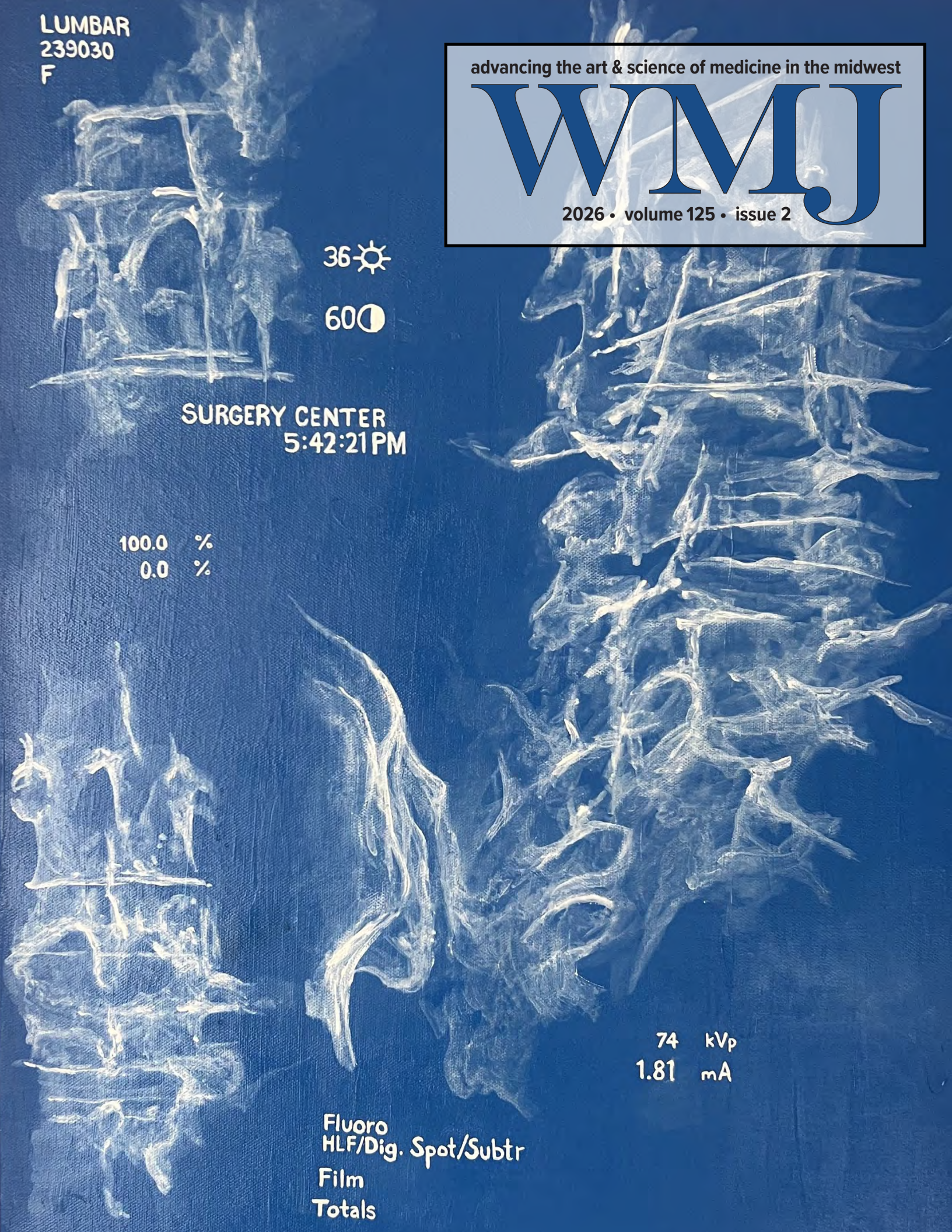

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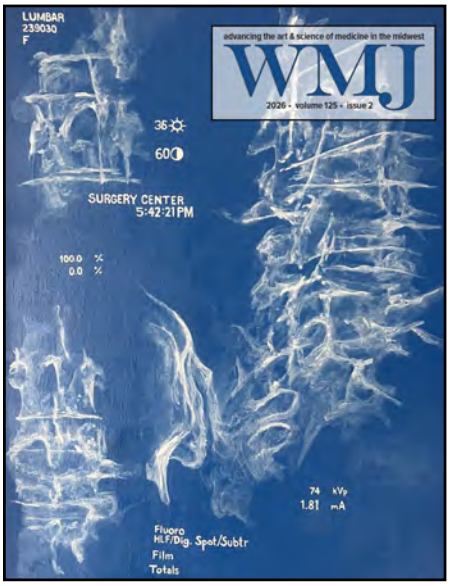

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COVER ART

Lumbar Spine Flouro

Leana Pande, DO

Gouache on canvas

Artist Statement:

This is the artsy rendering and interpretation of the spine and sacroiliac joints in fluoroscopy, emphasizing the beauty of medicine and anatomy in a graceful color selection that is more approachable to eyes outside of medicine.

See page 240 for information about the artist.

• • •

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

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

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ISSN 1098-1861 • Established 1903

Published 6 times a year, beginning in March

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Wisconsin's First Hantavirus Disease Case: A Reminder for an Index of Suspicion

To the Editor:

Recent attention has been directed to a cluster of hantavirus cases linked to a cruise ship, and the aftermath of global concern and response.[1] This cluster has been identified as resulting from the South American virus species (*Orthohantavirus andesense*). Whereas hantavirus infection has been, and likely will be a rare event in the United States – with 890 cases reported between 1993 and 2023[2] – rare events are worthy of careful consideration.

The openness of the *Wisconsin Medical Journal* (*WMJ*) to the publication of case reports, even if uncommon in clinical practice, underscores the essential role of a statewide medical journal. In 1997, the *WMJ* published a case report of hantavirus pulmonary syndrome (HPS) occurring in Wisconsin in May 1996.[3] Complete clinical information was provided though a succinct review of the symptoms, examination, laboratory and radiographic findings, and the clinical course of this fatal case.

This case is illustrative of rare events encountered by clinicians. On presentation, the patient reported common, nonspecific symptoms of fever, myalgias, and cough. A broad-spectrum antibiotic was prescribed; the patient returned with worsening cough and shortness of breath and was admitted to an outlying hospital, then transferred to a tertiary care hospital. Diagnosis was made through reverse transcriptase polymerase chain reaction performed on necropsy tissues at the Centers for Disease Control and Prevention.[3]

During 2002, I worked with a medical student identifying the primary care differential diagnosis of inhalational anthrax, another extremely rare infection.[4] We surveyed a random, national sample of practicing family physicians and documented 35 distinct diagnostic categories for inhalational anthrax. Seven diagnostic categories – pneumonia, influenza, viral syndrome, septicemia, bronchitis, central nervous system (CNS) infection, and gastroenteritis – accounted for 86.1% of all diagnoses.

The take-home lesson is thus: rare things usually present in common ways. Four-legged equines in the US are almost entirely horses and not zebras. As the authors of the first Wisconsin HPS case noted: "Differentiating HPS from other respiratory infections can be difficult, given the nonspecific symptoms associated with the prodromal stage."[3] In addition, they concluded, "Recognition of the clinical pattern, a history of rodent exposure, and a high index of suspicion are the keys to making the diagnosis."[3]

Rare events are detected by astute frontline physicians and laboratorians providing usual medical care to their patients as shown by Wisconsin's first HPS case. Accordingly, clinicians need to consider, with higher acuity, those troubling cases that are out of season, out of range, and out of context.

—Jonathan L. Temte, MD, PhD

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Financial disclosures: None declared.

Funding/support: None declared.

Mindfulness: An Invisible Yet Integral Tool for Physicians

To the Editor:

An insightful editorial in *WMJ* by Dr Fahad Aziz eloquently emphasized that mindfulness is not new to our profession, yet its impact remains underestimated and must be deliberately cultivated and practiced consistently.[1] In today's environment of continuous email, cell phones, and social media notifications, mindfulness offers an essential counterbalance by reinforcing present-moment awareness and directing attention in a nonjudgmental manner that supports clear thinking and open-heartedness.[2,3] Intentionally setting aside time for pause and reflection is a core expression of mindfulness. Emerging evidence shows that brief pauses create the cognitive space essential for strategic problem-solving, which enhances adaptability and responsiveness to complex environments.[2] Mindful self-reflection deepens self-awareness, clarifies our values, mission, and goals, and cultivates the growth mindset required to navigate challenges with clarity and intention.

For physicians, mindfulness is integral to professional competence, promoting effective clinical decision-making and reducing medical errors.[3] Mindfulness is vital for empathy and cultural awareness, as a distracted physician cannot fully hear the patient's story or appreciate the emotions and values that shape decision-making.[4] A study demonstrated that premedical and medical students who were randomly assigned to mindfulness training experienced decreased psychological distress and increased empathy.[3] Without mindfulness and empathy, clinicians may complete required tasks yet fail to connect meaningfully with patients, overlooking the nonverbal cues essential for trust, adherence, and shared decision-making.[4]

However, modern clinical practice increasingly strains this capacity for mindful presence. Secure electronic messaging – now integral to care coordination – creates constant digital interruptions.[5] Each alert demands cognitive switching, disrupting attention and interrupting the reflective thought necessary for accurate diagnosis. Ultimately, mindfulness is critical to patient-centered care as it strengthens the trust that lies at the heart of the patient–physician therapeutic relationship and supports healing. The next generation of physicians learns mindfulness from the attending physicians they observe, placing a profound responsibility on us as medical educators to uphold mindfulness as both a personal discipline and a professional legacy.

—Farzana Hoque, MD, MRCP

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Financial disclosures: None declared.

Funding/support: None declared.

Sponsorship: A Vital Leadership Strategy for Career Advancement in Academic Medicine

To the Editor:

Faculty development plays a vital role in satisfaction, retention, and career growth in academic medicine. It is commonly built around 4 pillars: mentorship, scholarship, sponsorship, and collaboration. While mentorship is well established in academic culture, sponsorship remains a less visible and underused strategy for faculty development.

Although mentorship and sponsorship are closely related, they serve distinct roles. Mentors provide guidance, advice, and support based on experience to help faculty navigate challenges and develop skills. Sponsorship, by contrast, is an intentional leadership practice that advances careers through the use of influence, credibility, and positional authority. Sponsors recommend individuals for leadership roles, nominate them for awards and committees, secure invited speaking opportunities, and expand access to professional networks.[1] Through these actions, sponsors open doors that might otherwise remain inaccessible. Core elements of sponsorship include recognizing talent, providing sustained support, increasing visibility, and advocating for opportunities that enable growth.[1-3]

This distinction is important because career advancement in academic medicine depends not only on productivity and merit but also on access to opportunity, visibility, and recognition. Access to leadership roles and professional networks is often uneven, and sponsorship can play a critical role in bridging these gaps. For faculty from underrepresented groups, sponsorship may be particularly impactful, helping to counter structural and implicit biases and ensuring that excellence is recognized rather than overlooked.[1,4-6]

Effective sponsorship can also be understood through the "ABCDs" framework: Amplifying achievements, Boosting credibility, Connecting to influential networks, and Defending against bias – actions that actively advance a mentee's career.[7]

At the individual level, sponsorship can accelerate promotion, facilitate leadership appointments, and expand recognition beyond one's home institution. At the organizational level, it contributes to stronger and more diverse leadership pipelines. Importantly, effective sponsorship does not require extraordinary resources. Rather, it depends on an intentional and proactive approach to recognizing both current strengths and future potential and acting on that recognition.

One of the most tangible expressions of sponsorship is the nomination of faculty for awards, committees, editorial boards, and leadership positions. These acts confer credibility and visibility that often compound over time. Sponsorship is not a single event but a longitudinal commitment that includes feedback, advocacy, and follow-through as careers evolve.[1,5]

Faculty awards represent a particularly powerful and often underrecognized form of sponsorship. Although awards are frequently viewed as symbolic, they function as strategic career accelerators. Awards support promotion, increase professional visibility, and create opportunities for leadership and collaboration. They also shape institutional narratives of excellence by signaling which contributions are valued.[1,3] In this way, recognition becomes more than acknowledgment; it becomes a mechanism through which equity can be advanced. Collective recognition benefits not only individuals but also teams and institutions.[4-6]

Sponsorship ultimately extends beyond individual career development and reflects a broader leadership responsibility. Leaders who engage in sponsorship actively shape the future of academic medicine by determining who is seen, supported, and advanced. By embracing sponsorship and using recognition thoughtfully, academic leaders can cultivate the next generation of leaders while building a more inclusive and supportive professional community.[1,4-6]

—Pinky Jha, MD; Sanjay Bhandari, MD

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Financial disclosures: None declared.

Funding/support: None declared.

When Everything Matters: Choosing What Truly Counts in Academic Medicine

Fahad Aziz, MD; Nizar Jarjour, MD;

"What makes life worth living in the face of death?"

—*Paul Kalanithi*

In his book *When Breath Becomes Air,* Kalanithi poses a deeper question: What truly matters? At the edge of the operating room, the focus shifts from what can be done to what is worth doing.

In academic medicine, we are trained to act, not to pause. Productivity becomes our measure, while clarity recedes. Yet the question returns. The challenge is rarely lack of opportunity, but lack of clarity.

The Burden of Opportunity

Academic medicine offers many opportunities—but little guidance—on what to choose. There are clinical responsibilities, committees, papers, projects, and teaching. Each matters, but together they make everything feel equally important.

In this environment, being busy can feel like having purpose. Calendars fill, CVs grow, yet something still feels off—not from lack of effort but from lack of alignment. The central question is not what can we do—because the answer is always "a lot"—but what should we do?

