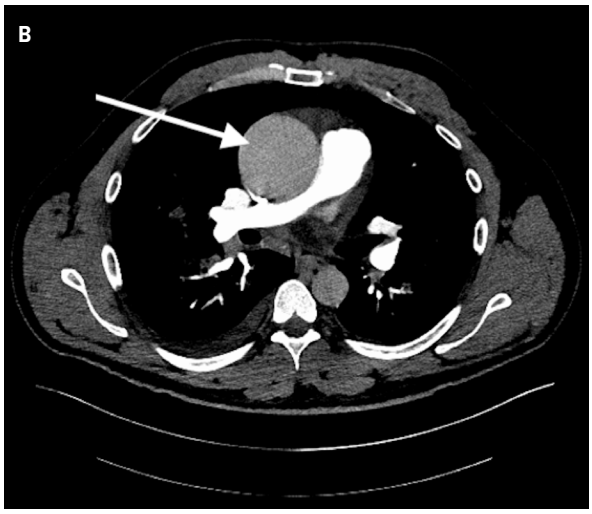
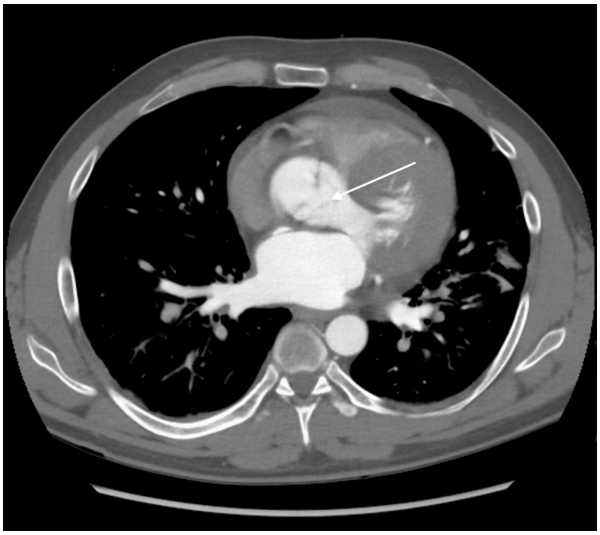


Figure 2. Computed Tomography Angiography Upon Admission Demonstrating an Intimal Flap Within the Aortic Arch Consistent With Acute Dissection (arrow)



focal pneumonia following a recent COVID-19 infection. Two weeks prior, he had been diagnosed with COVID-19 and subsequently developed suspected bacterial pneumonia, for which he was treated with doxycycline without symptom resolution.

At the outside facility, he reported pleuritic chest pain, orthopnea, cough, subjective fever and chills, and was hypoxemic. CT imaging revealed bilateral multifocal pneumonia and incidentally identified a 6.2-cm ascending aortic aneurysm with a small-to-moderate pericardial effusion (Figure 1). CT angiography ruled out pulmonary embolism. He was transferred to our tertiary center for further management and surgical evaluation.

Upon arrival, he was afebrile but required 4 L/min of supplemental oxygen via nasal cannula. Vital signs were notable for mild tachycardia (heart rate, 116 beats/min), oxygen saturation greater than 90%, and variable blood pressures. Physical examination revealed a loud diastolic murmur and bibasilar rhonchi; no signs of volume overload or Marfanoid features were noted. An extensive infectious workup, including testing for histoplasma, blastomycosis, syphilis, HIV, *Legionella*, *Streptococcus pneumoniae*, methicillin-resistant *Staphylococcus aureus* (MRSA), and respiratory viruses, was unrevealing. Empiric antibiotic therapy was narrowed to ceftriaxone on the recommendation of the infectious disease service.

Transthoracic echocardiogram revealed a left ventricular ejection fraction of 59%, a severely dilated ascending aorta, and severe aortic regurgitation. The N-terminal pro-B-type natriuretic peptide was markedly elevated at 8662 pg/mL, raising concern for acute decompensated heart failure. Given the bilateral infiltrates and elevated natriuretic peptide level, both pneumonia and pulmonary edema secondary to severe aortic regurgitation were considered. Empiric management for both conditions was initiated while awaiting further cardiac evaluation. Cardiology assumed primary management with plans for further cardiac evaluation, including left heart catheterization and cardiac magnetic resonance imaging.

On hospital day 6, the patient developed acute chest pain and asymmetric upper-limb pulses, with a diminished right radial pulse and a significant blood pressure differential between arms. Emergent CTA revealed a new dissection flap in the aortic arch (Figure 2), and he underwent emergent sternotomy with valve-sparing aortic root replacement (VSARR), total arch repair, and descending thoracic stent graft placement.

The postoperative course was notable for persistent pulmonary infiltrates and left lower lobe collapse, attributed to postopera-

tive atelectasis and residual inflammation, which improved with bilevel positive airway pressure support. He was gradually weaned to room air and discharged home in stable condition on postoperative day 12 with close follow-up arranged through adult congenital cardiology. Surgical pathology revealed focal myxoid (mucoid) degeneration within the intimo-medial layer of the aortic wall, consistent with IMMD.

DISCUSSION

IMMD is an uncommon cause of aortic aneurysm and dissection, with fewer than 100 cases described in the literature.[1,2] Its hallmark histopathologic feature is the accumulation of acid mucopolysaccharides within both the intima and media, accompanied by disruption of elastic lamellae and loss of smooth muscle cells.[2,6] This differs from cystic medial necrosis, which is confined to the media, and from cystic adventitial disease, which involves only the adventitia.[6]

While epidemiologic data suggest a predilection for young Black African women with hypertension,[1,3] cases have been reported in men, White individuals, and patients without hypertension.[4,5] The present case illustrates this atypical demographic profile. Clinically, IMMD can present with acute aortic syndromes, including aneurysm, dissection, and rupture, or with complications from valvular involvement, most commonly aortic regurgitation.[1,7] Our patient's presentation was unusual because his symptoms were initially attributed to multifocal pneumonia, likely reflecting pulmonary congestion from severe aortic regurgitation in the setting of a rapidly enlarging aneurysm rather than infection alone.

The temporal proximity between COVID-19 infection and presentation raises the theoretical possibility that SARS-CoV-2–induced endothelial dysfunction contributed to aortic wall weakening. COVID-19 is known to induce endothelial inflammation, cytokine release, and degradation of collagen and elastin fibers. Although IMMD is classically considered a noninflammatory process, viral endothelial stress could accelerate mucopolysaccharide accumulation or elastic fiber fragmentation in predisposed individuals. To our knowledge, no prior cases have linked IMMD directly to COVID-19 infection; however, this possibility warrants further investigation as delayed vascular complications of viral infections continue to be recognized.[8,9]

Diagnosis relies on correlation between imaging and histopathology. In our case, CT and CTA identified the ascending aortic aneurysm and subsequent dissection, while TTE confirmed severe aortic regurgitation. However, definitive diagnosis was made only after surgical excision and histopathologic examination, which demonstrated focal myxoid degeneration within the intimomedial layer.

Surgical management is the treatment of choice for symptomatic or complicated IMMD, given the high risk of rupture, dissection, and progression.[1,2] Surgical techniques depend on the location and extent of involvement and may include valve-sparing aortic root replacement, total arch repair, and adjunctive endovascular stenting.[3,5] Our patient underwent emergent valve-sparing aortic root replacement, arch repair, and descending thoracic stent grafting, with a favorable postoperative recovery.

An important perioperative consideration in IMMD is a tendency toward bleeding, reported in up to 14% of surgical cases and often attributed to primary fibrinolysis associated with the aneurysm wall.[1,5] Although our patient did not experience this complication, awareness of this potential risk and careful hemostatic management are warranted.

CONCLUSIONS

This case demonstrates that IMMD can occur in populations outside the classically described demographic and may present with symptoms that mimic respiratory infection. Clinicians should consider underlying structural cardiovascular disease in patients with unexplained dyspnea or presumed pneumonia that is unresponsive to antibiotics, particularly when cardiac murmurs are present or thoracic imaging reveals mediastinal abnormalities. Although causality cannot be established, recent viral infections such as COVID-19 may contribute to vascular injury in susceptible individuals. Early recognition, prompt surgical intervention, and histopathologic confirmation are essential for optimizing outcomes in patients with IMMD.

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A Rare Form of Hepatocellular Carcinoma in a Patient With Crohn's Disease

Mounica Konjeti, MD; Jessica Musto, MD

ABSTRACT

Introduction: Fibrolamellar carcinoma (FLC) is a rare variant of hepatocellular carcinoma (HCC) that affects people without underlying cirrhosis. The association between HCC and inflammatory bowel disease has been reported in patients with ulcerative colitis.

Case Presentation: A 23-year-old woman with newly diagnosed Crohn disease was incidentally found to have a large hepatic mass during evaluation of gastrointestinal symptoms. Imaging findings were concerning for HCC. Pathology after surgical resection revealed fibrolamellar variant of HCC. The patient developed recurrent FLC and underwent a portal lymphadenectomy and resection of a portal mass. She was started on lenvatinib and has remained in remission.

Discussion: Reports of HCC in patients with IBD are limited, and previously reported cases of FLC have occurred exclusively in patients with ulcerative colitis. We describe a case of FLC in a patient newly diagnosed with Crohn's disease. Although curative resection is possible, 50% to 100% of patients experience relapse and recurrence.

Conclusions: This case highlights the characteristic clinical, radiographic, histopathologic, and molecular features of FLC and expands the limited literature on the association between FLC and IBD.

INTRODUCTION

Fibrolamellar carcinoma (FLC) is a rare variant of hepatocellular carcinoma (HCC) that typically affects adolescents and young adults without underlying cirrhosis or primary liver disease. In the United States, FLC accounts for less than 1% of primary hepatic tumors. FLC's etiology and pathogenesis are poorly understood. Although FLC most often occurs in younger individuals, a bimodal age distribution has been reported, with peaks at 10 to 30 years and 70 to 79 years.[1] FLC affects males and females equally.