The system often rewards saying "yes." Over time, this becomes a habit, and careers grow by continually adding more instead of through deliberate choice. This is the burden of opportunity: too much to do without clarity about what truly matters.

> Thoughtful pruning does not limit growth; it directs it, creating strength, clarity, and sustainability over time.

The Big Rocks Concept

In academic medicine, the problem is rarely a lack of opportunity—it is knowing what deserves attention first. A simple way to think about this is the idea of "big rocks." Imagine a jar that represents a professional life. If it is filled first with small, nonurgent tasks, there is no room left for the work that truly matters. But if the big rocks go in first, everything else can fit around them.

The big rocks are the foundation of a meaningful career. They are not just tasks—they are what give work its purpose and lasting impact. For most physicians, these include caring for patients, advancing knowledge through research, mentoring the next generation, and protecting personal well-being and family. These commitments shape identity, sustain fulfillment, and define long-term success. When they are protected, everything else falls into place with clarity and direction. When they are not, even the busiest schedule can feel unfocused and unfulfilling.

Around these big rocks are the "pebbles"—important but secondary responsibilities like committees, reviews, and teaching activities. They support the system and add value, but they are not the foundation. Then comes the "sand"—the small, reactive tasks that fill time without adding meaningful progress. These are easy to say yes to and often feel urgent, but over time they crowd out what matters most.

What counts as a "big rock" is not always easy to define. One approach is pursuing what you enjoy most. Equally important is focusing on what you do well and what needs to be done.

Once these priorities are clarified, the challenge shifts to protecting them. Without clear boundaries, every request begins to feel equally important, and decision-making becomes reactive. Work increases, but focus is lost.

When the big rocks are clear and protected, decisions become easier. The question is no longer whether something is a good opportunity, but whether it supports what matters most. In that sense, clarity does not limit opportunity; it helps identify the right ones.

WHY → Mission → Vision: A Framework for Intentional Careers

Clarity in academic medicine does not happen on its own; it must be developed. A simple way to think about it is: WHY → Mission → Vision.

• • •

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This is how purpose translates into daily work and, over time, real impact.

The WHY is the starting point. It is neither a title nor a list of responsibilities, but the reason the work matters – especially on the difficult days. Finding this WHY comes from paying attention to moments that feel meaningful: a patient interaction that stays with us, a trainee who grows under our guidance, a discovery that excites us. These moments are signals. Over time, patterns emerge. The work that gives energy – the work that feels worth the effort – is where the WHY lives. When this is clear, decisions become easier and more grounded.

The mission is how that WHY shows up every day – reflected not in plans, but in what is actually done: how time is spent, what is prioritized, and where effort goes. A simple way to define it is: We are to… for… so that… For example, "I am to provide compassionate care for patients with complex medical conditions so they can live healthy, meaningful lives." This keeps daily work connected to a deeper purpose.

The vision looks ahead. It is less about tasks and more about direction – who we are becoming over time. It connects today's work to future impact, whether that means building programs, advancing a field, or shaping the next generation.

When these three are aligned, work feels focused and meaningful. When they are not, even a full and productive career can feel scattered.

Decision-Making and the Cost of 'Yes'

Clarity in academic medicine becomes more meaningful when it shapes decisions. The challenge is less about knowing what is important and more about making choices in real time, when opportunities appear reasonable, valuable, and difficult to decline.

A simple approach is to use an "opportunity filter" built on three questions: Does this align with core work? Will it create meaningful impact? Will it sustain energy? This structure brings consistency to decision-making and helps distinguish true progress from mere activity.

Yet every decision carries a cost. Each "yes" consumes time, affects energy, and fragments attention. These costs are often not immediate, but they accumulate. Hours are redistributed, energy is unevenly spent, and attention is divided across competing demands. Over time, this leads to a loss of focus and coherence.

Every "yes" is also a "no" to other priorities. A new committee may come at the expense of research time. An additional project may displace mentorship, reflection, or personal well-being. These trade-offs shape one's career trajectory, often quietly and gradually.

Over time, patterns of decisions – not any single choice – define a career's direction. The goal is to choose selectively, focusing on opportunities that create meaningful progress.

Strategic Yes vs Default Yes

In academic medicine, many decisions are made quickly and habitually, without reflection. Each "yes" contributes to a path that often recognized only in retrospect.

Most decisions follow a default yes – quick, automatic, and driven by habit, obligation, or the desire to be helpful. It comes without pause, leaving little time to consider alignment, impact, or cost. Over time, this leads to accumulation – more roles, more tasks, more responsibility – often without clarity.

A strategic yes is different. It is intentional and grounded in purpose. It introduces a pause and reframes the question: "Can this be done?" becomes "Should this be done?" It is guided by alignment, not pressure.

The difference is simple: a default yes is reactive; a strategic yes is intentional. Rather than saying yes less, the shift is about saying yes with clarity. Over time, these patterns of decisions – not isolated choices – guide the direction of a career.

The Discipline of Saying No

In addition to thoughtful "yes" decisions, careers are also built by the ability to say "no." Declining can feel uncomfortable, but without it, priorities blur, focus fragments, and meaningful work is replaced by accumulation.

A "strategic no" is best understood as clarity with respect. Rather than disengagement, it reflects alignment – a way to protect what matters while honoring the value of the request. In this sense, setting boundaries reflects leadership, focus, reliability, and self-awareness – not defensiveness.

Equally important is how the message is delivered. A clear, respectful response preserves relationships while maintaining direction. Simple statements are often sufficient: acknowledging the opportunity, expressing appreciation, and stating current priorities.

At times, decisions may not be easy or clear. In such situations, seeking guidance from mentors – particularly early in one's career – can help maintain focus on what matters most.

Refinement: The Practice of Pruning

Careers in academic medicine rarely become overextended all at once. They grow slowly – one committee, one project, one role at a time. Each addition seems reasonable, but over time, this accumulation fills schedules and drifts from its original purpose.

The challenge extends beyond growth to ongoing refinement. Pruning is the process of realignment, ensuring that current commitments still reflect mission and direction. As priorities evolve, not everything that once fit continues to do so.

This requires periodic pauses – stepping back to ask: Does this still matter? Does this still align? Without this reflection, past decisions persist by default instead of intentional design. Like a tree, growth without pruning leads to excess and imbalance. Thoughtful pruning does not limit growth; it directs it, creating strength, clarity, and sustainability over time.

Finally, periodic pruning can eliminate ongoing time commitments, freeing time and energy to explore more meaningful opportunities. In some cases, faculty who feel overburdened may need to address workload with academic leaders, including potential reduction of assigned responsibilities. Ideally, this follows careful self-reflection to distinguish assigned expectations from additional commitments voluntarily assumed over time, including committee work, teaching, travel, and consulting.

A Call to Intentional Practice

The question returns: What truly matters? Academic medicine will always offer more than can be done. The enduring challenge is to choose deliberately – because over time, a career is defined not by volume, but by direction and what is chosen.

Do We Really Care About Our Children's School Safety? The Proof Is in the Pudding

Steven Lippmann, MD

Gunshots are a major, tragic cause of death among American children,[1] and school shootings involving children have increased.[2-4] Too many are also dying by firearm-induced suicide, homicide, or accidents, often with associated emotional turmoil. Is our society sufficiently concerned to do something about it?

Firearm-related incidents have occurred for decades. However, gun-related events and shootings at US schools now occur much more often than in the past.[1-4] Indeed, our country is experiencing an epidemic of dangerous school shootings,[1-5] with the number of such incidents increasing by more than 700% in the last two decades.[2]

During 2023 and 2024, an average of 341 gun-related incidents were reported in schools each year.[2] Such events also included nonshooting circumstances. However, gunfire in each of those years resulted in approximately 260 firearm-related casualties. About 20% of cases resulted in death, and approximately 80% resulted in nonfatal injuries, either from gunshot wounds or injuries sustained while attempting to avoid a shooting.

A 2025 report on the sequelae of gunfire on school grounds documented 141 shootings, with 44 fatalities and 129 injuries.[4] However, these statistics also illustrate the difficulty of comparing data across incidents, locations, and years. The cited numbers vary considerably.[1-4] There is substantial variation in how such events are defined and counted, contributing to inconsistencies in news reports.[5]

For example, definitions may differ regarding whether deaths occurred immediately or later, and whether injuries resulted directly from gunshot wounds or from attempts to evade harm. Reported incident numbers also differ because some definitions include only the discovery of a gun or a shooting threat in or near a school – even when no one is shot or no one is present in the building (eg, a drive-by shooting at a school). Additional complexity arises when reports include events occurring away from school grounds, such as at games, field trips, or similar occasions, as well as on school buses or at distant school bus stops.[6] Other data inconsistencies arise when reports do or do not include threats of gun violence or the mere discovery of a firearm in a school. Regardless, all of these circumstances have a negative impact on kids.

Gun violence also has significant negative psychological effects, including fear of being shot, exposure to possible firearm threats or presence, and anxiety associated with news reports, metal detectors, increased police presence, and similar measures intended to prevent such events. Beyond the many tragic deaths, this is physically and emotionally harmful to society especially our children.

People voice concern about school safety, but is there sufficient evidence that our society is trying to address this trend? A large number of children have witnessed these events; they are the ones who must cope with the associated risk and/or trauma, especially during school hours. The general public rarely enters school buildings; thus, most adults do not experience these dangers firsthand. They are insulated, yet they are responsible for – and influential in – government policy and planning.

> Become an activist, write letters to newspapers or journals, and participate in community meetings to help shape the desired change.

What people do matters more than what they say. Given awareness of this crisis, Americans should work to address the well-being of school-age children. Physicians can play a productive role in such leadership.[7-11]

Efforts to reduce the risk of kids being shot at school and elsewhere may begin by talking to others about improving safety. This should include advocating for action from members of Congress, state legislators, governors, mayors, and local or school officials. Engaging with col-leagues and presenting at medical meetings are additional strategies. Become an activist, write letters to newspapers or journals, and participate in community meetings to help

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shape the desired change. A serious, focused national dialogue may help reduce this problem. Reducing firearm violence in this country would benefit us all – especially our children.

Funding/support: None declared.

Financial disclosures: None declared.

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Erratum

Correction to: Evidence-based heart failure management: a practical guide for hospitalists. *WMJ*. 2025;124(5):452-459. https://wmjonline.org/124no5/northway/

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In this article in Volume 124, Issue 5 of *WMJ*, there was an incorrect statement on page 456, right column, line 11. The text read:

> Furthermore, adding 50 mg per day of hydrochlorothiazide to usual care of patients with acute decompensated heart failure has been shown to improve diuretic response in the first few days of therapy, with patients experiencing fewer symptoms, less congestion, and lower mortality.[44]

It has been corrected to read:

> Furthermore, the addition of 50 mg of hydrochlorothiazide per day to usual care in patients with acute decompensated heart failure was associated with improved diuretic efficiency (defined as greater weight loss per dose of intravenous furosemide); however, no statistically significant differences were observed in mortality, symptom burden, or congestion.[44]

We apologize to the readers of this article for this error.

[44]Piardi DS, Butzke M, Mazzuca ACM, et al. Effect of adding hydrochlorothiazide to usual treatment of patients with acute decompensated heart failure: a randomized clinical trial. *Sci Rep.* 2021;11(1):16474. doi:10.1038/s41598-021-96002-6

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Living Through the Scientific Revolution From Droplet to Aerosol Transmission of a Coronavirus

Joseph M. Bettag, BS; Marvin J. Bittner, MD, MSc

When SARS-CoV-2 appeared, it was thought to spread (like other coronaviruses) by macroscopic droplets.[1] Studies such as the National Football League (NFL)-Centers for Disease Control and Prevention (CDC) study, however, shifted health care workers' understanding toward a contrary view: aerosol spread.[2] This was a paradigm shift, and a humbling one. It has relevance beyond infection prevention. Indeed, it has two important messages for physicians. First, since science is continually evolving, our efforts to communicate science to the general public need to place more emphasis on communicating uncertainty. Second, it reiterates the importance of evidence-based medicine (EBM).

At the onset of the pandemic, infectious diseases specialists "knew" that, like other coronaviruses, SARS-CoV-2 spread in macroscopic droplets traveling 1 to 2 meters from a patient who sprays droplets by coughing or sneezing. Aerosol scientists disagreed, and they were right. These scientists argued that SARS-CoV-2 often spreads within a meter or two simply because the concentration of aerosol particles is higher closer to the source. However, these tiny particles sometimes remain suspended for some distance, allowing transmission to occur at greater distances. Plexiglass barriers, they noted, may shield individuals from spray droplets but also may impair ventilation, which is critical for dispersing aerosol particles.[1] By the end of 2021, this perspective was supported in the medical literature.[3] Aerosol transmission was recognized as the predominant mode of transmission, and a droplet-based model became untenable.[4]

This paradigm shift was the sort of phenomenon at the heart of Thomas Kuhn's book, *The Structure of Scientific Revolutions*, which popularized the term "paradigm shift."[1,5] Kuhn's most striking example was the shift from the Ptolemaic view of the Earth at the center of the universe to the Copernican concept of the sun at the center of the solar system. Ptolemaic astronomers struggled to explain observations of planetary movements, constructing a complex system of cycles and epicycles. For example, they thought that Mercury episodically moved in retrograde. Copernicans, however, had simpler explanations for observations such as the movements of Mercury.

Like the Ptolemaic astronomers, droplet-oriented infectious diseases specialists struggled to explain some observations. Instead of constructing systems of cycles and epicycles, they posited explanations involving ventilation patterns and air currents. Consider the superspreader event involving multiple tables in a restaurant.[6] The source of the outbreak was well over 1 meter away from some contacts. Droplets ordinarily would not travel several meters across the room; a droplet-based explanation required positing special airflow patterns from the ventilation system. Aerosol transmission, in contrast, can readily explain this event. Consider also the NFL-CDC study. Its protocols required players to wear proximity tracking devices; data showed no transmissions occurring outdoors. Yet the droplet model would predict outdoor transmission given the heavy breathing and close contact inherent in football.[2] For defenders of the droplet model, the absence of transmission on the field posed a substantial challenge. The aerosol model, however, can point to dilution of viral particles outdoors.[4] This challenge to the droplet model parallels the challenges faced by the Ptolemaic model.

Taken together, these observations suggest that we have lived through a "scientific revolution" or, as Kuhn would say, a paradigm shift.

> Kuhn reminds us that scientific concepts evolve, sometimes rapidly. This message warrants emphasis, especially when physicians communicate medical information to the public, some of whom may perceive science as a static collection of facts.

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Recognizing this paradigm shift (admittedly one with far less significance than the Copernican revolution) has more than intellectual interest alone. In his book, Kuhn elaborates a conception of science and scientific revolutions that offers two lessons directly relevant to physicians.

First, Kuhn reminds us that scientific concepts evolve, sometimes rapidly. This message warrants emphasis, especially when physicians communicate medical information to the public, some of whom may perceive science as a static collection of facts. Physicians should communicate uncertainty. Indeed, the communications chapter of the CDC's instructions for investigating an epidemic, *The CDC Field Epidemiology Manual*, advises telling the public about what remains unknown.[7]

Second, some concepts from old paradigms may still have practical utility. In identifying which concepts retain usefulness, EBM plays a crucial role. Aspects of old paradigms persist in some settings. For example, we still speak of "sunrise" and "sunset," although the apparent motion of the sun up and down is an illusion created by the Earth's rotation. Even the "flat Earth" paradigm persists in limited applications: when surveying small land areas, the curvature of the Earth is often not considered. Which infection prevention measures, grounded in the older droplet transmission paradigm, still have value in an era recognizing the importance of aerosols? For example, meningococci were historically thought to spread via droplets, and infection prevention precautions for meningococcal meningitis patients were designed with that in mind. Rooms with ordinary hospital ventilation (rather than airborne isolation rooms with negative air pressure) were considered acceptable. As the aerosol paradigm supplants the droplet paradigm for respiratory infections, should isolation practices for meningococcal meningitis change? Ultimately, evidence will answer that question for those practicing EBM. In some cases, elements of older paradigms retain value even in the peer-reviewed medical literature. Indeed, 500 years after Copernicus, the terms sunrise and sunset are still a part of our vernacular.

Financial disclosures: None declared.

Funding/support: None declared.

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"Lumbar Spine Flouro"

About the Artist

Leana Pande, DO, is a self-taught artist in watercolor, acrylic paint, gouache, pen, and other media. She is a neurology resident in the Hudson Valley, New York. She is a published artist whose work has been displayed in hospitals, galleries, and discussed on WVIA National Public Radio. She received the 2022-2023 Artist in Residence Award from the American Medical Women's Association (AMWA) and serves as the resident co-chair of the AMWA Studio Art Committee.

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The Physician Ethic

Joseph Edward Fojtik, MD, MPH

The dysfunctional status of the United States health care system persists. Proclamations that an effective, sustainable health care system is only one disruptive innovation away remain unfulfilled, and the high cost of health care, along with its inequities, inconsistencies, and inadequate quality outcomes,[1-4] continue to constrain meaningful transformation. Among several other initiatives, Donald Berwick and associates have suggested that the Triple Aim approach – improving the patient experience of care, improving the health of populations, and reducing the per capita cost of care – offers a path forward.[5] However, 17 years later, there remain insufficient data to demonstrate that the Triple Aim has had any tenable impact on the US health care system. In a previous commentary, I suggested that 3 potential barriers, among others, may confound the Triple Aim from achieving these goals: the decline of the generalist specialties, physician burnout, and unmeaningful work.[6] Of these three, unmeaningful work may be the least understood and most underestimated.

Any cognitive work associated with patient care could be considered meaningful. However, it may be unmeaningful to the physician performing that work if it is perceived to provide no clinical value. Unmeaningful work can be defined as cognitive work in a clinical encounter demanded of a physician that is not license-level appropriate, must be completed before a clinical encounter is considered complete, adds no clinical value, and acts as a barrier to care. In another commentary, I reviewed the potential adverse effects of unmeaningful work and considered 3 initial categories – Unmeaningful Work Units, Electronic Frustrations, and Redundant Layers of Complexity – and suggested that unmeaningful work may adversely affect the physician's workflow and thought processes within a cognitive space during clinical encounters. I further suggested that a new ethic should be conceptualized to define that space and mitigate the effects of unmeaningful work.[7]

> A new physician ethic could not only define cognitive space boundaries and mitigate the adverse effects of unmeaningful work but also improve physician well-being.

Defining a physician's cognitive space and the need to protect that space from unmeaningful work have thus far received little attention. Other professions have recognized this need and have utilized various elements of cognitive ergonomics, including aspects of the Yerkes-Dodson Law to protect practitioners while performing highly complex cognitive tasks.[8-10] The Yerkes-Dodson Law demonstrates empirical correlation between arousal and performance and asserts that performance decreases when stress levels are too high. Aviation safety is often cited as an example of how a profession may reduce unnecessary stress – or, by extension, unnecessary tasks – during critical phases of flight through "sterile cockpit" federal regulations. It is these potentially preventive measures that have thus far eluded medicine, and physicians remain vulnerable to increasing amounts of unmeaningful work. A new physician ethic could not only define cognitive space boundaries and mitigate the adverse effects of unmeaningful work but also improve physician well-being.

Physician burnout, with its domains of emotional exhaustion, depersonalization of patients, and a reduced sense of personal achievement, has been well described for over 20 years.[11-13] Its converse – physician well-being – has not. A formal definition of physician well-being is needed, and one element of that definition is the preservation of the cognitive space a physician must safely and consistently occupy while performing core clinical functions in a manner that does not compromise the phy-

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sician's long-term psychological and physical well-being.

Professions draw their unity, cohesiveness, and outward-facing authority in part from internal ethics. Medicine, likewise, has developed expectations of conduct that have evolved into formal ethics defining the profession, including a high standard of professionalism expected of physicians toward patients, colleagues, and society.[14,15] There is a continuum from "I will do no harm" to "The needs of the patient come first" to "A physician shall, while caring for a patient, regard responsibility to the patient as paramount."[16-18] There is, however, no ethical construct that defines the converse. Specifically, there is no ethic describing how the medical profession should treat its physicians, nor is there a formal ethic that seeks to protect physician well-being.

With no ethical precedent within the profession to develop such a construct, medicine may look elsewhere and consider how other disciplines have generated their own set of ethics. One unlikely source may be the early 20th century American conservation movement. In retrospect, by the mid-20th century it was evident that national stewardship of natural resources required a disruptive innovation due to ongoing destructive, man-made effects on the environment. A sustainable, balanced approach to land management was not widely practiced, and an ethical construct – treating the land in an ethical manner – was unknown.

Aldo Leopold, the first chair of the University of Wisconsin Department of Wildlife Management and considered the father of American conservation, radically changed that paradigm when he wrote *The Sand County Almanac*. Published in 1949, Leopold, in deceptively simple and clear logic, described the Land Ethic as "A thing is right when it tends to preserve the integrity, stability, and beauty of the biotic community. It is wrong when it tends otherwise."[19] *The Sand County Almanac* is now considered a modern classic in nature literature, and its Land Ethic is a central, cornerstone principle of contemporary land management.[20]

Medicine may now be at a similar precipice as conservation in the 1940s and may benefit from a comparable construct to develop a new ethic – the Physician Ethic – to improve physician well-being and to recognize the physician as a resource deserving protection and preservation. Borrowing liberally from Leopold, the Physician Ethic could be described as follows: "A thing is right when it tends to preserve the integrity, stability, and safety of the physician's cognitive space. It is wrong when it tends otherwise." At the risk of being perceived as overly simplistic, this ethic may serve as a new construct to protect the physician's cognitive space in clinical settings by evaluating any proposed cognitive work within this framework. If, for example, the proposed cognitive work preserves the integrity, stability, and safety of the physician's cognitive space, it may be appropriate and meaningful. If it does not, it may be inappropriate and unmeaningful.

Medicine is in an unprecedented time of transition, and it has become increasingly evident that it is unsustainable for a physician to both remain current in the medical literature and manage the ever-increasing burden of unmeaningful work. By defining and upholding the Physician Ethic, the profession can begin the long-overdue process of recognizing and protecting the physician's cognitive space and, in doing so, potentially improve physician well-being as well.

Funding/support: None declared.

Financial disclosures: None declared.

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Incarceration and Health Care in the United States

Aniketh Naidu, BS; Farzana Hoque, MD

A Real Case Scenario

A 32-year-old incarcerated man presented with abdominal pain and diarrhea. Later that day, he expressed a desire to return to prison without treatment against medical advice. A resident physician was called to evaluate the patient, who was alert and oriented. The resident informed the patient that he could not leave against medical advice due to his incarcerated status. In response, the patient became visibly agitated, asserting his right to refuse treatment and using profane language toward the resident and nursing staff. The attending physician was notified and subsequently evaluated the patient. A thorough assessment confirmed that the patient had decision-making capacity. The attending clarified that, in the absence of legal or safety-related restrictions, the patient retained the right to refuse treatment against medical advice.

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The United States has the highest incarceration rate in the world, representing only 5% of the global population but 20% of the world's incarcerated population.[1] As a result of widespread incarceration, nearly half of all American families have had a loved one incarcerated in jail or prison.[2] Incarceration is a major social determinant of health in the United States, exacerbating disparities by limiting access to care during and after imprisonment and affecting individuals, families, and communities.[3] It adversely affects health at individual, institutional, and societal levels, contributing to entrenched health disparities.[1,4] Research suggests that each year spent in prison can reduce life expectancy by up to 2 years, due to poor health care access and harsh living conditions.[4] Mental health services in correctional facilities are often underresourced, leading to untreated or misdiagnosed conditions such as depression, anxiety, posttraumatic stress disorder, and substance use disorders.[5] The opioid epidemic has disproportionately affected incarcerated populations; fewer than half of US jails offer medications for opioid use disorder (MOUD), and only 12.8% provide MOUD to all eligible individuals.[5] Racial and ethnic minorities – particularly Black individuals – face additional barriers to care, with studies linking social vulnerability and racial inequality to lower rates of MOUD access.[5] Stigma and discrimination may discourage individuals after incarceration from seeking health care, leading to poorer health outcomes.

Given the prevalence of incarceration and the high health needs of incarcerated individuals, many hospitalists care for these patients – even without working in a jail or prison. While incarcerated patients remain under the custody of the correctional system, their right to make informed decisions about medical care – including the decision to refuse treatment against medical advice – is generally upheld, provided they have decision-making capacity.[6] Exceptions may include specific legal or medical restrictions, such as court orders or risks to public safety. In the case described above, the patient was determined to have capacity, meaning he understood the risks, benefits, and alternatives involved. Ethical dilemmas frequently arise when incarcerated patients refuse court-mandated treatments. In such situations, if capacity is confirmed, their autonomy should be respected, even if their choices conflict with medical or legal directives.[6] If a patient lacks decision-making capacity, clinicians must engage surrogate decision-makers or act in the patient's

> While national organizations recognize incarceration as a significant social determinant of health, there is currently no formal requirement for correctional health content within US medical education.

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best interest, as they would for nonincarcerated patients.[6]

US medical education has traditionally offered limited training on health care for incarcerated populations, leaving clinicians underprepared to navigate the ethical and clinical complexities of their care.[7] Although some medical schools have begun integrating correctional health curricula through electives, case-based discussions, or clinical experiences, these efforts remain rare, nonstandardized, and often student-driven. While national organizations recognize incarceration as a significant social determinant of health, there is currently no formal requirement for correctional health content within US medical education.

To effectively prepare future physicians, institutions must integrate structured, justice-informed training across multiple curricular levels. Educational strategies should include didactic sessions addressing incarceration as a social determinant of health. Interdisciplinary panels featuring clinicians, legal experts, and individuals affected by incarceration can enrich learners' understanding through diverse, real-world perspectives. Clinical training should also expand to include rotations or shadowing experiences in jail-based clinics or hospital settings that frequently serve incarcerated patients. Objective Structured Clinical Examinations (OSCEs) and simulation scenarios focused on correctional health care dilemmas should be systematically incorporated to provide hands-on experience. Without formalized and widespread implementation of these educational measures, medical education will continue to fall short in preparing physicians to equitably care for this disproportionately ill and often stigmatized population. By proactively addressing the health care challenges associated with incarceration, we reaffirm our profession's commitment to justice, dignity, and equitable care for all patients.

Funding/support: None declared.

Financial disclosures: None declared.

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Visual Impairment and Living in Poverty Are Associated in Wisconsin

Breanna N. Aldred, MD; Suzanne W. van Landingham, MD

ABSTRACT

Introduction: Studies have found that the odds of visual impairment decrease as affluence increases. This retrospective cross-sectional study evaluates the association between poverty status and visual impairment in Wisconsin.

Methods: The Survey of the Health of Wisconsin (SHOW) is a household-based study that collects health and demographic data from a representative sample of Wisconsin residents. Participants with demographic, income, and vision data collected at Timepoint 1 (2008-2013) were included. Self-reported eyesight quality was categorized into visual impairment scores: none/mild, moderate, and severe. Univariable and multivariable logistic regression models, adjusting for demographic characteristics, were used to evaluate the association of visual impairment with poverty status. Longitudinal analysis investigated the relationship between visual impairment and incident poverty for participants with Timepoint 2 (2017) data.