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The clinical presentation of FLC is highly variable and may include nausea, abdominal pain or discomfort, abdominal fullness, weight loss, night sweats, and jaundice. A review of 95 cases of FLC found that 60% of patients had extrahepatic metastases at diagnosis, with regional lymph node involvement being the most common site, followed by the lungs and peritoneum.[2]

Diagnosis of FLC is typically supported by clinical presentation, imaging findings, and normal serum alpha-fetoprotein (AFP) levels. The diagnostic gold standard is characteristic histopathology with confirmation of characteristic gene mutation. Computed tomography (CT) and magnetic resonance imaging (MRI) typically demonstrate a large, heterogeneous, well-defined lesion with lobulated contours, a central scar, calcifications, and areas of necrosis.[3] FLC tumors demonstrate a characteristic DNAJB1-PRKACA fusion; however, this alteration is not specific to FLC and has been identified in other malignancies.[4] Histopathologic findings include large, well-differentiated, polygonal tumor cells with eosinophilic cytoplasm and large central nuclei surrounded by fibrous bands arranged in a lamellar pattern.[5] Immunohistochemical staining is typically positive for CK7, epithelial membrane antigen, CK19 and EpCAM.[3,6] FLC also displays stem cell markers CD133 and CD44.[7]

The most effective treatment for FLC is complete surgical resection with regional lymphadenectomy, which remains the primary curative therapy.[8-11] Liver transplantation may be considered for selected patients with unresectable liver-confined disease.[8,10,11] Locoregional therapies, including radiofrequency ablation, hepatic artery chemoembolization, and external beam

radiotherapy, may provide local disease control or palliation in select patients.[12] Systemic therapy and immunotherapy have been used for advanced, unresectable, recurrent, or metastatic disease, although no standard systemic treatment regimen has been established.[8,13]

The association between HCC, particularly FLC, and inflammatory bowel disease (IBD) has not been clearly established. To our knowledge, only 4 cases of FLC have been reported in patients with IBD—all occurring in patients with ulcerative colitis.[14] Given the rarity of FLC and the limited literature regarding its association with IBD, we present the case of a 23-year-old patient with newly diagnosed Crohn's disease who was found to have FLC.

CASE PRESENTATION

A 23-year-old woman with no significant past medical history presented to urgent care with a 6-week history of intermittent bloody diarrhea, fever, polyarthralgia, night sweats, erythema nodosum, oropharyngeal aphthous ulcers, and fatigue.

Initial laboratory values revealed a negative gastrointestinal pathogen panel and negative Clostridioides difficile testing, a white blood cell count of 12.5 K/μL, platelet count of 407 K/μL, erythrocyte sedimentation rate of 48 mm/hour, C-reactive protein level of 14.8 mg/dL, fecal calprotectin level of 309 μg/g, albumin level of 2.6 g/dL, aspartate aminotransferase level of 19 U/L, alanine aminotransferase level of 17 U/L, alkaline phosphatase level of 94 U/L, and total bilirubin level of 0.4 mg/dL.

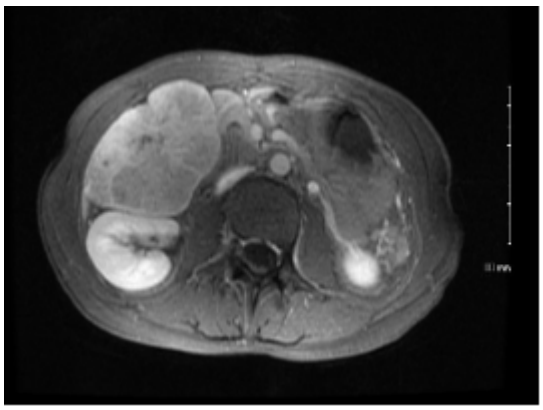
Computed tomography of the abdomen and pelvis demonstrated diffuse sigmoid colonic wall thickening with associated pericolonic fat stranding and incidentally identified a large hepatic lesion. Flexible sigmoidoscopy revealed erythematous mucosal ulcers, and biopsy findings were consistent with Crohn's disease. The patient was started on a prednisone taper and mesalamine.

MRI of the abdomen performed for further evaluation of the hepatic mass (Figure 1) revealed a large lobulated 9-cm hepatic mass arising from segments 4 and 5 with a calcific focus; enhancement characteristics were concerning for HCC.

Additional laboratory testing demonstrated an AFP level of < 2.0 ng/mL and carbohydrate antigen 19-9 (CA 19-9) level of < 2.0 U/mL. Serologic testing for hepatitis A, B, and C and HIV was negative. The tumor was classified as stage IIIB (pT4).

Following diagnosis, the patient underwent resection of segments 4 and 5 with en bloc cholecystectomy, achieving negative surgical margins. Figure 2A shows a well-demarcated multinodular mass with a central scar. Final histopathology confirmed FLC with focal visceral peritoneal involvement and small-vessel vascular invasion. Histologic examination demonstrated large polygonal neoplastic cells with eosinophilic granular cytoplasm and round nuclei with prominent nucleoli arranged in trabeculae separated by bundles of lamellar collagen (Figure 2B and 2C). Tumor cells also showed positive staining for cytokeratin 7 (CK7) and CD68. Additional trichrome staining highlighted abundant lamellar fibrosis. Next-generation sequencing demonstrated the characteristic DNAJB1-PRKACA mutation.

Figure 1. Lobulated Exophytic 9-cm Hepatic Mass Extending Inferiorly Off Segments 4 and 5



Enhancement characteristics concerning for hepatocellular carcinoma.

On surveillance imaging 1 year later, recurrent FLC in the porta hepatis was confirmed by biopsy. At that time, the patient reported night sweats but no other symptoms. She subsequently underwent staging laparotomy, portal lymphadenectomy, and resection of the portal mass. Months later, surveillance CT demonstrated an enlarging portocaval lymph node concerning for recurrent disease. Positron emission tomography-computed tomography revealed a left lower lobe pulmonary nodule suspicious for metastasis but showed no evidence of local abdominal recurrence, including no uptake within the portocaval lymph node. The patients subsequently underwent right portal lymph node dissection, and pathology was negative for malignancy.

The decision was made to initiate lenvatinib, a tyrosine kinase inhibitor, to reduce the risk of further recurrence. Subsequent imaging demonstrated spontaneous resolution of the pulmonary nodule. After completing 1 year of lenvatinib therapy, serial imaging of the chest, abdomen, and pelvis obtained every 3 months showed no evidence of residual or recurrent disease. As a result, lenvatinib was discontinued, and the patient has remained in remission.

DISCUSSION

FLC is a rare primary hepatocellular carcinoma variant, accounting for about 1% to 9% of all hepatocellular carcinomas, according to the Surveillance, Epidemiology, and End Results (SEER) Program database, and most commonly arises in noncirrhotic livers.[15,16] FLC tumors present with unique radiologic and histopathologic findings. While there is no specific data or recommendations regarding posttreatment surveillance, most clinicians

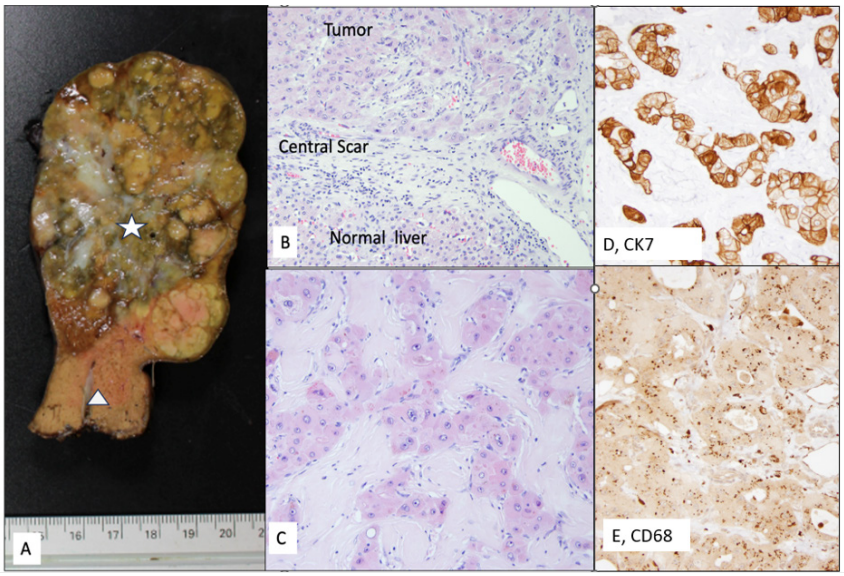
perform surveillance imaging at 3-month or 6-month intervals for the first few years after resection.[17]

Surgical resection with regional lymphadenectomy remains the cornerstone of curative therapy for FLC.[8-11] Reported 5-year survival rates after complete resection approach 70% to 76%; however, recurrence remains common, occurring in 50% to 100% of patients in published series.[17-21] Our patient's disease course reflects this pattern, with biopsy-confirmed recurrence in the porta hepatis 1 year after initial resection despite negative surgical margins. For patients with unresectable liver-confined disease, liver transplantation may be considered in carefully selected cases, although long-term outcomes are generally less favorable than those reported following complete resection.[8,10,11]

Management of recurrent, unresectable, or metastatic FLC remains challenging because no standard systemic therapy has been established.[8,13] Locoregional therapies, including radiofrequency ablation, transarterial chemoembolization, and radiotherapy, may provide local disease control or palliation in selected patients.[12] Systemic therapies, including cytotoxic chemotherapy, targeted therapies, and immune checkpoint inhibitors, have been used with variable success.[13,22,23] In the present case, lenvatinib was initiated following recurrence and concern for metastatic disease. Although the contribution of lenvatinib to the patient's favorable outcome cannot be determined, she has remained disease-free following treatment, highlighting the individualized nature of therapeutic decision-making in FLC.