Results: There were 3292 participants included in Timepoint 1 analysis. Multivariable analysis revealed that poverty was associated with visual impairment: compared with those with no/mild visual impairment, those with moderate visual impairment had greater odds of living in poverty [Odds Ratio (OR), 2.43; 95% CI, 1.59-3.71; $P < .001$], as did those with severe visual impairment (OR, 2.69; 95% CI, 1.26-5.72; $P = .01$). Among 706 participants in the longitudinal analysis, visual impairment was associated with incident poverty: those with moderate visual impairment were more likely to become impoverished over time compared with those without visual impairment (OR, 2.79; 95% CI, 1.01-7.77; $P = .05$).

Conclusions: Poverty is associated with subjective visual impairment in Wisconsin. Subjective visual impairment is also associated with incident poverty, suggesting a bidirectional relationship between poverty and vision impairment.

INTRODUCTION

Social determinants of health, including income, strongly influence health outcomes around the world. The Healthy People 2030 initiative of the US Department of Health and Human Services has identified social determinants of health as one of 3 priority areas for improving health in the United States,[1,2] and the World Health Organization's Commission on Social Determinants of Health (2005-2008) recommended addressing wealth inequality as an important means of improving health for global populations.[3] In ophthalmology, studies have shown that the prevalence of blindness and a country's economic development are inversely related;[4] most studies conclude that the risk of visual impairment is higher in more impoverished groups.[5,6]

Studies have found that the odds of visual impairment decrease substantially as affluence increases in many countries, suggesting that poverty increases the impairment risk.[7-12] Reversible causes of blindness, such as cataracts, are more common among individuals of lower socioeconomic status, potentially due to limited access to health care. For example, members of poorer households in 1 Nigerian study were 6 times more likely to be blind from cataracts compared to members of affluent households.[8] Access to adequate health care, such as eye exams, corrective lenses, and cataract surgery, is better in more affluent regions in multiple countries.[9,13,14] Conversely, individuals with impaired vision have been shown to have lower employment rates than the general population,[15] which may lead to higher poverty rates, suggesting a bidirectional relationship between poverty and vision

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impairment. This association between income and poverty status with visual impairment has also been noted in pediatric populations.[16,17]

Most prior research on socioeconomic risk factors for visual impairment has been conducted in other countries, but several US studies have found an inverse relationship between visual impairment and annual income.[18-21] Williams and Sahel reviewed social determinants of health as they pertain to vision in both US and international populations and cited studies showing an inverse relationship between income level and visual impairment, complexity of care, and eye care utilization.[22] Analysis of data from the National Health and Nutrition Examination Survey (NHANES) and National Health Interview Survey (NHIS) found that participants with lower income were less likely to visit eye doctors or be able to afford glasses.[23] In Wisconsin, the Beaver Dam Eye Study found that lower education and income were associated with cataract formation, need for cataract surgery, and impaired vision scores in a Wisconsin-based population examined from 1988 to 1990.[21]

Our study aimed to investigate the association between vision impairment and poverty in a contemporary Wisconsin population using data from the Survey of the Health of Wisconsin (SHOW). This study also investigates this relationship longitudinally, which, to the authors' knowledge, has not been done before. This may shed light on a link between vision impairment and incident poverty.

METHODS

Study Design

Since 2008, SHOW has conducted waves of cross-sectional and longitudinal surveys to examine social determinants of health and population health in Wisconsin adults as part of the University of Wisconsin's Real-World Evidence to Advance Community Health (REACH) program.[24,25] Individuals in households representative of the Wisconsin population were interviewed and administered questionnaires, with increased sampling of previously unrepresented groups. Survey weights were used to increase the representativeness of the data collected at Timepoint 1 (2008-2013). The survey weights incorporate design weights and adjustments for nonresponse and poststratification, calibrated to the US 2010 Census population totals by age, sex, and race.[25]

A subset of Timepoint 1 participants was resurveyed at Timepoint 2 (2017). Eligibility for Timepoint 2 participation included consenting to be contacted by SHOW for future studies and living in select counties that covered the full spectrum of urbanicity and county health rankings across Wisconsin. Certain counties and populations were selected to avoid underrepresentation and increase the generalizability of the data to the wider Wisconsin population. This study analyzes data collected at Timepoint 1 (2008-2013) and the longitudinal follow-up at Timepoint 2 (2017).

Table. Study Participant Characteristics

Variable	Frequency (%) Timepoint 1 (n = 3292)	Timepoint 2 (n = 706)
Visual impairment score		
None to mild	2887 (88%)	607 (86%)
Moderate	324 (10%)	76 (11%)
Severe	81 (2%)	23 (3%)
No response	0 (0%)	0 (0%)
Age (years), mean	47.3 (±14.4)	53.8 (±13.9)
Individual annual income (USD), mean	$37 110	$45 414
Sex		
Male	1445 (44%)	284 (40%)
Female	1847 (56%)	422 (60%)
Race/ethnicity		
Non-Hispanic White	2801 (85%)	559 (79%)
Non-Hispanic Black	232 (7%)	93 (13%)
Hispanic	107 (3%)	22 (3%)
Other/multiracial	148 (5%)	30 (4%)
No response	4 (<1%)	2 (<1%)
Education		
≤ High school education	844 (26%)	159 (23%)
> High school education	2445 (74%)	547 (77%)
No response	3 (<1%)	0 (0%)
Incarceration status		
Not incarcerated in the last year	2852 (87%)	609 (86%)
Incarcerated in the last year	40 (1%)	5 (1%)
No response	400 (12%)	92 (13%)
Insurance status		
Insured for 12 months	2769 (84%)	665 (94%)
Insured for <12 months	515 (16%)	40 (6%)
No Response	8 (<1%)	1 (<1%)
Poverty status		
Below the federal poverty level	402 (12%)	60 (8%)
Above the federal poverty level	2890 (88%)	646 (92%)
No response	0 (0%)	0 (0%)

Abbreviations: USD, US dollars.

Self-reported demographic variables analyzed in this study include age, sex, race/ethnicity, postsecondary education, history of recent incarceration, and health insurance status. A participant was considered to have an incarceration history if they reported jail or other institutional detention in the previous 12 months. A participant was considered to have health insurance if they reported coverage for all 12 months of the previous year.

Poverty status was determined by comparing the participant's reported combined household income from the previous 12 months (before taxes) with the reported number of people supported by that income. This was then compared to the federal poverty level (FPL) of the year of data collection.[26]

To assess vision, participants were asked, "At the present time, would you say your eyesight, with glasses or contact lenses, if you wear them, is excellent, good, fair, poor, or very poor?" Participant responses were grouped into visual impairment scores: "excellent" and "good" were categorized as "No/Mild Visual Impairment;" "fair" as "Moderate Visual Impairment;" "poor" and "very poor"

as "Severe Visual Impairment." This question originated from NHANES.[27]

The study population excluded SHOW participants who did not respond to either the household income question or the subjective visual quality question. The longitudinal analysis excluded participants who did not respond to both questions at both timepoints.

The SHOW protocol and informed consent documents were approved by the University of Wisconsin-Madison Health Sciences Institutional Review Board. This study adhered to the tenets of the Declaration of Helsinki.

Figure 1. Visual Impairment Scores of Participants Living Above the Federal Poverty Level (A) and Below the Federal Poverty Level (B) at Timepoint 1

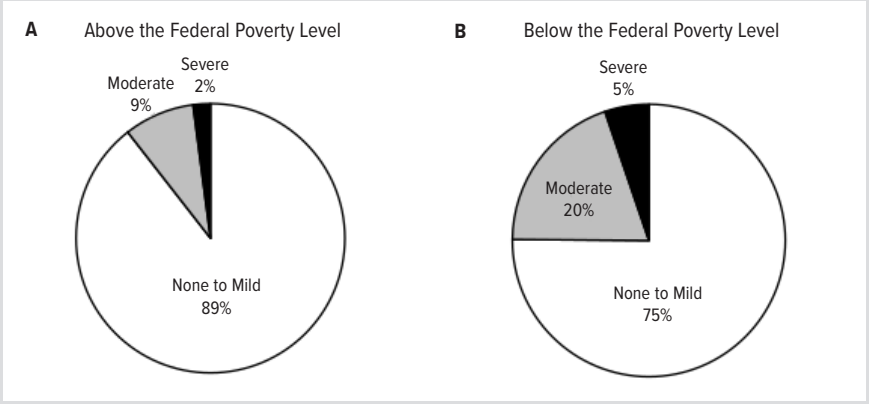
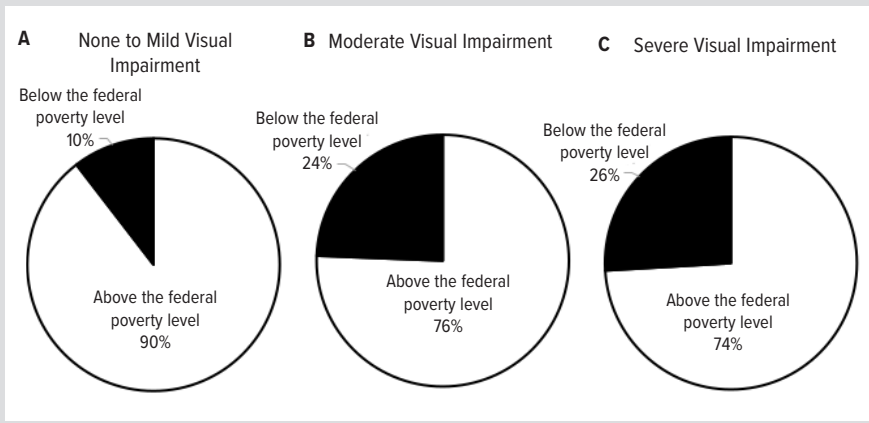


Figure 2. Poverty Status of Participants With No or Mild Visual Impairment (A), Moderate Visual Impairment (B), and Severe Visual Impairment (C) at Timepoint 1



Statistical Analysis

StataSE 17.0 (StataCorp LLC) was used for data analysis. Chi-square analysis was used to compare demographic characteristics between our study population and the full SHOW group. Univariable and multivariable logistic regression analyses utilizing survey weights were used to compare vision and demographic variables to poverty status at Timepoint 1. The longitudinal analysis involved univariable and multivariable logistic regressions comparing visual impairment scores at Timepoint 1 with incident poverty from Timepoint 1 to Timepoint 2. Poverty at Timepoint 1 was also compared with incident visual impairment at Timepoint 2. Statistical significance was defined as $P \leq .05$ for this hypothesis-generating study.

RESULTS

Population Characteristics

A total of 3292 participants were included in the Timepoint 1 analysis (97% of the 3380 total SHOW participants). A total of 706 participants were eligible for the longitudinal analysis (97% of the 725 total longitudinal SHOW participants).

Population characteristics are displayed in the Table. Age and income data were normally distributed. Most participants were female, non-Hispanic White, had more than a high school education, no incarceration history, health insurance, and income above the FPL. There were no significant demographic differences between our study population, and the total SHOW population or among our Timepoint 1 and Timepoint 2 subgroups.

Of the individuals living above the FPL at Timepoint 1, 89% had no/mild visual impairment, 9% had moderate visual impairment, and 2% had severe visual impairment. Of the individuals living below the FPL at Timepoint 1, 75% had no/mild visual impairment, 20% had moderate visual impairment, and 5% had severe visual impairment (Figure 1). At Timepoint 1, of the individuals with no or mild visual impairment, 90% lived above the FPL and 10% lived below. Of those with moderate visual impairment, 76% lived above the FPL and 24% lived below. Of those with severe visual impairment, 74% lived above the FPL and 26% lived below (Figure 2).

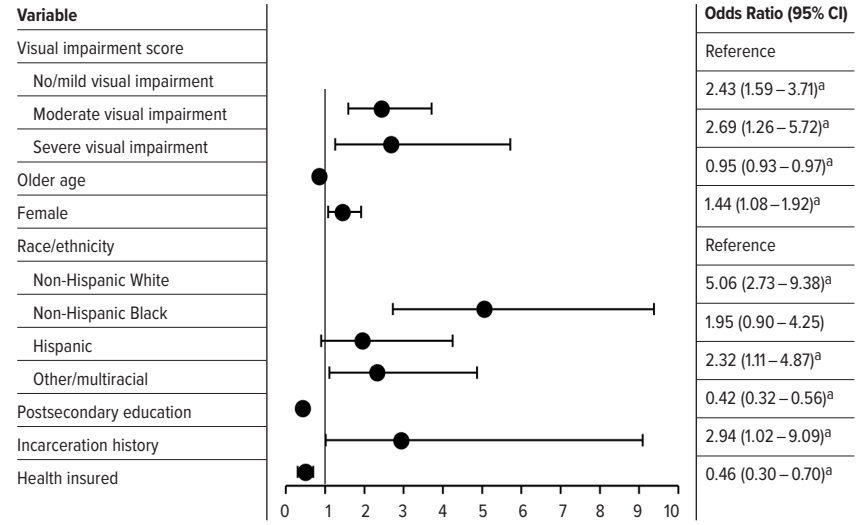
Timepoint 1 Analysis

Univariable logistic regression found that younger age, female sex, non-Hispanic Black and other/multiracial race/ethnicity, lack of postsecondary education, incarceration history, and lack of health insurance were all significantly associated with poverty.

A multivariable logistic regression model was built to evaluate the association between poverty and visual impairment, adjusting for age, sex, race/ethnicity, educational attainment, incarceration history, and health insurance status (Figure 3). Individuals with moderate and severe visual impairment were 2.43 times (OR, 2.43; 95% CI, 1.59-3.71; $P < .001$) and 2.69 times (OR, 2.69;

95% CI, 1.26-5.72; $P = .01$) more likely to live in poverty than those with no/mild visual impairment, respectively. Younger age, female sex, non-Hispanic Black and other/multiracial ethnicity, lack of post-secondary education, and incarceration history were all also associated with living in poverty in the multivariable model.