There are limited reports of hepatocellular carcinoma in patients with inflammatory bowel disease, and all previously reported cases of FLC have occurred in patients with ulcerative colitis. Herein, we describe a case of FLC in a patient with newly diagnosed Crohn disease. The diagnosis was supported by characteristic clinical, radiographic, histopathologic, immunohistochemical, and molecular findings. The patient was a young adult without underlying liver disease who was incidentally found to have a large, well-demarcated hepatic mass with a calcified central scar and a normal AFP level. Histopathologic examination demonstrated large polygonal neoplastic cells arranged in trabeculae separated by lamellar fibrous stroma, with positive CK7 and CD68 staining. Molecular analysis identified the characteristic DNAJB1-PRKACA fusion. Collectively, these findings are highly characteristic of FLC and help distinguish it from conventional HCC.[3-7]

Figure 2.



A. Resection specimen of segments 4 and 5, a well-demarcated variegated multinodular mass with a central scar (white star), normal tan liver in the lower portion (white triangle).

B. Interface of tumor with normal liver at central scar. Note small size of hepatocytes compared to large tumor cells.

C. Large polygonal cells with abundant bright pink granular cytoplasm and round nuclei with prominent nucleoli, arranged in trabeculae, characteristically interspersed with bundles of lamellar collagen, pathognomonic of fibrolamellar carcinoma.

D and E. Tumor cells show characteristic positive staining with cytokeratin 7 (CK7) and CD68, in addition to hepatocellular markers, HSA and arginase. On molecular analysis, via next generation sequencing, tumor cells displayed characteristic DNAJB1-PRKACA mutation.

CONCLUSIONS

Fibrolamellar carcinoma is a rare primary hepatic malignancy that typically occurs in young adults without underlying liver disease and may be discovered incidentally during evaluation of unrelated gastrointestinal symptoms. This case highlights the importance of recognizing the characteristic clinical, radiographic, histopathologic, and molecular features of FLC to facilitate timely diagnosis and treatment. To our knowledge, this represents the first reported case of FLC in a patient with Crohn disease, expanding the limited literature describing a possible association between FLC and inflammatory bowel disease. Continued reporting of similar cases may help clarify whether this association is coincidental or reflects a shared pathogenic mechanism.

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Dose-Dependent Proteinuria and Renal Dysfunction With High-Intensity Rosuvastatin: Case Report and Literature Review

Tyler Gorman, PA; James Alstott, MD

ABSTRACT

Introduction: Rosuvastatin is a widely prescribed, high-potency statin for cardiovascular risk reduction. Rare cases of nephrotoxicity have been reported, particularly in patients with reduced kidney function.

Case Presentation: We present a case of a 57-year-old Black man who developed proteinuria and declining renal function following initiation of high-dose rosuvastatin (40 mg daily) after an acute coronary event. After other causes were excluded, the rosuvastatin was gradually reduced to 10 mg, resulting in improvement of renal function and resolution of proteinuria.

Discussion: Prior reports have linked rosuvastatin to acute interstitial nephritis and tubular injury, with recovery following drug discontinuation. This case is notable because the patient's baseline creatinine level was normal prior to rosuvastatin initiation, and recovery occurred with dose reduction rather than complete drug cessation.

Conclusions: Clinicians should consider rosuvastatin-associated nephrotoxicity in patients with unexplained renal dysfunction or proteinuria. Early recognition and dose reduction or drug discontinuation may prevent long-term renal sequelae while maintaining adequate lipid control.

INTRODUCTION

Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, a key enzyme for hepatic cholesterol synthesis. These lipid-lowering medications are widely prescribed for the management dyslipidemia and for the primary and secondary prevention of cardiovascular events. Statin-induced myopathy and hepatotoxicity are well-recongized side effects; however, statin-associated renal toxicity may be less widely recognized. Two large observational studies found an association between statin use and a significantly increased risk of acute kidney injury, with greater risk observed at higher-potency doses across all statins.[1,2] While a 2013 meta-analysis of 23 trials involving 29 147 participants found that rosuvastatin was not associated with worsening renal function or proteinuria, cases of rosuvastatin-associated nephrotoxicity with rosuvastatin without rhabdomyolysis have been described since its approval by the US Food and Drug Administration.[3-5] Additionally, a 2022 observational study reported that, compared with atorvastatin, rosuvastatin was associated with an increased risk of hematuria, proteinuria, and kidney failure. The risk was greater risk at higher rosuvastatin doses and among patients with lower kidney function (estimated glomerular filtration rate [eGFR] < 30 ml/min/1.73 m2).[6]

We present a case of reversible kidney dysfunction and subnephrotic-range proteinuria in a patient receiving high-dose rosuvastatin that resolved after dose adjustment. This case highlights the importance of timely recognition of this form of renal toxicity and provides an opportunity to compare our findings with the few reported cases of rosuvastatin-related proteinuria without rhabdomyolysis in the literature.

CASE PRESENTATION

A 56-year-old Black man with a history of hypertension, hyperlipidemia, and coronary artery disease was found to have worsening renal function and proteinuria. His cardiovascular history was significant for ST-segment elevation myocardial infarction (STEMI) 1.5 years earlier. The STEMI was complicated by cardiac arrest

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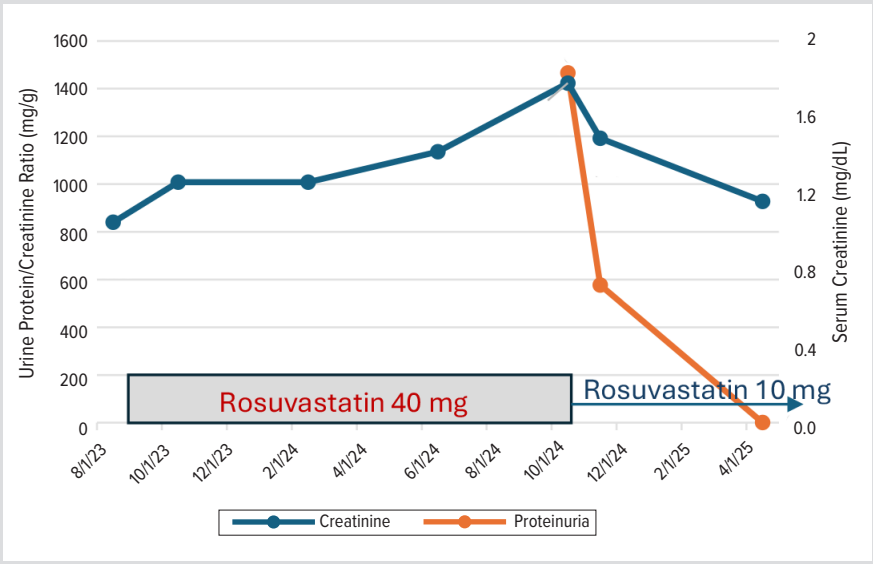
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due to ventricular fibrillation. After resuscitation, he underwent percutaneous coronary intervention, and 6 drug-eluting stents (DES) were placed. He subsequently made a full recovery.

During the index cardiac hospitalization, a lipid panel revealed a total cholesterol level of 209 mg/dL and elevated low-density lipoprotein (LDL) cholesterol level of 139 mg/dL. He was started on rosuvastatin 40 mg daily for secondary prevention in addition to guideline-directed medical therapy. Renal function at that time was normal, with a serum creatinine of 1.0 mg/dL (eGFR 89 ml/min/1.73 m^2, calculated using the 2021 CKD-EPI creatinine equation without a race coefficient). He did have reduced left ventricular systolic function (ejection fraction 40%), and sacubitril-valsartan was initiated, with a subsequent increase in serum creatinine to 1.2 to 1.5 mg/dl.

Figure. Patient's Trend in Kidney Function and Proteinuria Over Time With Rosuvastatin Dosing



Six months after his initial cardiac hospitalization, he presented to the emergency department with chest pain and was found to have a non-STEMI, which required balloon angioplasty, and 1 additional DES was placed.

Six months later, during a routine cardiology follow-up visit, his creatinine level had increased to 1.78 mg/dL (eGFR 44 ml/min/1.73 m^2). He denied recurrent chest pain but reported persistent shoulder and muscle pain. He did not report gross hematuria, flank pain, or dysuria. He denied use of nonsteroidal anti-inflammatory drugs. He was a lifelong nonsmoker and did not drink alcohol or use illicit drugs. Medications included low-dose aspirin, famotidine, metoprolol succinate, sacubitril-valsartan, ticagrelor, rosuvastatin, and as-needed sublingual nitroglycerin.

On examination he was afebrile, his pulse was 52 beats/min, and his blood pressure was 119/69 mm Hg. He was not acutely ill-appearing and was clinically euvolemic. Laboratory testing showed a normal complete blood cell count. Urinalysis showed a specific gravity of 1.010, pH 6.5, trace protein, +1 blood, and negative leukocyte esterase and nitrites. Automated microscopic examination of the urine showed no white blood cells, red blood cells, bacteria, or squamous epithelial cells. Creatine kinase (CK) was mildly elevated at 216 U/L (reference range 50-170 U/L). The urine protein-creatinine ratio was markedly elevated at 1467 mg/g (reference range, < 150 mg/g). A 24-hour total urine collection revealed an elevated total protein excretion of 990 mg. Urine protein electrophoresis was positive for albumin and various globulin fractions, but no monoclonal protein was identified. Renal ultrasound showed no abnormalities of the kidneys, ureters, or bladder.

Given his symptoms and laboratory abnormalities, sacubitril-valsartan was discontinued, and the rosuvastatin was reduced to 30 mg daily. Repeat testing showed an improvement in creatinine to 1.49 mg/dL, but CK remained elevated at 260 U/L. Rosuvastatin was further reduced to 10 mg daily, which resulted in normalization of the serum CK level. Six months after the initial laboratory abnormalities, while remaining on rosuvastatin 10 mg daily, the patient's renal function had significantly improved, with a serum creatinine level of 1.16 mg/dL (eGFR 72 ml/min/1.73 m^2). Urinalysis was negative for blood and protein, and urine protein-creatinine ratio was undetectable because of the absence of urinary protein. A fasting lipid profile showed a total cholesterol level of 131 mg/dL, triglyceride 56 mg/dL, high-density lipoprotein cholesterol 86 mg/dL, and LDL cholesterol 34 mg/dL.

DISCUSSION

Rosuvastatin at high-intensity doses (20-40 mg daily) has the potential to cause nephrotoxicity, as was demonstrated in our patient, who developed marked proteinuria and a concurrent decline in renal function, both of which improved after rosuvastatin dose reduction without evidence of new chronic kidney disease. Our case is consistent with previously published reports of rosuvastatin-associated nephrotoxicity (Table). Previous cases involved older adults receiving rosuvastatin doses of 20 mg daily or greater who developed subnephrotic-range proteinuria without rhabdomyolysis or alternative etiologies of renal disease. Our patient developed musculoskeletal symptoms and mild elevation in serum CK. Among previously reported cases, 2 patients (66%) had either myalgias or elevated muscle enzyme levels, and 1 patient had no clinical or laboratory evidence of muscle injury. Drug cessation led to resolution of proteinuria and recovery of renal function in all cases. Subsequent lipid-lowering therapy was achieved with an alternative statin in all previously reported

Table. Case Reports of Nephrotoxicity Related to Rosuvastatin Without Rhabdomyolysis

Report	Age (years)/ Sex	Dose (mg)	Duration of Statin Therapy Before Renal Injury (months)	Peak Serum Creatinine	Proteinuria (g/g)	Musculoskeletal Symptoms or Muscle Enzyme Elevation	Additional Finding	Outcomes With Dose Reduction or Rosuvastatin Discontinuation
van Zyl-Smit et al, 2004[4]	58/M	80	19	1.58 mg/dL	UPC 1.6	None	Urine microscopy: granular casts Kidney biopsy: acute and chronic TIN EM-increased size of many mitochondria of the proximal tubules	Resolution of proteinuria, no CKD
Ward et al, 2017[5]	53/F	40	15	1.86 mg/dL	UPC 1.8	CK 301 (ref range <195 U/L)	Urine microscopy: granular casts, isomorphic RBCs Kidney biopsy: proximal tubular toxicity, interstitial edema	Resolution of proteinuria, no CKD
Goyal et al, 2025[13]	70/F	20	3	0.70 mg/dL	UAC 0.3	+Myalgias	NR	Resolution of proteinuria

Abbreviations: CKD, chronic kidney disease; EM, electron microscopy; NR, not reported; TIN, tubulointerstitial nephritis; UAC, urine albumin/creatinine ratio; UPC, urine protein/creatinine ratio.

patients. However, our patient was able to continue rosuvastatin at a moderate-intensity dose of 10 mg daily, which maintained his LDL cholesterol level at < 70 mg/dL, a recommended target following acute coronary syndrome.[7]

The renal injury associated with rosuvastatin appears predominantly tubular in nature. Urine microscopy in 2 reported cases revealed granular casts, and renal biopsy findings have demonstrated tubular damage characterized by luminal ectasia, loss of brush border, variegated cytoplasmic staining, and shedding of renal tubular cells into the tubular lumen.[4,5] It has been hypothesized that inhibition of HMG-CoA reductase by rosuvastatin interferes with receptor-mediated endocytosis in proximal tubular cells, leading to proteinuria.[8] Mitochondrial toxicity related to oxidative stress has also been implicated, based on the finding of enlarged mitochondria in renal tubular cells on electron microscopy.[4]

This case highlights the differential diagnosis clinicians should consider in patients with proteinuria or renal dysfunction while receiving rosuvastatin. Rhabdomyolysis is an uncommon cause of statin-related renal toxicity that can be severe enough to require kidney replacement therapy. Myoglobin is a low-molecular-weight protein that is freely filtered by the glomerulus and is normally present urine only in very low concentrations. Elevated serum myoglobin levels during rhabdomyolysis result in increased filtration of myoglobin into the urinary space, causing direct tubular injury. The macroscopic appearance of the urine in rhabdomyolysis is characteristically reddish-brown to dark brown and is often described as tea- or cola-colored. Because myoglobin cross-reacts with the peroxidase on urine dipstick testing, urinalysis in patients with rhabdomyolysis is typically positive for hemoglobin despite a negative microscopic examination for visible red blood cells (RBCs).[9] Our patient's urinalysis demonstrated this characteristic discrepancy; however, rhabdomyolysis was not the cause of his kidney dysfunction because CK levels in rhabdomyolysis are typically more than 5 times the upper limit of normal, with levels > 5000 U/L are associated with an increased risk of acute kidney injury.[10]

Drug-induced acute interstitial nephritis (AIN) should also be considered as a possible intrinsic cause of kidney injury when renal function worsens. Statins are generally not regarded as a high-risk medication class for AIN. In the case described by van Zyl-Smit et al, kidney biopsy demonstrated evidence of acute and chronic interstitial nephritis.[4] Additionally, 1 case of biopsy-confirmed AIN attributed to rosuvastatin has been reported. The patient was an 83-year-old man with chronic kidney disease who developed significant worsening of renal function and proteinuria (500 mg/day) after 3 weeks of exposure to rosuvastatin. Following kidney biopsy diagnosis, drug discontinuation, and a 4-week tapering course of prednisolone, renal function returned to baseline.[11] A high index of suspicion is necessary when renal dysfunction occurs in the context of new drug exposures. Prompt withdrawal of the offending medication may improve renal function. In more severe cases or in patients with persistent renal dysfunction despite drug cessation, glucocorticoid therapy may attenuate renal damage.

As in our patient, who was also receiving guideline-directed medical therapy (GDMT) for ischemic heart disease and heart failure with reduced ejection fraction, clinicians must consider the impact of medications other than statins on renal function. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor-neprilysin inhibitors (ARNIs), sodium-glucose cotransporter-2 inhibitors, and mineralocorticoid receptor antagonists all have hemodynamic effects at the glomerular level. An acute decline in eGFR up to 50% with multidrug therapy may be tolerable in the absence of hyperkalemia or symptomatic hypotension because cardiorenal outcomes are improved with GDMT.[12] Our patient's creatinine level increased from 1.0 mg/dL to 1.2 to 1.5 mg/dL after initiation of an ARNI following

acute coronary syndrome. The ARNI was discontinued because of worsening renal function after recovery of left ventricular function. This resulted in partial improvement in GFR, as would be expected following withdrawal of an angiotensin receptor blocker; however, further improvement in renal function and resolution of proteinuria did not occur until the rosuvastatin dose was further reduced.

Our case adds to the growing literature on rosuvastatin-associated nephrotoxicity. Clinicians should remain vigilant for this important adverse effect, which may manifest as proteinuria with variable accompanying findings, including mild muscle injury, hematuria, or declining renal function. Patients receiving high-potency doses (≥ 20 mg daily) and those with preexisting chronic kidney disease (eGFR < 30 mL/min per 1.73 m^2) appear to be particularly vulnerable. Accordingly, rosuvastatin should be reduced to 5 to 10 mg daily in patients with eGFR < 30 mL/min per 1.73 m^2 to avoid nephrotoxicity. In suspected cases, clinicians should promptly obtain assessment of renal function, muscle enzyme levels, urinalysis, and quantification of proteinuria. Renal biopsy and additional serologic testing may be warranted in selected cases. However, rosuvastatin-associated proteinuria and renal injury appear to resolve with rosuvastatin cessation or dose reduction. Long-term renal outcomes following cases of rosuvastatin-associated renal injury are currently unknown. For patients who previously experienced rosuvastatin nephrotoxicity, ongoing lipid management with reduced-dose rosuvastatin or a less potent statins may be indicated to achieve lipid goals while reducing future cardiovascular risk.

CONCLUSIONS

This case highlights the importance of considering rosuvastatin-associated nephrotoxicity in patients with unexplained renal dysfunction or proteinuria. Early recognition combined with timely dose adjustment or discontinuation of rosuvastatin may facilitate renal recovery and reduce the risk of long-term kidney damage while maintaining satisfactory lipid control.

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Three's (Autoimmune) Company: A Co-occurrence of Thrombotic Thrombocytopenic Purpura, Warm Autoimmune Hemolytic Anemia, and Sjögren's Syndrome

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ABSTRACT

Introduction: This case highlights the successful management of atypical, refractory thrombotic thrombocytopenic purpura (TTP), including co-occurring autoimmune conditions, treatment-related adverse effects, and disease sequelae.

Case Presentation: A Hispanic woman in her early 50s presented to the emergency department of an academic, tertiary medical center after a syncopal episode. She reported flu-like symptoms during the preceeding 2 days. Physical examination was remarkable only for scattered ecchymoses on the upper extremities and petechiae of the lower extremities. Despite her clinical stability, she was ultimately found to have refractory TTP, warm autoimmune hemolytic anemia (wAIHA), and Sjögren's syndrome.

Discussion: No reports have described the co-occurrence of TTP, wAIHA, and Sjögren's syndrome. Isolated case reports have described co-occurring TTP and Sjögren's syndrome, as well as co-occurring or sequential TTP and wAIHA, with or without lupus.

Conclusions: We report what is, to our knowledge, one of the first cases of co-occurring TTP, wAIHA, and Sjögren syndrome. This case underscores the importance of multidisciplinary care in the management of refractory TTP and its associated complications.