Figure 3. Odds Ratios for Living Below the Federal Poverty Level at Timepoint 1 in a Multivariable Analysis That Included All Variables LIsted



a$P < .05$.

Longitudinal Analysis

Incident poverty (poverty at Timepoint 2 but not Timepoint 1) was compared with baseline vision and demographic characteristics. Twenty-two participants (3% of the longitudinal study population) fell below the poverty line between Timepoint 1 and Timepoint 2. In a univariable analysis, participants with moderate visual impairment were 3.26 times more likely to enter poverty than those with no or mild visual impairment (OR, 3.26; 95% CI, 1.23-8.69; $P = .02$). Those with severe visual impairment were also 3.26 times more likely to enter poverty (OR, 3.26; 95% CI, 0.40-26.77; $P = .27$), though this was not statistically significant.

After adjusting for age, sex, race/ethnicity, and educational attainment, individuals with moderate visual impairment were 2.79 times more likely to become impoverished over time compared to those with no or mild visual impairment (OR, 2.79; 95% CI, 1.00-7.77; $P = .05$). Those with severe visual impairment were 2.84 times more likely to become impoverished (OR, 2.84; 95% CI, 0.32-25.0; $P = .35$), which was not statistically significant. Other demographic variables were not associated with incident poverty.

Incident visual impairment (worse visual impairment score at Timepoint 2) was also compared with baseline poverty status. Participants with baseline poverty were 2.95 times more likely to report a subjective decrease in vision between timepoints (OR, 2.95; 95% CI, 1.64-5.34; $P < .001$). However, after adjusting for age, sex, race/ethnicity, and post-secondary education, this relationship was no longer significant (OR, 1.87; 95% CI, 0.89-3.92; $P = .10$).

DISCUSSION

In this representative sample of Wisconsin adults, visual impairment is associated with both prevalent and incident poverty. Severe visual impairment showed a stronger association with poverty than mild impairment. The association with prevalent poverty is consistent with previous studies showing higher visual impairment risk in impoverished groups,[4-6] including the Beaver Dam Eye Study.[21] Our study also confirms that certain demographic factors—younger age, female sex, non-White ethnicity, lower educational attainment, incarceration history, and lack of health insurance—carry increased odds of living below the FPL, consistent with US Census Bureau data.[28]

Previous studies exploring the relationship between visual impairment and poverty have not investigated this relationship longitudinally. This study identified a positive association between moderate visual impairment and incident poverty. Lower employment rates among individuals with visual impairment may drive these higher poverty rates.[15] After controlling for demographics, we did not find a significant relationship between baseline poverty and incident vision impairment, suggesting that vision loss may be a driver of low income rather than the inverse.

Several mediators may influence this bidirectional relationship. For example, low vision may hinder job acquisition, and employment support for visually impaired workers may be inadequate. Furthermore, workers with low vision may require more medical leave. Conversely, impoverished individuals may have higher levels of visual impairment due to increased rates of eye disease, including conditions like cataracts and diabetic retinopathy,[8,21,29] coupled with decreased access to health care, corrective lenses, and cataract surgery.[9,13,14] Implementing or expanding routine vision screening programs for adults may help bridge this gap by identifying impairment early and connecting high-risk individuals with both ophthalmic care and social services.[30] Chronic stress from poverty may also exacerbate systemic illnesses such as diabetes and hypertension, further affecting ocular health. The association between visual impairment and poverty status is surely complex and merits further consideration.

Limitations

A primary limitation of this study is the use of subjective vision status. While studies have shown that self-reported vision assessments are a suitable indicator of visual impairment when compared with visual acuity testing,[31] some studies suggest that they can be subject to bias. For instance, a study examining the concordance of self-reported vision status and visual acuity found that Black participants and those with lower educational attainment were more likely to be "visually optimistic," reporting higher vision scores despite worse objective acuity.[32] Age has also been shown to cause discrepancies in self-reported vision status, with older individuals underestimating their visual impairment.[33,34] A recent study found that sex, ethnicity, income status, additional medical comorbidities, and depressive and anxiety symptoms also influence self-reported vision impairment.[34] However, the cohort in that study differs from our study population as it only included individuals over age 65 insured by Medicare and may disproportionately exclude individuals at the extremes of income and those who are not insured.

Thus, while it has limitations, self-reported vision status has been widely used to estimate visual impairment and validated in national surveys, such as NHANES, and is often the only measure of visual impairment available in large population-based health surveys.[27,35]

Another study limitation is that the Timepoint 2 analysis included a smaller sample size than the Timepoint 1 analysis, potentially introducing response bias. However, the demographic characteristics of our study groups did not differ significantly from the baseline SHOW population. The lack of survey weights for Timepoint 2 and nuanced clinical health information may further limit the generalizability of the data to the overall Wisconsin population and our ability to determine the reason for participants' visual impairment.

CONCLUSIONS

Vision impairment is associated with prevalent and incident poverty in this contemporary, representative Wisconsin population. Recognizing the health characteristics that increase poverty risk is essential for making systemic changes to address these disparities and creating a more equitable system. These findings support the need for and value of state and federal programs for individuals with visual impairment and suggest a need for employment support. Furthermore, expanding vision screening or recommending routine visual screening for adults may help identify visual impairment and connect individuals with ophthalmic care and social services. Further research is needed to characterize potential mediators and confounders in the association between vision impairment and poverty.

Financial disclosures: None declared.

Funding/support: Research reported in this publication was supported by the Real-world Evidence to Advance Community Health (REACH) program, which is funded by federal grants (70%) and by nongovernmental sources (30%). The program receives funding from the National Institute of Environmental Health Sciences (U24ES036005) and the National Cancer Institute (P30CA014520) of the National Institutes of Health (NIH). The content of this publication is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. This work was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc to the University of Wisconsin School of Medicine and Public Health Department of Ophthalmology and Visual Sciences. The sponsor or funding organization had no role in the design or conduct of this research.

Acknowledgments: The authors would like to thank the University of Wisconsin School of Medicine and Public Health as well as the study participants for their contributions.

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Multidisciplinary Bedside Huddles Reduce Readmissions in High-Risk Patients

Lara Voigt, MD; Brian Hilgeman, MD; Ankur Segon, MD, MPH

ABSTRACT

Introduction: Readmission rates have a significant impact on hospital systems, from financial performance to patient satisfaction. Determining efficient, effective interventions to reduce readmission rates is imperative to improving hospital and patient outcomes.

Objectives: To develop and evaluate a multidisciplinary discharge process for high-risk patients that is cost-effective, achieves high uptake in a large academic health center, and decreases readmissions.

Methods: A multiphase intervention was implemented at a large academic hospital. The Phase 1 pilot, performed on a single inpatient unit, implemented a multidisciplinary bedside huddle 24 to 48 hours prior to discharge for patients at high risk for readmission based on a previously validated risk score.

Results: Phase 1 showed a reduction in readmission rates for high-risk patients from 36% (preintervention) to 20% (post-intervention). In Phase 2, the huddle was expanded to 2 units: 1 "opt-in" and 1 "opt-out." Huddle uptake was higher on the opt-out unit (89% vs 4%) and associated with lower readmission rates for patients receiving huddles (20.9% vs 40%) and for those on the opt-out unit (28.3% vs 38.7%). In Phase 3, the huddle was expanded to all units and showed a sustained lower readmission rate for those receiving a predischarge huddle than those who did not (26.13% vs 33.78%).

Conclusions: For patients at high risk of readmission, a predischarge multidisciplinary bedside huddle utilizing an opt-out implementation model reduces readmissions.

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INTRODUCTION

Readmission rates and efforts to decrease them have been persistent challenges for medical institutions for decades. With the initiation of Hospital Readmissions Reduction Program (HRRP) penalties for excess 30-day readmissions in 2010, hospital systems have focused increasingly on decreasing these rates. In a retrospective financial analysis at our institution for 2017, preventing a readmission was found to save an average of $9396 per patient. Baldwin et al[1] found that over $9 million was spent on 153 patients with 4 or more nonelective or nonplanned admissions over a 6-month period. In that study, readmission rates significantly decreased within this high-utilization group following implementation of a post-discharge, multidisciplinary care team program focused on improving patient communication, medication reconciliation, and outpatient follow-up. This discharge clinic translated to a savings of more than $330,000 per patient.

Not only is there a negative financial impact on health systems for readmissions deemed avoidable, unplanned readmissions also signal poor quality of care and have been associated with lower patient satisfaction scores, longer length of stay, higher mortality, and increased resource use.[2-4] Studies have found that readmission causes are highly variable and include lack of scheduled follow-up, lack of awareness of post-discharge contact points, and a higher number of comorbidities.[5,6] It can be postulated that an interdisciplinary care conference focusing on these items prior to discharge may help these risks.

Just as the causes of readmissions are highly variable, so are the strategies to decrease readmissions. Examples include predischarge patient education, pharmacy-led medication reconciliation and education, transitional programs bridging the pre- and post-discharge gap, and post-discharge tools such as follow-up phone calls and in-person transitional care clinics. In a review by Braet et al,[7] the most successful intervention models incorporated both pre-discharge and post-discharge elements and patient activation. Coffey et al[8] also found that programs beginning before discharge were most successful. In a 2-phase multidisciplinary care coordination intervention incorporating daily inpatient evaluation with subsequent outpatient care coordination until the first follow-up, Labrada et al[9] found a 50% decrease in 30-day readmissions (from 23% to 11%). Often these successful interventions are intensive; Goodwin et al[10] found that while programs showed short-term success, many demonstrated regression to the mean over time.

Evidence suggests that the most effective methods of decreasing readmissions in high-risk populations include a multidisciplinary group to bridge the discharge gap. Multidisciplinary huddles have been used in the inpatient setting to improve quality outcomes – including length of stay, patient safety, and team communication[11-19] – but not specifically to reduce readmissions.

This report describes the phased development of a predischarge huddle process at an academic institution and its impact on 30-day readmission rates among high-risk patients.

METHODS

Setting

The facility is a 550-bed academic medical center with 3 dedicated general internal medicine units. Overall readmission rates for internal medicine teams ranged from 15% to 23% from September 2015 through December 2019.

Readmission Risk Tool

The Hospital Admission Readmission Risk Discriminator (HARRD) score was developed internally to identify patients at high risk of readmission. The score incorporates multiple measures easily extracted from the electronic health record and based on determinants of readmission risk (Table). Scores ranged from 0 to 5; higher scores indicated higher risk. The area under the receiver operating characteristic curve (ROC) of the HARRD score was 0.86. For patients with a score of 4 or 5, readmission risk was 36%. It was this high-risk population that was targeted for intervention.

Phase 1: Single Unit Pilot

In Phase 1, a small pilot study was conducted on 1 inpatient unit as a proof of concept. A bedside huddle was convened 24 to 48 hours prior to discharge for patients with a HARRD score of 4 or 5. The multidisciplinary bedside huddle team consisted of the patient's primary inpatient clinician (attending physician, advanced practice provider, or internal medicine resident), bedside nurse, charge nurse, pharmacist, case manager or social worker, and physical or occupational therapist. Charge nurses led the huddle.

Table. Components of the Hospital Admission Readmission Risk Discriminator Score

Component	Weight
Emergency department visits ≥ 3 in past 6 months or ≥ 1 inpatient readmission(s) within the last 90 days	2 points
≥ 2 chronic diseases: diabetes, congestive heart failure, COPD, liver disease, dementia, connective tissue disease, HIV, stroke, peripheral vascular disease, cancer, psychiatric diagnosis (bipolar, schizophrenia, depression)	1 point
Age > 65	1 point
>10 medications	1 point

Abbreviations: COPD, chronic obstructive pulmonary disease.

A standardized questionnaire assessing patient and family concerns about the discharge process was completed. Concerns were addressed on a priority basis, followed by education on expected disease course, symptoms and management, medication management, hospital follow-up, and the role of family and caregivers. Following the huddle, the charge nurse documented completion and attendance in the electronic medical record (Figure 1). Patients discharged to a facility were excluded. This pilot occurred from July through September 2017.