INTRODUCTION

First described by Moschcowitz in 1924, thrombotic thrombocytopenic purpura (TTP) is a hematologic emergency characterized by severe thrombocytopenia, microangiopathic hemolytic anemia (MAHA), end-organ ischemia, and neurologic abnormalities.[1,2] The annual incidence of TTP is unknown but is estimated at 1 to 13 cases per million people globally, varying by location.[3] TTP is caused either by inherited Upshaw-Schulman syndrome or acquired ADAMTS-13 dysfunction. TTP is typically acquired, occurring secondary to the formation of immunoglobulin (Ig) G, IgA, or IgM autoantibodies (inhibitors) against ADAMTS-13, which block its proteolytic activity or increase its clearance from plasma.1 ADAMTS-13 normally cleaves von Willebrand factor (vWF) multimers into smaller, less prothrombotic fragments. When ADAMTS-13 is impaired, the enzyme is unable to properly cleave vWF, and the aberrant vWF multimers bind platelets avidly. This leads to accumulation of platelet-rich thrombi in the small vessels (thrombotic microangiopathy), causing MAHA and end-organ ischemia. Acquired TTP (aTTP) is twice as common in biological females and can be triggered by malignancy, infection, pregnancy, and drugs, such as nonsteroidal antiinflammatory drugs, estrogen-containing contraceptives, proteosome inhibitors, quetiapine, eptifibatide, and clopidogrel.[1,4]

The MAHA associated with TTP is due to shearing of red blood cells as they traverse thrombi-laden microvasculature, evidenced by schistocytes on peripheral blood smear. Unlike TTP, immune thrombocytopenic purpura (ITP) does not yield schistocytes. Hemolysis mediated by IgG autoantibodies (warm autoimmune hemolytic anemia [wAIHA]) yields spherocytes on blood smear due to the action of splenic macrophages on IgG-bound erythrocytes. An established association exists between wAIHA and ITP, a condition known as Evans syndrome.[5] In contrast, no established association exists between wAIHA and TTP, although case reports have described concurrent disease or sequential presentation, with and without lupus.[6-8]

Like TTP, wAIHA can be caused by cancers (eg, chronic lym-

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phocytic leukemia [CLL]), viral infections (eg, Epstein-Barr virus, hepatitis A, B, and C, and HIV), lupus, and drugs.[9]

Sjögren's syndrome results from immune-mediated destruction of the lacrimal and salivary glands, leading to chronic dry eyes and dry mouth (sicca symptoms) and potential involvement other organ systems.[10] Sjögren's syndrome often occurs alongside other autoimmune conditions. The diagnosis is clinical, and Sjögren's syndrome is highly likely when anti-Ro/SSA and/or anti-La/SSB autoantibodies are detected in a patient with sicca symptoms.

Despite the presence of one autoimmune condition increasing the risk of developing another, no case reports have described the co-occurrence of TTP, wAIHA, and Sjögren's syndrome.[11] While there is a rare but documented association between TTP and Sjögren's syndrome, we present what is, to our knowledge, one of the first reported cases of a patient with co-occurring TTP, wAIHA, and Sjögren's syndrome.[12]

CASE PRESENTATION

The patient is a woman in her early-50s with a past medical history of allergic rhinitis, undifferentiated anemia, vitamin B_{12} deficiency, cholecystitis secondary to cholelithiasis, eczema, and recurrent tonsillitis. Her only home medication was intranasal fluticasone daily. She also reported taking magnesium, turmeric, and ashwagandha supplements daily. Her surgical history was significant only for cesarean delivery, laparoscopic cholecystectomy, and childhood tonsillectomy. She denied recreational drug, tobacco, and alcohol use. Her family history was remarkable only for type 2 diabetes in her biological parents, unspecified colon cancer in one biological parent, and easy bruising beginning after menopause in her sister. She had no known allergies and no history of cancer or solid organ or hematopoietic stem cell transplantation.

Case History

The patient presented to our emergency department (ED) following a collapse witnessed by her husband. She reportedly awoke from sleep and lost consciousness; the first event she recalled was being assisted to the bathroom by her husband. He reported that she stumbled and became "glassy-eyed" and unresponsive for approximately 30 seconds. She reported feeling unwell for 2 days prior to presentation, with malaise, nausea, nonbloody, nonbilious vomiting, and myalgias. Several days before symptom onset, her child had an upper respiratory infection, and she consumed a meatless hamburger that "did not taste right." Review of systems was positive for a 2- to 3-year history of easy bruising and a 1-week history of "pink" urine, oozing epistaxis, and light vaginal bleeding but negative for recent gumline bleeding.

Physical Exam

In the ED, the patient's blood pressure was 129/75 mmHg, pulse 104 beats/minute, respiratory rate 18 breaths/minute, temperature 97.9 °F (36.6 °C), peripheral oxygen saturation 100% on room air, and body mass index 29.39 kg/m². She appeared well, and physical examination was remarkable only for fatigue, stripe-like bruising on the flexor surface of the left wrist, and circumferential bruising of the right bicep that she attributed to a blood pressure cuff. Physical examination was negative for oral petechiae, Grey Turner sign, focal neurologic deficits, and altered mental status.

Table 1. Abnormal Laboratory Results Obtained on Admission

Component	Value	Reference Range
Red blood cell count	3.09 m/uL	3.80–5.20 m/uL
Hemoglobin	9.5 gm/dL	11.5–15.5 gm/dL
Hematocrit	27.4%	34.0%–46.5%
Red cell distribution width	16.9%	11.0%–15.0%
Platelets	6 k/uL	150–400 k/uL
Sodium	135 mmol/L	136–144 mmol/L
Blood urea nitrogen	37 mg/dL	7–22 mg/dL
Blood glucose	160 mg/dL	70–100 mg/dL
Alanine aminotransferase	59 U/L	7–35 U/L
Aspartate aminotransferase	107 U/L	10–40 U/L
Total bilirubin	2.6 mg/dL	0.2–1.4 mg/dL
Direct bilirubin	0.6 mg/dL	0.0–0.3 mg/dL
Serum bicarbonate	22 mm/L	24–30 mm/L
D-dimer	5769 ng/mL FEU	< 500 ng/mL FEU
PLASMIC score[a]	7	0–4
HS-troponin (every 2.5 hours)	593 →709→780→680 ng/L	0–14 ng/L
HS-C-reactive protein	20.31 mg/L	< 1.0 mg/L[b]
Erythrocyte sedimentation rate	45 mm/hr	0–35 mm/hr
Uncorrected reticulocytes	3.3%	0.6%–1.8%
Corrected reticulocytes	2%	0.6%–1.8%
Haptoglobin	< 30 mg/dL	36–195 mg/dL
Lactate dehydrogenase	2122 U/L	108–212 U/L
Ferritin	1403 ng/mL	11–241 ng/mL
Iron	320 ug/dL	35–140 ug/dL
Iron saturation	95%	20%–50%
Vitamin B12	199 pg/mL[c]	180–914 pg/mL[c]
Direct antiglobulin (Coombs) test	(+) polyspecific Coombs antibody; (+) anti-IgG antibody; (+) warm antibody	(–)
ADAMTS-13 activity	< 3%	> 69%
ADAMTS-13 inhibitor	1.9 IU	< 0.5 IU
Antinuclear antibody	1:1280 (speckled pattern)	< 1:40
Complement C4	9 mg/dL	16–38 mg/dL
Anti-Ro/SSA	65 U/mL	< 7.0 U/mL

Abbreviations: anti-Ro/SSA, anti-Ro/Sjögren syndrome-related antigen A autoantibody; FEU, fibrinogen equivalent units; HS, high sensitivity.

[a] Platelet count, combined hemolysis variable, absence of active malignancy, absence of solid organ or stem cell transplant, mean corpuscular volume, international normalized ratio, and creatinine score.

[b] >10.0 reflects acute inflammatory process.

[c] <200 considered low by many institutions.

Laboratory Results

Abnormal results from the comprehensive metabolic panel, complete blood cell count (CBC), mixed venous blood gas, and ancillary testing are listed in the Table.[13] Prothrombin time, interna-

tional normalized ratio, and activated partial thromboplastin time were within normal limits, as were phosphorus, magnesium, and hemoglobin A1C (HbA1c).

Respiratory pathogen polymerase chain reaction (PCR) testing was negative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), influenza A/B, respiratory syncytial virus, adenovirus, coronavirus 229E/HKU1/NL63/OC43, human metapneumovirus, human rhinovirus/enterovirus, parainfluenza virus types 1 through 4, *Bordetella pertussis* and *Bordetella parapertussis, Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*.

Viral testing was negative for active cytomegalovirus and Epstein-Barr virus infection; HIV 1/2 antibodies and antigens; acute hepatitis A, B, and C; anti-hepatitis B core antibody; and coxsackie A antibodies. Nasal PRC testing was negative for methicillin-resistant *Staphylococcus aureus*.

Gastrointestinal pathogen PCR testing was negative for *Campylobacter*, toxigenic *Clostridioides difficile* A/B, *Pleisomonas shigelloides*, *Salmonella*, *Vibrio* spp., *Yersinia enterocolitica*, enteroaggregative *Escherichia coli* (E coli), enteropathogenic *E coli,* enterotoxigenic *E coli*, Shiga-toxin producing E coli, *Shigella*/invasive *E coli*, *Cryptosporidium*, *Cyclospora*, *Entamoeba histolytica*, *Giardia lamblia*, adenovirus F40/41, astrovirus, and norovirus GI/GII.

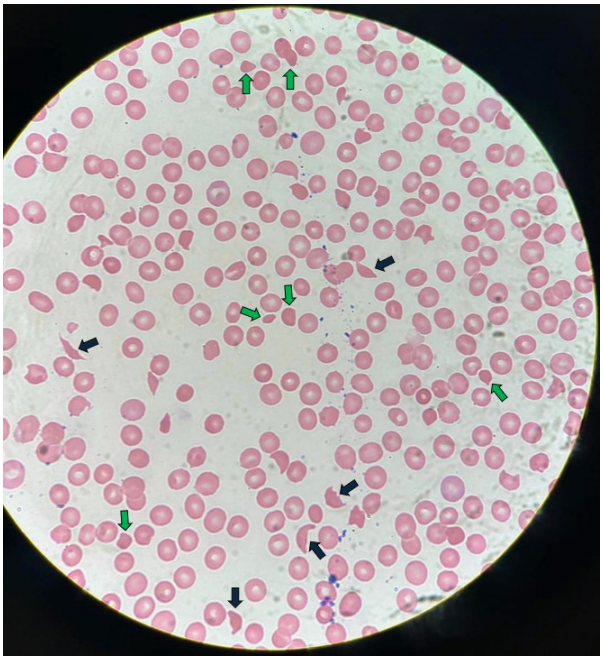
Complement C3 was within normal limits. Rheumatologic workup was negative for rheumatoid factor, lupus anticoagulant, cardiolipin, β2-glycoprotein 1, Smith, La/SSB, Scl-70, Jo-1, and double-stranded DNA autoantibodies. During rheumatology evaluation, the patient reported a 1-year history of dry eyes without other rheumatologic symptoms.

Admission electrocardiography (ECG) revealed sinus tachycardia (QT/QTcB, 318/414 ms) and low-voltage QRS complex. ECGs throughout admission continued to demonstrate a low-voltage QRS complex and occasional nonspecific T-wave abnormalities.

Chest radiography was negative for consolidation. Noncontrast computed tomography (CT) of the head was unremarkable. CT of the cervical spine without IV contrast was negative for fracture or subluxation. CT of the chest, abdomen, and pelvis with IV contrast was remarkable only for diverticulosis. There were no acute abnormalities or lymphadenopathy.

Peripheral blood smear revealed schistocytes, microspherocytes, and severe thrombocytopenia (Figure 1). Type and screen confirmed O-positive blood type and was negative for alloantibodies. Direct antiglobulin test was negative for complement antibodies.

Figure 1. Image of Patient's Peripheral Blood Smear



Schistocytes (blue arrows), microspherocytes (green arrows), and severe thrombocytopenia are evident (1000x).

Hospital Course

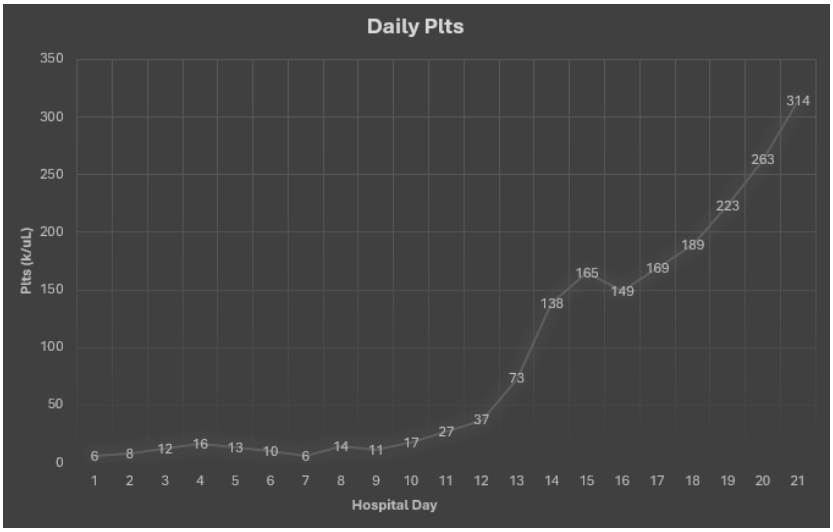
Methylprednisolone was initiated at a dosage of 1000 mg daily for 3 days followed by prednisone 80 mg daily for 4 days. Therapeutic plasma exchange (PLEX) at a rate of 1.0 plasma volume was initiated on hospital day 1 and planned daily until a platelet count of at least at least 140 k/uL (reference range, 150–400 k/uL) was achieved for 2 consecutive days. However, the patient's platelet count failed to rise above 20 k/uL after 7 PLEX sessions. PLEX therefore was escalated to 1.5 plasma volumes daily for 5 sessions before being reduced to 1.0 plasma volume. Prednisone was replaced with methylprednisolone 125 mg daily for 3 days before being tapered to 80 mg daily. Rituximab was initiated on the final PLEX session (hospital day 16) and scheduled for 375 mg/m^2 weekly for an additional 4 doses. Caplacizumab-yhdp was prepared but ultimately not required. Daily platelet counts from admission to discharge are shown in Figure 2. Cyanocobalamin 1000 mcg and folate 1 mg daily were initiated in the setting of hemolytic anemia.

On hospital day 3, the patient began to experience transient ischemic attacks (TIAs) characterized by syncope and focal deficits, including dysarthria, facial hemiparesis, and lower-extremity drift. Transthoracic echocardiography (TTE) revealed a dilated inferior vena cava and a small pericardial effusion. Cardiology diagnosed myocarditis and effusive-constrictive pericarditis based on TTE findings, troponinemia, and elevated erythrocyte sedimentation rate/high-sensitivity C-reactive protein levels; the patient's ongoing glucocorticoid therapy was expected to ameliorate the cardiac inflammation. CT angiography and perfusion imaging of the head with and without IV contrast revealed no abnormalities. Aspirin 81 mg daily was initiated for secondary prevention of ischemic neurologic events. TIAs continued during the following week, prompting magnetic resonance imaging

(MRI) of the head without contrast. MRI demonstrated 2 punctate foci of diffusion restriction in the posterior right frontal lobe, consistent with acute ischemia, and a small signal abnormality in the subcortical white matter of the right insula without diffusion restriction on fluid-attenuated inversion recovery sequence. The TIAs and focal deficits resolved as the platelet count recovered.

On hospital day 9, *Proteus vulgaris* bacteremia was detected via blood cultures obtained in the setting of altered mental status. Levofloxacin was initiated after testing revealed ceftriaxone resistance. Repeat blood cultures obtained shortly thereafter confirmed clearance of bacteremia. Sulfamethoxazole-trimethoprim 800-160 mg 3 times weekly and pantoprazole 40 mg daily were initiated because of high-dose glucocorticoid therapy.

Figure 2. Run Chart Depicting Patient's Daily Platelet Count From Admission to Discharge



Plasma exchange was performed daily from hospital day 1 to 16.

On hospital day 14, the patient reported somatic concerns, intermittently declined to speak or eat, displayed a flat affect, and demonstrated thought content concerning for Cotard delusion. Given the absence of prior psychiatric history, the psychiatry team deemed her sudden behavior change likely glucocorticoid-induced depression. Mirtazapine was initiated at 7.5 mg nightly with a target dose of 15 mg. However, she deteriorated over the next day, displaying signs of psychosis and catatonia (Bush-Francis Catatonia Rating Scale [BFCRS] score = 8). Mirtazapine was discontinued and clonidine 0.05 mg was prescribed as needed up to 3 times daily. Her BFCRS score quickly decreased to 3, although she continued to display signs of psychosis; therefore, olanzapine 2.5 mg nightly was added. She responded well to olanzapine, which was continued until 1 week after completion of glucocorticoid therapy. She subsequently developed elevated blood glucose levels reaching 200 to 250 mg/dL, for which insulin was initiated during inpatient hospitalization and metformin 500 mg was prescribed after discharge until glucocorticoid cessation.

After a 21-day admission, the patient was discharged with a platelet count of 314 k/uL, ADAMTS-13 activity of 23%, and an undetectable ADAMTS-13 inhibitor level. At her final rituximab infusion (1 month postdischarge), she reported feeling closer to her baseline status and complete resolution of psychiatric symptoms without neurologic deficits. Abnormal values from CBC, comprehensive metabolic panel, and hemolysis studies performed at follow-up were red blood cell count 3.53 × 106/μL, MCV 112.5 fL (reference range, 82.0–99.0 fL [88.7 fL on admission]), mean corpuscular hemoglobin 36.0 pg (reference range, 27.0–34.0 pg), mean platelet volume 8.9 fL (reference range, 9.0–13.0 fL), absolute neutrophil count 8.3 (reference range, 1.5–7.0 k/mm^3), lactate dehydrogenase 272 U/L, blood glucose 160 mg/dL, and alanine aminotransferase 48 U/L.

DISCUSSION

Our patient presented with a challenging case of TTP. Despite initially appearing well enough to suggest ITP, she ultimately was diagnosed with refractory TTP complicated by co-occurring wAIHA and Sjögren's syndrome. Patients with TTP frequently present with altered mental status, focal neurologic deficits, gastrointestinal symptoms, acute kidney injury (AKI), bleeding secondary to thrombocytopenia, abdominal pain, fever, and headache.[3,14] Although reported frequencies vary, the classic Amorosi-Ultmann TTP pentad of thrombocytopenia, MAHA, fever, AKI, and neurologic abnormalities is present in only 5% to 35% of cases.[3,14]

Guidelines for the management of aTTP were reviewed in 2024 by the International Society on Thrombosis and Haemostasis (ISTH).[15] For an initial episode of aTTP, ISTH-recommends frontline treatment with PLEX with glucocorticoids, rituximab, and caplacizumab. Given the patient's clinical complexity and elevated risk of adverse events, PLEX and glucocorticoids were initiated first, whereas rituximab and caplacizumab were considered subsequently.