Phase 2: Two Units

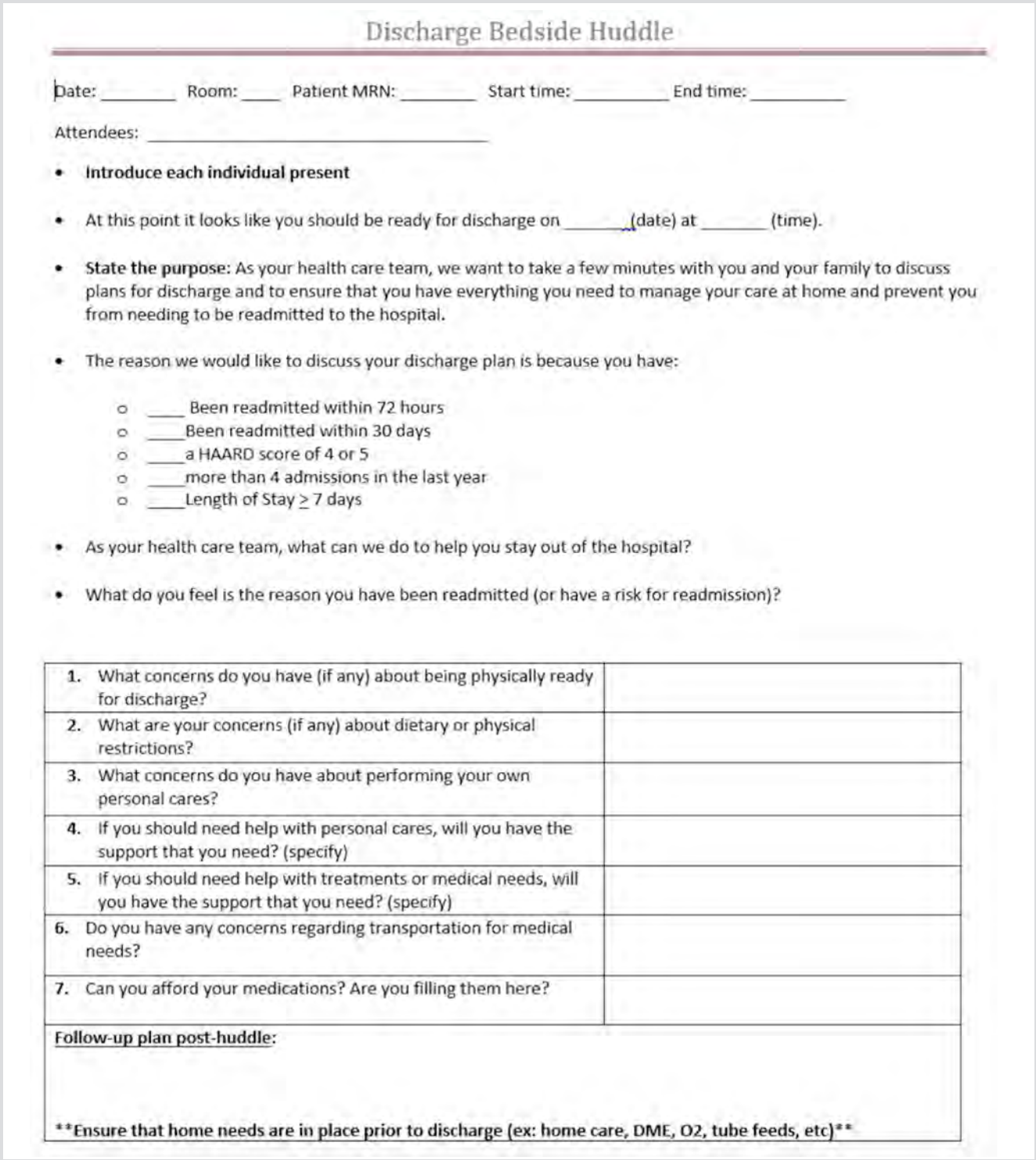
The time needed for the charge nurse to coordinate all multidisciplinary team members for huddle attendance was a challenge in Phase 1. To target patients most likely to benefit from the huddle, the team implemented an opt-in model when expanding to a second unit during Phase 2 (September 2017 to January 2018).

Phase 3: Expansion to All Medicine Units

In Phase 3, huddles were extended to all medicine units using an opt-out approach due to low engagement in the opt-in pilot. To capture the maximum number of patients at high risk of readmission, the following criteria for huddles were added: patients readmitted within 30 days, patients with 4 or more readmissions within 30 days, unanticipated length of stay greater than 7 days, and patients refusing recommended discharge disposition. These criteria were chosen based on institutional data demonstrating high readmission risk. Conversely, certain specialty populations who already had excellent post-discharge follow-up, such as those followed by the sickle cell team, were excluded (see Supplemental Figure).

The care team could also include patients who did not meet inclusion criteria if a team member was concerned about readmission risk. We modified the standardized questionnaire based on team input, adding new questions specifically exploring the patient's discharge needs and eliminating questions related to the

Figure 1. Modified Checklist Used for Bedside Huddles for Phase 3



Discharge Bedside Huddle

Date: _____ Room: ____ Patient MRN: _____ Start time: _____ End time: _____

Attendees: _____

- **Introduce each individual present**
- At this point it looks like you should be ready for discharge on _____(date) at _____ (time).
- **State the purpose:** As your health care team, we want to take a few minutes with you and your family to discuss plans for discharge and to ensure that you have everything you need to manage your care at home and prevent you from needing to be readmitted to the hospital.
- The reason we would like to discuss your discharge plan is because you have:
  - ____ Been readmitted within 72 hours
  - ____Been readmitted within 30 days
  - ____a HAARD score of 4 or 5
  - ____more than 4 admissions in the last year
  - ____Length of Stay ≥ 7 days
- As your health care team, what can we do to help you stay out of the hospital?
- What do you feel is the reason you have been readmitted (or have a risk for readmission)?

1. What concerns do you have (if any) about being physically ready for discharge?	
2. What are your concerns (if any) about dietary or physical restrictions?	
3. What concerns do you have about performing your own personal cares?	
4. If you should need help with personal cares, will you have the support that you need? (specify)	
5. If you should need help with treatments or medical needs, will you have the support that you need? (specify)	
6. Do you have any concerns regarding transportation for medical needs?	
7. Can you afford your medications? Are you filling them here?	
Follow-up plan post-huddle:	
****Ensure that home needs are in place prior to discharge (ex: home care, DME, O2, tube feeds, etc)****	

expected medical course (Figure 1). Patients discharged to a facility who otherwise met huddle criteria were no longer excluded to reduce the likelihood of readmission. So that any team member could lead a huddle, we developed scripting as part of the education process. Finally, the charge nurse and clinician were given flexibility to hold a modified huddle with fewer team members for patients with limited discharge needs (eg, excusing social workers or case managers for patients being discharged home without support services). The overall process is shown in the Supplemental Figure.

Data Analysis

Readmission was defined as an unplanned admission within 30 days of discharge. Patients discharged to hospice were excluded. Comparison populations differed by phase: Phase 1 used histori-

cal controls; Phases 2 and 3 prospectively compared patients who received a huddle with those on the same units who did not.

Ethical Approval

The host institution's institutional review board considered the study exempt, as it was a quality improvement project rather than research.

RESULTS

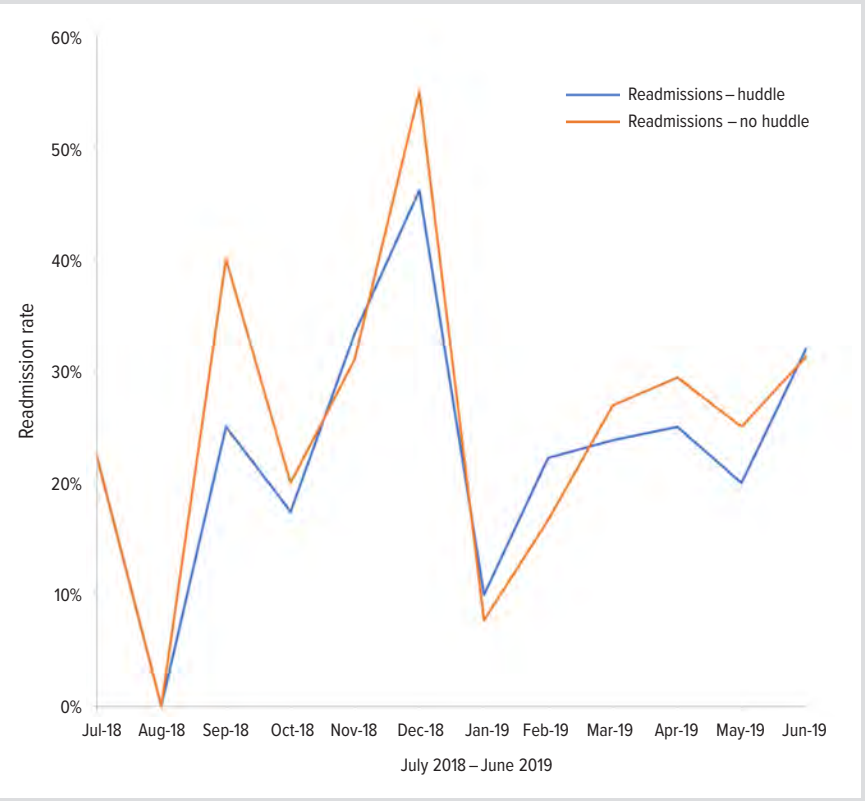
Phase 1

Thirty-four huddles were conducted over 2 months. The 30-day readmission rate for patients receiving a huddle was 20%, compared with the historical 36% readmission rate for patients with a HAARD score of 4 or 5 at our institution.

Phase 2

In Phase 2, readmission rates were compared between patients who were eligible for and received a huddle and those who were eligible but did not receive one. A total of 43 huddles were performed across both units over 5 months. The overall readmission rate was lower among high-risk patients who received a bedside huddle versus those who did not (20.9% vs 41%). Significantly fewer huddles were held on the opt-in unit (4% vs 89% of eligible patients). The 30-day readmission rate for high-risk patients on the opt-in unit was 38.7%, compared with 28.3% on the opt-out unit.

Figure 2. Comparison of Readmission Rates Over Time for Huddled vs Not Huddled Patients



Phase 3

In Phase 3, 79.5% of eligible patients (287/361) received a huddle. The 30-day readmission rate in high-risk patients who received a huddle was ` among those who did not (Figure 2).

DISCUSSION

This phased, purposeful deployment demonstrates that multidisciplinary bedside huddles prior to discharge can achieve high uptake and measurable reductions in readmissions for high-risk patients.

Given the complexities of an academic health center – including multiple co-occurring readmission reduction tactics and competing priorities – the 79% uptake is impressive. This likely resulted from the intervention's slow, purposeful, and human-centered deployment. Multiple stakeholders were involved in the project's initial design, and weekly input from all members of the multidisciplinary team was sought during the implementation of each phase. Key changes included allowing more flexibility regarding team attendance and questionnaire content. Incorporating staff and provider input on patient selection was important to improve uptake. Furthermore, automating this process with clear inclusion and exclusion criteria was important. Support and buy-in from hospital leadership was essential, as was support from hospital leadership. The chief quality officer and chief nursing officer sponsored the project and leveraged necessary institutional resources, while the medical director of nursing and hospitalist directors co-led the project and helped maintain frontline staff engagement.

Phase 2 highlighted the impact of opt-in versus opt-out strategies on uptake and readmissions. An opt-in strategy led to significantly lower huddle uptake and a subsequent increase in readmission rates. Our findings align with previous studies showing higher uptake with opt-out versus opt-in approaches in outpatient settings. While both approaches honor participant autonomy, decision-makers often prefer the default plan of care over interventions offered as a choice. This status quo bias[20] has been observed in a variety of settings ranging from organ donation[21] to retirement savings.[22] In addition to improving patient engagement, the opt-out approach is preferred by clinicians in the outpatient setting as it reduces task load and saves time.[23] Our study shows that an opt-out strategy is a more robust method for deploying interventions in a complex inpatient environment as well.

Our intervention has opportunities for improvement as we grow this process. Expansion to nonmedicine units will be important, as other specialties face different barriers and needs. For instance, addressing postoperative wound care, diet, and activity instructions will be important for surgical units. Streamlining this process with other health system interventions is also necessary; for example, understanding how huddle findings can be communicated to outpatient clinics and care coordination teams will be essential. Furthermore, while our huddle process showed success, existing literature suggests that measurable and sustained reductions in readmissions often require a comprehensive "bundle' of multiple interventions rather than a single process change.[25,26] Additionally, understanding why patients opt out of the intervention may reveal how we can better engage and support them.

Limitations

This study has limitations, including its retrospective, observational nature, which introduces selection bias. Furthermore, multiple concurrent readmission reduction tactics—including increased outpatient follow-up scheduling, care coordination telephonic outreach post-discharge for select populations under risk-based contracts, and care coordination rounds on all units—may confound our analysis. Exposure to multiple concurrent interventions is a known challenge in interpreting the results of process improvement studies.[24]

We deployed several strategies to address this challenge. Our comparison of opt-in and opt-out groups in Phase 2 involved 2 medicine units equally exposed to these confounders. While we could not statistically adjust for all confounders, our intervention targeted a unique patient population, ie, high-risk patients, whereas other prevailing readmission reduction tactics were deployed more broadly. The consistent reduction in readmission rates across all 3 phases supports the validity of our conclusions.

CONCLUSIONS

Our intervention demonstrates that a systematic, iterative, and data-driven quality improvement initiative can improve the process and uptake of multidisciplinary bedside huddle communication at discharge. Our stepwise approach led to a system-wide intervention that reduced high-risk readmissions. While our findings underscore the value of predischarge communication, achieving sustained improvements in readmission rates likely requires integrating these huddles into a broader bundle of transitional care interventions. Future studies should evaluate the best methods to synchronize bedside huddles with other system-wide tactics. It will be important to study the impact of our intervention on surgical units before hospital-wide implementation. Finally, a qualitative approach could yield deeper insights into why high-risk patients elect to opt out of predischarge huddles.

Financial disclosures: None declared.

Funding/support: None declared.

Supplemental Figure: Available at www.wmjonline.org in the Appendix.

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Clinical Presentation and Diagnostic Patterns of Multisystem Inflammatory Syndrome in Children in a Pediatric Emergency Department

Alexander B. Rosiejka, MD; Danny G. Thomas, MD, MPH; Mark Nimmer, BA; Patrick S. Walsh, MD, MS

ABSTRACT

Introduction: Multisystem inflammatory syndrome in children (MIS-C) is a severe postinfectious complication of COVID-19, and diagnosis remains challenging because of overlapping features with other illnesses. We sought to describe emergency department (ED) evaluations of children with suspected MIS-C at a southeast Wisconsin pediatric referral center and to identify factors that distinguish MIS-C from alternative diagnoses.

Methods: This retrospective study included children evaluated for MIS-C in the Children's Wisconsin ED from July 2020 through December 2022. We compared clinical and laboratory characteristics of children diagnosed with MIS-C with those of children with alternative diagnoses and used logistic regression to identify factors associated with MIS-C.