Before ADAMTS13 testing became available, the patient's presentation was highly suggestive of TTP based on the PLASMIC score, a validated clinical prediction tool used to estimate the likelihood of severe ADAMTS13 deficiency in patients with suspected thrombotic microangiopathy.[13] Our patient met multiple high-risk criteria, including severe thrombocytopenia, laboratory evidence of hemolysis, absence of active malignancy, absence of transplant

history, normal coagulation studies, and preserved renal function, supporting prompt initiation of empiric PLEX while definitive testing was pending.

CONCLUSIONS

Despite the well-established observation that the presence of one autoimmune disease increases the risk of developing additional autoimmune diseases, we found no reports documenting co-occurring TTP, wAIHA, and Sjögren's syndrome. Herein, we describe the successful treatment of a highly complex case, highlighting the importance of multidisciplinary care and providing support for use of the PLASMIC score to justify empiric PLEX.

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Zoledronate-Associated Orbital Inflammation: A Case Series and Literature Review

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ABSTRACT

Introduction: Bisphosphonates are known to cause acute systemic inflammation through stimulation of proinflammatory cytokines. This reaction can include conjunctivitis, anterior uveitis, episcleritis, scleritis, and, rarely, orbital inflammation. We present 2 cases of zoledronate-associated orbital inflammation and a literature review highlighting treatment challenges.

Case Presentation: The first case was managed with intravenous (IV) methylprednisolone, 1 mg/kg, followed by a short steroid taper. Symptoms recurred after completion of the taper. The second case presented with optic perineuritis and preseptal and postseptal inflammation. Initial treatment with IV methylprednisolone, 1 mg/kg, resulted in incomplete response, necessitating escalation to high-dose corticosteroid therapy.

Discussion: A literature review identified 19 additional cases of zoledronate-associated orbital inflammation. There was no clear consensus regarding treatment and only 1 reported case of relapse was identified.

Conclusions: We recommend initial treatment with IV methylprednisolone, 1 mg/kg, followed by a prolonged taper. If symptoms do not improve within the first day of treatment or if the optic nerve sheath is involved, escalation to IV methylprednisolone, 1 g daily, may be warranted.

INTRODUCTION

Bisphosphonates are a class of pharmaceuticals commonly prescribed for osteoporosis, Paget disease, osteoclastic bone metastases, and multiple myeloma. These medications bind to the bone hydroxyapatite matrix and inhibit osteoclast function, thus preventing bone resorption and relieving bone-related pain.[1] One well-known adverse effect of bisphosphonates is a systemic inflammatory state called the acute-phase response, characterized by fever, fatigue, and nausea within 72 hours of administration and thought to result from transient stimulation of proinflammatory cytokines.[2] In addition to systemic inflammation, bisphosphonates are known to cause ocular inflammation, most commonly conjunctivitis, anterior uveitis, episcleritis, and scleritis.[3]

In rare cases, orbital inflammation has also been associated with bisphosphonates.[4-22] Bisphosphonate-associated orbital inflammation can present with a variety of symptoms that mimic infection, including fever, nausea, ocular pain, diplopia, restricted eye movements, conjunctival injection, chemosis, and periorbital edema.[23] Given the rare association between bisphosphates and orbital inflammation, diagnosis is often delayed, and there is no clear consensus on treatment.

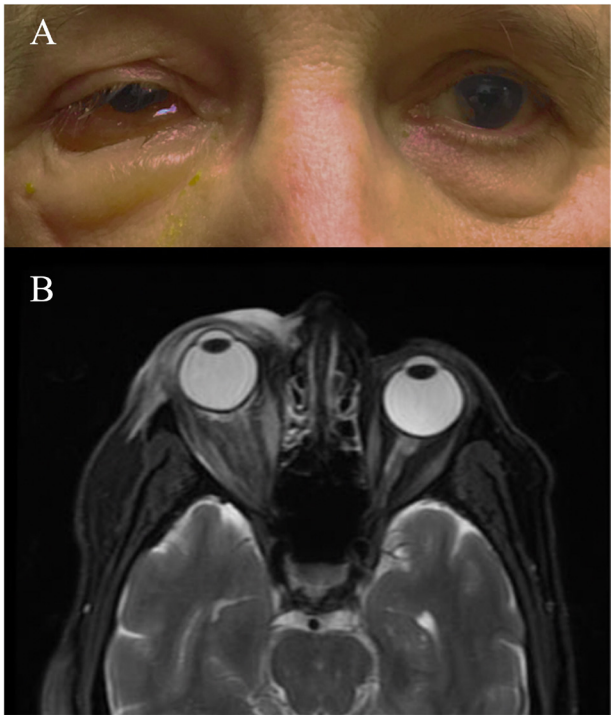
We present 2 cases of orbital inflammation following zoledronate infusion, along with a literature review of the manifestations and management of zoledronate-associated orbital inflammation. All data handling was compliant with the Health Insurance Portability and Accountability Act and the Declaration of Helsinki. The first case was notable for recurrent inflammation following a steroid taper, which has only been described once previously. The second case was notable for optic perineuritis and required higher doses of intravenous (IV) steroids to achieve remission. Management of both cases was challenging because of the limited guidance available in the literature. Thus, the aim of this review is to describe the reported cases of zoledronate-associated orbital inflammation and offer guidance on treatment.

• • •

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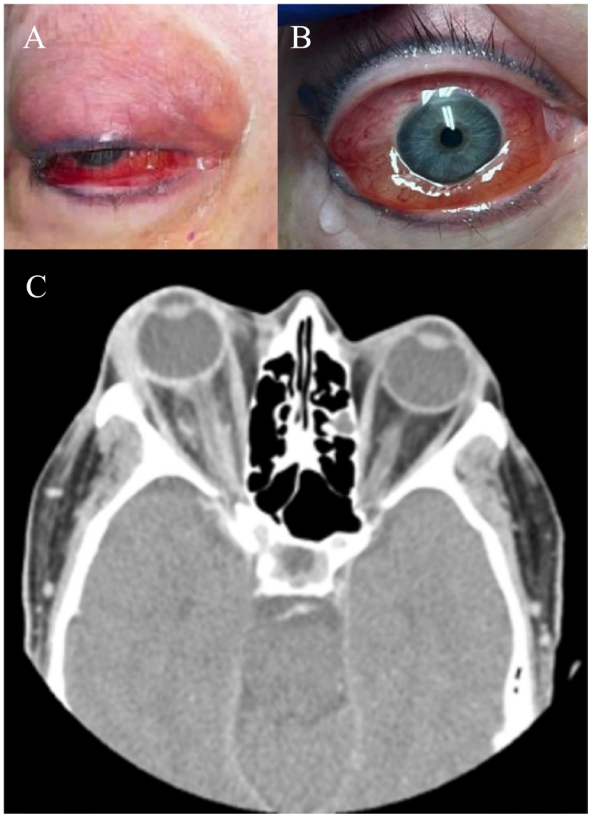
Figure 1. Case 1 Presentation



A) Initial presentation of a 72-year-old man presenting with right eye pain, proptosis, and chemosis three days after zoledronate infusion (Case 1).

B) T2-weighted magnetic resonance imaging orbit from the initial presentation of Case 1 demonstrating right-sided diffuse preseptal and postseptal edema and fat stranding with extraocular muscle thickening.

Figure 2. Case 2 Presentation



A-B) Initial presentation of a 60-year-old woman presenting with weakness, fever, chills, vomiting, right eye pain and swelling, and photophobia.

C) Contrast-enhanced computed tomography orbit from the initial presentation of Case 2 demonstrating right-sided diffuse pre- and post-septal edema and fat stranding with optic nerve sheath enhancement.

CASE PRESENTATION

Case 1

A 72-year-old man presented with headaches, vomiting, and right eye pain and swelling 3 days after his first zoledronate infusion for prostate cancer bone metastases. His medical history was notable for hypertension, hyperlipidemia, and coronary artery disease. Best-corrected visual acuity was 20/20 in the right eye and 20/20 in the left eye. Intraocular pressure, pupils, and confrontational fields were within normal limits bilaterally. There was no relative afferent pupillary defect. Right eye abduction and depression were mildly limited. There was 6 mm of relative proptosis and chemosis (Figure 1A). Dilated fundus examination revealed no optic disc edema. Magnetic resonance imaging (MRI) revealed diffuse preseptal and postseptal edema and fat stranding with extraocular muscle thickening (Figure 1B). Pain, proptosis, and chemosis improved rapidly with 1 dose of IV methylprednisolone, 1mg/kg; however, inflammation recurred after a 9-day taper of oral prednisone (80 mg for 5 days, 60 mg for 1 day, 40 mg for 1 day, 20 mg for 1 day, and 10 mg for1 day), necessitating a longer prednisone taper (40 mg for 1 week, 30 mg for 1 week, and 20 mg for 1 week before resumption of the patient's maintenance dose of prednisone, 10 mg daily, for prostate cancer).

Case 2

A 60-year-old woman presented with weakness, fever, chills, vomiting, photophobia, and right eye pain and swelling 20 hours after a zoledronate infusion for osteoporosis. Her medical history was notable for hypertension, hyperlipidemia, hypothyroidism, and type 2 diabetes. Best corrected visual acuity was 20/30 in the right eye and 20/20 in the left eye. Color vision, pupils, and confrontational fields were within normal limits bilaterally. There was no relative afferent pupillary defect. Right intraocular pressure was 24 mm Hg, compared with 22 mm Hg in the left eye. Motility of the right eye was moderately limited in all directions except supraduction. Examination revealed right upper eyelid erythema and conjunctival chemosis (Figure 2A-B). Dilated fundus exam revealed no optic disc edema. Imaging demonstrated preseptal and postseptal edema and fat stranding with optic nerve sheath enhancement (Figure 2C). IV antibiotics were administered because of concern for infection; however, there was no improvement over 24 hours. Treatment with IV methylprednisolone, 1 mg/kg, was initiated with immediate improvement in pain, chemosis,

Table. Literature Review of Zoledronate-associated Orbital Inflammation, Plus Current Cases

Publication	Age (Sex)	Time From Last Dose to Onset	Indication for Zolendronate	Other Medical History	Sites of Orbital Inflammation	Treatment[a]	Time to Resolution
Sharma, et al; 2008[4]	57 (M)	3 days	Knee osteonecrosis	None listed	Preseptal, postseptal	1g IV MP for 3 days, then oral pred taper	3 days
Phillips, et al; 2008[5]	55 (M)	1 day	Metastatic renal cancer	None listed	Preseptal, postseptal	60 mg oral pred tapered for 10 weeks	3 days
Seth, et al; 2009[6]	68 (M)	1 day	Metastatic prostate cancer	HTN	Preseptal, postseptal, scleritis, AION	100 mg oral pred	7 days
Missotten, et al; 2010[7]	71 (M)	Minutes	Metastatic prostate cancer	None listed	Preseptal, postseptal for 3 weeks	32 mg oral pred	5 days[b]
Yeo, et al; 2010[8]	62 (M)	1 day	Charcot arthropathy	Type 1 diabetes	Preseptal	None listed	10 days
Yang, et al; 2010[9]	89 (F)	3 days	Osteoporosis	None listed	Preseptal, postseptal, scleritis, optic perineuritis, myositis	1g IV MP for 3 days, then oral pred taper	3 days
Procianoy, et al; 2010[10]	60 (F)	1 day	Osteoporosis	Autoimmune thyroiditis, breast cancer	Preseptal, postseptal	80 mg oral pred tapered for 6 weeks	12 days
Ortiz-Pere, et al; 2011[11]	70 (F)	1 day	Paget disease	None listed	Preseptal, postseptal	Oral pred for 3 weeks	21 days
Kaur, et al; 2011[12]	57 (F)	Several hours	Osteoporosis	Esophageal, breast, lung cancer	Preseptal, postseptal	2 MP dose packs	14 days
Schwab, et al; 2012[13]	55 (F)	4 days	Osteoporosis	Type 1 diabetes, hypothyroidism, osteoarthritis, GERD	Preseptal, postseptal, scleritis, optic perineuritis, myositis	1g IV MP for 2 days, then 60 mg oral pred tapered for 3 weeks	7 days
Boni, et al; 2013[14]	75 (F)	2 days	Osteoporosis	None listed	Preseptal, postseptal, anterior uveitis	IV MP	Several days
Rahimy, et al; 2013[15]	68 (M)	1 day	Osteoporosis	None listed	Preseptal, postseptal	1g IV MP for 3 days then 60 mg oral pred tapered for 5 weeks	3 days
Manuylova, et al; 2015[16]	66 (M)	4 days	Osteoporosis	HTN, HLD, GERD	Preseptal, postseptal, optic perineuritis, anterior uveitis	High-dose oral pred	After treatment
Umanakwe, et al; 2017[17]	68 (F)	12 hours	Osteoporosis	HTN, HLD, depression/ anxiety, migraines	Preseptal, postseptal, scleritis, anterior uveitis	1g IV MP for 1 day, then then 60 mg oral pred tapered for 10 weeks	80 days
Herrera, et al; 2019[18]	56 (F)	1 day	Osteoporosis	Sjogren's syndrome, SLE, inflammatory demyelinating polyneuropathy	Preseptal, postseptal, scleritis, optic perineuritis	50 mg oral pred for 1 week, then slow weekly taper	7 days
Chehade, et al; 2019[19]	65 (F)	4 days	Osteoporosis	Lymphoma, breast cancer anterior uveitis	Preseptal, postseptal, scleritis, optic perineuritis, weeks	Topical prednisolone 3x/day tapered for 5	35 days
Keren, et al; 2019[20]	58 (F)	Several hours	Metastatic thyroid cancer	None listed	Preseptal, postseptal, scleritis, anterior uveitis	None listed	14 days
Khalid, et al; 2021[21]	62 (M)	3 days	Metastatic prostate cancer	Type 2 diabetes, HLD, AAA	Preseptal, postseptal	1mg/kg oral pred	7 days
Faryal, et al; 2021[22]	45 (M)	3 days	IgG kappa myeloma	None listed	Preseptal, postseptal	500 mg IV MP for 3 days, then 60 mg oral pred taper	21 days
Arzbecker, 2025[d]	72 (M)	3 days	Metastatic prostate ancer	None listed	Preseptal, postseptal	1mg/kg IVMP for 1 day, then 80 mg oral pred taper for 9 days	30 days[c]
Arzbecker 2025[d]	60 (F)	20 hours	Osteoporosis	HTN, HLD, GERD, type 2 diabetes, hypothyroidism	Preseptal, postseptal, optic perineuritis	1mg/kg IV MP for 1 day, then 1g IV MP for 3 days, then 80 mg oral pred tapered for 8 weeks	21 days

Abbreviations: AAA, abdominal aortic aneurysm; AION, anterior ischemic optic neuropathy; CAD, carotid artery disease; F, female; GERD, gastroesophageal reflux disease; HLD, hyperlipidemia; HTN, hypertension; IgG, immunoglobulin gamma; IV MP, intravenous methylprednisolone; M, male; pred, prednisone; SLE, system lupus erythematosus.

[a]Where the type of medication but not the dose was published, the same information is included in the treatment column.

[b]Recurred 7 months later.

[b]Recurred and required 4-week taper.

[d]Case presented in this report.

and extraocular movements, but symptoms recurred completely within 24 hours. Given the limited initial response to treatment and imaging findings of optic perineuritis, the steroid dosage was increased to IV methylprednisolone, 1 g daily, for 3 days, which is standard treatment for optic neuritis.[24] The patient was then transitioned to oral prednisone, 80 mg daily (slightly less than 1 mg/kg), which was successfully tapered over 8 weeks.

LITERATURE REVIEW

A PubMed literature search was conducted using combinations of medication-related terms (zoledronate, zoledronic acid, Aclasta, Zometa, Reclast) and orbital terms (orbit, orbital, orbitopathy). Abstracts without full-text articles were excluded. This search identified 28 cases of zoledronate-associated orbitopathy, of which 19 had full-text reports available for review (Table).[4-22] The median age of patients was 62 years, and 53% were female. Zoledronate was indicated for osteoporosis (53%), cancer with bone metastasis (26%), osteonecrosis (5%), Paget disease (5%), Charcot arthropathy (5%), and IgG kappa myeloma (5%). All cases presented with unilateral ocular pain and swelling and occurred within 4 days of the most recent infusion. The median onset of symptoms was 1 day after infusion. All cases treated with steroids reported improvement in symptoms on the first day of treatment, and the median time to complete symptom resolution was 7 days. Patterns of inflammation included preseptal and postseptal inflammation (95%), scleritis (37%), optic perineuritis (26%), myositis (11%), anterior uveitis (26%), anterior ischemic neuropathy (5%), and preseptal inflammation (5%). Patients typically received IV steroids (37%) or oral steroids (47%), with 1 patient receiving topical steroids (5%) and 2 patients receiving no reported treatment (11%). Starting doses varied widely. Among those receiving systemic steroids, doses ranged from oral prednisone, 32 mg, to IV methylprednisolone, 1 g (equivalent to approximately 800mg oral prednisone).

DISCUSSION

Orbital inflammation is a rare adverse reaction to bisphosphonates. Specifically, IV aminobisphosphonates (zoledronate, ibandronate, alendronate) have been reported to induce orbital inflammation. This is thought to be due to the presence of a nitrogen group involved in sensitization and activation of macrophages and osteoclasts, which are derived from macrophages. Activation of these cell types stimulates the release of proinflammatory cytokines, causing an acute-phase response. Up to 40% of patients receiving IV aminobisphosphonates experience an acute-phase response within 3 days of administration.[2] All reported cases of zoledronate-associated orbital inflammation occurred within a similar time frame (within 4 days) and mimicked infection, with prodromal symptoms of unilateral orbital pain and swelling. Therefore, it is hypothesized that the proinflammatory cytokines involved in the acute-phase response are responsible for inducing orbital inflammation.

Currently, steroids are the standard treatment for bisphosphonate-associated orbital inflammation; however, no consensus exists regarding appropriate dosing. Among reported cases of zoledronate-associated orbital inflammation, approximately half of patients received IV steroids and half received oral steroids. Many authors described dosing at 1mg/kg, which is typical for idiopathic orbital inflammation. Despite differences in dose and duration, all cases reported improvement in symptoms on the first day of treatment and complete resolution thereafter. Only 1 case experienced a relapse 7 months later.[7]

Here, we present a second case of recurrent inflammation occurring 10 days after treatment with IV methylprednisolone, 1 mg/kg. This was likely due to the rapid steroid taper, given that the patient remained in remission after a longer taper. Additionally, we describe the first reported case of incomplete initial treatment with IV methylprednisolone, 1 mg/kg. For this patient, treatment was escalated to IV methylprednisolone, 1 g daily, for 3 days, resulting in immediate improvement in symptoms and sustained remission after an 8-week oral prednisone taper. This case was notable for optic nerve sheath involvement. Two previously reported cases with optic perineuritis were treated with IV methylprednisolone, 1 g daily, for 2 to 3 days. Symptoms improved rapidly and did not recur.[9,13] Thus, the presence of optic perineuritis may necessitate a higher initial steroid dose.

CONCLUSIONS

Bisphosphonate-associated orbital inflammation should be suspected in any patient presenting with acute orbital inflammation within several days of an aminobisphosphonate infusion. We recommend treating newly diagnosed bisphosphonate-associated orbital inflammation with IV methylprednisolone, 1 mg/kg/day (or the oral equivalent), for 1 week, followed by a slow taper over 3 to 4 weeks. If symptoms do not improve on the first day of treatment, or if there is optic nerve sheath involvement, escalation to IV methylprednisolone, 1 g daily, should be considered.

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