Results: Among 792 children evaluated, 86 (11%) were diagnosed with MIS-C; case counts declined over time. Children with MIS-C were older (median age, 7.4 vs 2.9 years; $P < .001$) and had greater odds of cardiac (OR, 50.4; 95% CI, 27.4–96.4), mucocutaneous (OR, 3.57; 95% CI, 2.18–6.04), gastrointestinal (OR, 2.36; 95% CI, 1.36–4.36), and hematologic (OR, 8.81; 95% CI, 5.41–14.4) system involvement than children with other diagnoses. Odds of MIS-C were reduced among children with a positive non-COVID-19 viral test (OR, 0.12; 95% CI, 0.02–0.41), but alternative diagnoses made before the ED visit were not associated with MIS-C risk.

Conclusions: In this cohort of children evaluated for MIS-C in southeast Wisconsin, specific symptoms aligned with MIS-C diagnostic criteria were associated with increased odds of MIS-C, whereas positive non-COVID-19 viral tests were associated with alternative diagnoses. These findings may assist clinicians in risk stratification and diagnostic decision-making for children with suspected MIS-C in the emergency department setting.

INTRODUCTION

Multisystem inflammatory syndrome in children (MIS-C) is a life-threatening post-viral inflammatory illness that emerged during the COVID-19 pandemic, prompting widespread screening among pediatric patients.[1,2] As of April 2024, nearly 9700 cases of MIS-C had been confirmed in the United States,[3] with up to 59% requiring intensive care unit admission,[4] and 79 reported deaths.[3] As the pandemic transitions into an endemic phase, MIS-C is expected to become a more sporadic and infrequent diagnosis. Nonetheless, its potential for severe illness remains a critical clinical concern. The goal of this study was to evaluate our institutional MIS-C screening experience to identify factors that may help refine and improve future screening processes.

Early and appropriate treatment of MIS-C is essential to mitigate morbidity. First-line treatment often involves the use of both intravenous immune globulin and high-dose glucocorticoids.[5] However, it remains difficult to distinguish MIS-C from other acute presentations in the emergency department (ED), including Kawasaki disease, sepsis, or common viral infections.[6] The Centers for Disease Control and Prevention (CDC) has published a case definition for MIS-C that includes fever, hospitalization for severe illness, elevated C-reactive protein (CRP), and evidence of inflammation affecting at least 2 systems, including cardiac, mucocutaneous, gastrointestinal, hematologic, or shock-related involvement.[7] Many of these symptoms are nonspecific, and their ability to accurately distinguish MIS-C from illnesses in

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the ED setting has not been well described. Similarly, it is unclear whether other pertinent historical or examination findings may aid ED clinicians when attempting to rule out MIS-C.

ED providers must be able to distinguish children with MIS-C from those with other common illnesses and infections to ensure timely treatment while avoiding unnecessary resource utilization.[6,8] Accordingly, the objectives of this study were to describe a cohort of children evaluated in the ED for suspected MIS-C and to determine differences in clinical presentation and initial laboratory evaluation between those eventually diagnosed with MIS-C and those with alternative diagnoses.

METHODS

Study Design, Setting, and Population

This was a single-center, retrospective observational study of children evaluated for MIS-C in the Children's Wisconsin ED from July 1, 2020, through December 31, 2022. Children's Wisconsin is a tertiary pediatric referral center serving southeast Wisconsin, and its dedicated pediatric ED has more than 70 000 visits annually. The Institutional Review Board of the Medical College of Wisconsin approved this study.

We included children younger than 18 years who were assessed for MIS-C in the ED, defined as any child for whom the institutional MIS-C order panel was utilized. The MIS-C order panel could be employed at the clinician's discretion if there was clinical suspicion for MIS-C. The panel was developed based on CDC case reports and definitions for MIS-C published in May 2020.[7]

The tests included in the order panel were a complete blood cell count (CBC), comprehensive metabolic panel (CMP), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), troponin, and COVID-19 polymerase chain reaction (PCR) and antibody tests. COVID-19 PCR testing was used to assess for acute or recent SARS-CoV-2 infection, whereas COVID-19 antibody (immunoglobulin G) testing was used as a marker of prior COVID-19 infection. Based on initial results, second-line testing and hospital admission were recommended.

We excluded children who were transferred from other hospitals, those receiving chronic immunosuppression or chemotherapy, those with congenital heart disease, and those with a previous diagnosis of MIS-C.

Data Collection

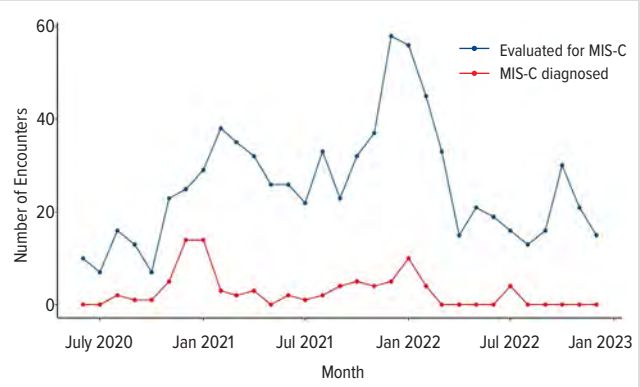
Study data for all patients meeting inclusion criteria were collected and managed using Research Electronic Data Capture (REDCap) hosted at the Medical College of Wisconsin.[9,10] REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation; (3) automated export procedures to common statistical packages; and (4) tools to support data integration and interoperability with external sources.

Table 1. Demographics of Children Evaluated for MIS-C

Characteristic	No MIS-C N = 706[a]	MIS-C N = 86[a]	*P value*[b]
Age, years	2.9 (1.3–6.7)	7.4 (4.4–11.1)	<.001
Sex			>.9
Female	333 (47%)	41 (48%)	
Male	373 (53%)	45 (52%)	
Race			0.2
American Indianor Alaska Native	2 (0.3%)	0 (0%)	
Asian	35 (5%)	1 (1%)	
Black	187 (26%)	30 (35%)	
Hawaiian or Pacific Islander	2 (0.3%)	1 (1%)	
Multiple races	38 (5%)	4 (5%)	
Unknown	27 (4%)	5 (6%)	
White	415 (59%)	45 (52%)	
Ethnicity			0.4
Hispanic or Latino	162 (23%)	15 (17%)	
Not Hispanic or Latino	533 (75%)	69 (80%)	
Unknown	11 (2%)	2 (3%)	
Primary insurance			0.8
Commercial	305 (43%)	37 (43%)	
Public	395 (56%)	48 (56%)	
Self-pay	6 (1%)	1 (1%)	
Emergency department disposition			<.001
Discharge	388 (55%)	0 (0%)	
Hospital admission	318 (45%)	86 (100%)	

[a]Median (interquartile range); n (%).
[b]Wilcoxon rank sum test; chi-square test; Fisher exact test.
Abbreviation: MIS-C, multisystem inflammatory syndrome in children.

Figure. Emergency Department Encounters With MIS-C Testing and Diagnosis by Month



Objective variables, including patient demographics, laboratory test results—including CBC, CRP, troponin, COVID-19 PCR and antibody testing, and any respiratory viral panel results—and ED disposition, were populated directly into REDCap. Manual chart review was performed to obtain clinical variables, including history of present illness, physical examination findings, recent diagnoses, treatments administered, and final discharge diagnosis. Patients were classified as having MIS-C if the diagnosis was documented by the treating team at the time of discharge. The study

team reviewed all cases manually to confirm a clinical diagnosis of MIS-C, rather than reliance on discharge codes alone. We did not independently apply a uniform diagnostic algorithm, as the objective was to assess real-world screening and diagnostic practices rather than retrospectively apply standardized criteria that may have evolved over the study period.

Analysis

We first described demographic characteristics of the cohort, comparing patients with and without a final diagnosis of MIS-C using chi-square tests for categorical variables and Wilcoxon rank sum tests for continuous variables. We calculated the number of monthly encounters in which MIS-C was evaluated for and diagnosed and illustrated the pattern over the study period.

Next, we evaluated the performance of each variable included in the CDC case definition for MIS-C.[7] CDC clinical criteria include fever, severe clinical illness, elevated CRP (>3.0 mg/dL), and involvement of at least 2 organ system categories: cardiac, mucocutaneous, shock, gastrointestinal, and hematologic. We used univariate logistic regression to compare the odds of meeting each criterion between patients who were diagnosed with MIS-C and those with an alternative final diagnosis. Analyses were conducted for both overall system categories and individual symptoms within each category.

Because acute viral infections are a common cause of febrile illness in children and may mimic MIS-C, we performed a sensitivity analysis limiting the comparison group to children with positive viral tests for respiratory viruses other than COVID-19 (eg, influenza, adenovirus). Children with positive COVID-19 PCR tests were excluded from this analysis because of the difficulty distinguishing acute SARS-CoV-2 infection from residual viral RNA detection during MIS-C, and because COVID-19 PCR positivity is included in the CDC MIS-C diagnostic criteria.

Finally, we analyzed additional variables

Table 2. Presence of CDC MIS-C Diagnostic Criteria in Children With and Without MIS-C

Characteristic	N	No MIS-C, N = 706[a]	MIS-C, N = 86[a]	OR for MIS-C Diagnosis OR	95% CI	*P* value
C-reactive protein >3.0 mg/dL	766	274 (40%)	80 (93%)	23.8	10.5–68.3	<.001
Cardiac involvement	762	19 (3%)	51 (59%)	50.4	27.4–96.4	<.001
Cardiac function; decreased	792	6 (0.8%)	23 (27%)	42.6	17.8–119	<.001
Coronary artery involvement (echocardiogram)	792	1 (0.1%)	10 (12%)	92.8	17.4–1714	<.001
Troponin elevated	762	14 (2%)	38 (44%)	37.4	19.4–76.1	<.001
Mucocutaneous involvement	792	317 (45%)	64 (74%)	3.57	2.18–6.04	<.001
Skin rash	792	208 (29%)	40 (47%)	2.08	1.32–3.28	.002
Oral mucosa inflammation	792	79 (11%)	16 (19%)	1.81	0.98–3.21	.048
Eye redness/injected conjunctiva	792	125 (18%)	48 (56%)	5.87	3.69, 9.42	<.001
Hand or feet swelling	792	23 (3%)	4 (5%)	1.45	0.42–3.88	0.5
Gastrointestinal involvement	792	471 (67%)	71 (83%)	2.36	1.36–4.36	.004
Abdominal pain	792	166 (24%)	55 (64%)	5.77	3.62–9.36	<.001
Vomiting	792	305 (43%)	49 (57%)	1.74	1.11–2.75	.016
Diarrhea	792	206 (29%)	33 (38%)	1.51	0.94, 2.39	.081
Heme involvement	766	79 (12%)	45 (52%)	8.81	5.41–14.4	<.001
Thrombocytopenia	766	34 (5%)	23 (27%)	7.19	3.95–12.9	<.001
Lymphopenia	766	51 (7%)	38 (43%)	10.2	6.10–17.2	<.001
COVID-19 IgG reactive	587	260 (37%)	79 (92%)	37.4	11.6–229	<.001

Abbreviations: CDC, Centers for Disease Control and Prevention; MIS-C, multisystem inflammatory syndrome in children; OR, odds ratio; IgG, immunoglobulin G.
[a]n (%).

Table 3. Presence of CDC MIS-C Diagnostic Criteria in Children with MIS-C Compared With Children With Positive Viral Test

Characteristic	N	Positive Viral Test N = 95[a]	MIS-C N = 84[a]	OR for MIS-C Diagnosis vs Viral Test Positive OR	95% CI	*P* value
C-reactive protein >3.0 mg/dL	175	39 (42%)	78 (93%)	21.2	8.53–64.7	<.001
Cardiac involvement	176	3 (3%)	51 (61%)	45.8	15.5–197	<.001
Cardiac function; decreased	179	1 (1%)	23 (27%)	35.4	7.18–642	<.001
Coronary artery involvement (echocardiogram)	179	0 (0%)	10 (12%)			
Troponin elevated	176	2 (2%)	38 (45%)	37.2	10.7–235	<.001
Mucocutaneous involvement	179	38 (40%)	64 (76%)	4.80	2.54–9.34	<.001
Skin rash	179	17 (18%)	40 (48%)	4.17	2.15–8.38	<.001
Oral mucosa inflammation	179	10 (11%)	16 (19%)	2.00	0.86–4.83	0.11
Eye redness/injected conjunctiva	179	23 (24%)	48 (57%)	4.17	2.23–8.01	<.001
Hand or feet swelling	179	2 (2%)	4 (5%)	2.33	0.44–17.1	.3
Gastrointestinal involvement	179	65 (68%)	71 (85%)	2.52	1.23–5.39	.013
Abdominal pain	179	20 (21%)	55 (65%)	7.11	3.71–14.1	<.001
Vomiting	179	45 (47%)	49 (58%)	1.56	0.86–2.82	.14
Diarrhea	179	28 (29%)	33 (39%)	1.55	0.83–2.90	.2
Heme involvement	171	9 (9%)	45 (54%)	10.8	4.98–25.8	<.001
Thrombocytopenia	171	3 (3%)	23 (27%)	11.2	3.68–48.6	<.001
Lymphopenia	171	7 (7%)	38 (45%)	10.1	4.40–26.5	<.001
COVID-19 IgG reactive	166	63 (66%)	77 (92%)	14.7	4.14–93.5	<.001

Abbreviations: CDC, Centers for Disease Control and Prevention; MIS-C, multisystem inflammatory syndrome in children; OR, odds ratio; IgG, immunoglobulin G.
[a]n (%).

outside the CDC MIS-C case definition that may influence ED clinician suspicion for MIS-C or other inflammatory illnesses. These included respiratory symptoms (difficulty breathing, cough), a positive non-COVID-19 viral test during the encounter, duration of fever, and a prior health care encounter during the same illness resulting in an alternative diagnosis. Because COVID-19 vaccination became available for children during the study period, we also assessed the proportion of children with and without MIS-C who had received at least 1 dose of a COVID-19 vaccine before their encounter, based on electronic medical record documentation. Statistical analyses were conducted in R version 4.2.1 (R Foundation for Statistical Computing), and a 2-sided $P<.05$ was considered statistically significant.

Table 4. Performance of Other Clinical Criteria in Identification of MIS-C

Characteristic	No MIS-C, N = 706[a]	MIS-C, N = 86[a]	N	OR for MIS-C Diagnosis vs Other		
				OR	95% CI	*P* value
Difficulty breathing	57 (8%)	5 (6%)	792	0.70	0.24–1.65	.5
Cough	385 (55%)	28 (33%)	792	0.40	0.25–0.64	<.001
Virus; non-COVID-19	95 (13%)	2 (2%)	292	0.12	0.02–0.41	.004
Alternate diagnosis prior to ED encounter			792			
None	297 (42%)	28 (33%)		—	—	
Nonspecific virus	257 (36%)	37 (43%)		1.53	0.91–2.58	.11
Positive viral test before encounter	46 (7%)	8 (9%)		1.84	0.75–4.13	.2
Prescribed antibiotic	106 (15%)	13 (15%)		1.30	0.63–2.56	.5
Fever length			748			
No fever	34 (5%)	0 (0%)				
<48 hours	42 (6%)	9 (10%)		1.00	—	
2 – 4 days	218 (31%)	32 (37%)		0.69	0.31–1.62	.4
5 – 9 days	335 (47%)	39 (45%)		0.54	0.25–1.27	.13
>10 days	69 (10%)	4 (5%)		0.27	0.07–0.89	.039
Not documented	8 (1%)	2 (2%)				

Abbreviations: MIS-C, multisystem inflammatory syndrome in children; OR, odds ratio; ED, emergency department.
[a]n (%).

RESULTS

Characteristics of Children Evaluated for MIS-C

There were 843 ED encounters in which MIS-C was evaluated during the study period, of which 36 were transfers from other hospitals and 15 involved children with immunosuppression, congenital heart disease, or a prior MIS-C diagnosis, leaving 792 encounters included in the analysis. The median age was 3.4 years (interquartile range [IQR], 1.4–7.6 years), and 47% were female. The cohort was 27% Black, 58% White, and 22% Hispanic, and 56% had public insurance. Compared with children with alternative final diagnoses, those diagnosed with MIS-C were older (median age, 7.4 vs 2.9 years; $P<.001$) but did not differ significantly by other demographic characteristics (Table 1).

Diagnostic Outcomes for Children Evaluated for MIS-C and Patterns Over Time

Of the 792 children included, 86 (11%) received a final diagnosis of MIS-C. Other clinically significant diagnoses included Kawasaki disease in 25 children (3.2%), bacteremia with a confirmed pathogen on blood culture in 20 (2.5%), culture-negative sepsis in 8 (1.0%), and toxic shock syndrome in 1 (0.1%). Additionally, 26 children (3.3%) were diagnosed with community-acquired pneumonia, and 97 (12%) had a positive viral test other than COVID-19. All children diagnosed with MIS-C were admitted to the hospital, compared with 45% of those with alternative final diagnoses. No deaths were recorded in this cohort.

Both MIS-C testing and confirmed MIS-C diagnoses varied by month during the study period (Figure). The highest numbers of MIS-C cases were diagnosed in December 2020 and January 2021, with a secondary peak in January 2022. MIS-C testing volumes increased during and immediately after months with higher confirmed case counts.

Association of CDC Criteria With Eventual MIS-C Diagnosis

Compared with children with alternative final diagnoses, children eventually diagnosed with MIS-C were more likely to meet each CDC diagnostic criterion. Those with MIS-C were more likely to have a CRP >3.0 mg/dL (94% vs 40%; odds ratio [OR], 23.8; 95% CI, 10.5–68.3) and to have at least 1 symptom of cardiac involvement (59% vs 2.8%; OR, 50.4; 95% CI, 27.4–96.4), mucocutaneous involvement (74% vs 45%; OR, 3.57; 95% CI, 2.18–6.04), gastrointestinal involvement (83% vs 67%; OR, 2.36; 95% CI, 1.36–4.36), and hematologic involvement (54% vs 12%; OR, 8.81; 95% CI, 5.41–14.4). Among the 587 children with COVID-19 immunoglobulin G (IgG) serology results, reactive IgG was more common in those with MIS-C (98% vs 51%; OR, 37.4, 95% CI, 11.6–229). Results for system involvement and individual symptoms are presented in Table 2.

In a sensitivity analysis, we conducted the same comparisons between only children with a positive non-COVID viral test and children with a final diagnosis of MIS-C. Two children with MIS-C also had a positive viral test and were excluded. Similar associations were observed between MIS-C diagnosis and elevated CRP, cardiac involvement, mucocutaneous symptoms, gastrointestinal symptoms, hematologic involvement, and COVID-19 IgG seropositivity (Table 3).

Performance of Other Diagnostic Criteria in Distinguishing MIS-C

In addition to the CDC diagnostic criteria, we evaluated additional clinical factors that might be relevant to ED assessment. Of note,

fever duration did not readily distinguish MIS-C. Compared with fever lasting less than 48 hours, fever durations of 2 to 4 days and 5 to 9 days were not associated with significantly different odds of MIS-C, whereas fever lasting more than 10 days was associated with lower odds (OR, 0.27; 95% CI, 0.07–0.89). Similarly, having an alternative diagnosis before the ED visit in which MIS-C was assessed did not significantly alter the odds of MIS-C. Compared with children with no prior diagnosis during the same illness, odds of MIS-C were not significantly different among those previously diagnosed with a nonspecific viral illness (OR, 1.53; 95% CI, 0.91-2.58), those with a positive viral test (OR, 1.84; 95% CI, 0.75–4.13), or those prescribed antibiotics for presumed bacterial infection (OR, 1.30; 95% CI, 0.63–2.56).

COVID-19 Vaccination Status

Twenty-one children had documentation of receipt of at least 1 COVID-19 vaccine dose before their ED encounter. Among the 706 children without MIS-C who had vaccination data available, 20 (2.8%) were vaccinated before their visit. Among the 86 children diagnosed with MIS-C, 1 (1.2%) had received their first vaccine dose 5 days before presentation. Given the small number of vaccinated children, no further statistical comparisons were performed.

DISCUSSION

In this retrospective study, 11% of children evaluated for MIS-C in a southeastern Wisconsin pediatric ED ultimately received the diagnosis. Testing patterns and MIS-C frequency varied over time and generally declined over the study period. Children diagnosed with MIS-C tended to be older than those with alternative diagnoses. Involvement of each system included in the CDC case definition—cardiac, gastrointestinal, mucocutaneous, and hematologic—was associated with an eventual diagnosis of MIS-C, with the strongest association observed for cardiac involvement, followed by hematologic involvement. In contrast, a positive non-COVID-19 viral test was associated with greatly reduced odds of MIS-C, whereas diagnoses from prior ED encounters did not significantly alter risk.

Overall, our findings are consistent with prior literature describing the clinical features of MIS-C. As expected, each CDC diagnostic criterion was positively associated with MIS-C diagnosis. The proportions of children with MIS-C who had conjunctivitis, rash, and mucous membrane involvement in our cohort were similar to those previously reported.[11] A meta-analysis[12] of observational studies of children with MIS-C reported that 68% had vomiting and 73% had abdominal pain or diarrhea, which is similar to our findings.

However, when assessing the discriminatory value of these features compared with other febrile illnesses, our data differ somewhat from prior literature. One study found substantially higher odds ratios for abdominal pain (OR, 12.5 vs 5.8 in our cohort), conjunctivitis (OR, 31 vs 5.7), extremity swelling or rash (OR, 99), and mucous membrane involvement (OR, 12 vs 1.8).[13] These differences likely reflect variation in study design. Our cohort included only children who underwent laboratory testing for MIS-C, thus, the mucocutaneous and gastrointestinal symptoms likely prompted evaluation. Notably, among children without MIS-C in our study, 45% had mucocutaneous symptoms and 67% had gastrointestinal symptoms. This finding underscores the nonspecific nature of some of these criteria and their overlap with common pediatric illnesses. Therefore, it is unsurprising that the criteria based on laboratory tests or echocardiography (CRP elevation, cardiac function, coronary artery dilation, troponin elevation, thrombocytopenia, lymphopenia) demonstrated the strongest associations with MIS-C in this study.

In addition to CDC criteria, ED clinicians must consider other factors when evaluating MIS-C risk. Prior studies have demonstrated that most children with MIS-C have a prior health care encounter.[14,15] Our data suggest that clinicians should avoid anchoring on prior diagnoses, as those diagnosed with bacterial infection requiring an antibiotic had a similar risk to those with no previous diagnosis during the present illness. Conversely, the presence of cough or a positive viral test during the ED visit significantly reduced odds of MIS-C, suggesting that extensive MIS-C testing may be unnecessary in children with clear viral respiratory symptoms.

Temporal trends in MIS-C diagnoses and testing in our cohort mirrored national patterns, with peaks in late 2020 and late 2021 and a marked decline beginning in March 2022.[3] These trends may be related to the emergence of new SARS-CoV-2 variants during the study period, including Alpha in early 2021, Delta in the summer of 2021, and Omicron beginning in late 2021.[16,17] We did not obtain viral sequencing data for individual patients; however, these variant transitions may have influenced both the incidence and clinical phenotype of MIS-C. While MIS-C severity appears to have decreased over time, cases continue to occur.[3,18-20]

Despite declining case counts, MIS-C testing remained relatively steady through 2022. This may reflect continued high rates of COVID-19 infection and subsequent viral illnesses, sustaining clinician concern for inflammatory complications. Further, the increase in MIS-C evaluations during a surge in viral illnesses in late 2022[21] highlights the importance of distinguishing MIS-C from other common febrile conditions to avoid unnecessary testing and hospitalization.

Due to the evolving clinical understanding, the CDC updated the MIS-C diagnostic criteria in 2023,[22] introducing a strict CRP cutoff (≥ 3 mg/dL); removing respiratory, neurologic, and renal criteria; and requiring specific evidence of dysfunction in 1 or more of 5 organ systems: cardiac, mucocutaneous, shock, gastrointestinal, and hematologic.[7,22] Because our study predates these changes, some children classified with MIS-C may not meet the current definition. Nonetheless, our findings remain clinically

relevant, as they reflect real-world screening practices and system involvement in the ED and provide context for diagnostic stewardship as definitions evolve.

This study has limitations. It was conducted at a single tertiary pediatric ED, which may limit generalizability. Use of the MIS-C order panel as the inclusion criteria may have resulted in missed cases or inclusion of children with minimal clinical concern. Diagnostic criteria and clinician awareness evolved during the study period, and diagnoses were based on chart review, which reflects the clinical judgment of the treating team. As with all retrospective studies, findings may be affected by documentation inaccuracies and misclassification.

CONCLUSIONS

MIS-C cases in southeastern Wisconsin occurred in waves and declined over time. Elevated CRP and involvement of cardiac, gastrointestinal, mucocutaneous, and hematologic systems defined in the CDC case definition were associated with increased odds of MIS-C, whereas the presence of cough or positive non-COVID-19 viral test results were associated with lower odds. These findings may assist clinicians in risk stratification, diagnostic stewardship, and decision-making regarding ED referral and evaluation for suspected MIS-C.

Financial disclosures: None declared.

Funding/support: Funding provided in part from the Clinical and Translational Science Institute of Southeastern Wisconsin via the Medical College of Wisconsin.

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Moral Injury and Planetary Health in Primary Care Clinicians and Medical Trainees

Kevin Dunn, MD; Jonathan Temte, MD, PhD, MS

ABSTRACT

Introduction: Climate change is a serious and worsening public health crisis. Primary care clinicians and medical trainees understand the health effects of climate change yet participate in a carbon-intensive industry and often maintain lifestyles linked to high carbon footprints. Moral injury occurs when individuals perpetrate, witness, or fail to prevent acts that transgress deeply held moral beliefs. We hypothesized that primary care clinicians and medical trainees experience morally injurious circumstances in response to climate change.

Methods: A cross-sectional survey was sent to University of Wisconsin family medicine clinicians and medical trainees. The survey assessed participant climate change attitudes, levels of moral injury specific to climate change (using an adapted Moral Injury Symptom Scale), and general dysphoria.

Results: A total of 131 surveys were completed (42.5% response rate). The average moral injury score was 45.5 (±11.8); 80.2% of participants scored at or above the established threshold of 36. A significant, moderate positive correlation was found between climate change attitudes and moral injury ($r = 0.561$; $P < .0001$), as well as between moral injury and associated functional impairment and distress ($r_S = 0.463$; $P < .0001$).

Conclusions: A high rate of climate change-related moral injury was detected in this sample. The degree of moral injury appears to be associated with climate change attitudes and awareness. Family medicine clinicians and medical trainees may represent motivated agents of change in the global climate health response.

INTRODUCTION

Climate change is a serious and worsening public health crisis with substantial effects on physical and mental health.[1,2] Health care professionals are generally aware of climate change and its effect on patient health[3] but also contribute to the carbon-intensive health care industry, which accounts for approximately 4.4% to 4.6% of global greenhouse gas emissions.[4,5] Physicians, other health care professionals, and trainees also have potential for relatively high incomes, which have been linked to lifestyles with large carbon footprints.[6] Furthermore, health care professionals—specifically family medicine physicians—have reported uncertainty regarding their role in addressing the climate crisis.[3] This combination may be a recipe for climate change-related moral injury in primary care clinicians, other health care professionals, and trainees.

Moral Injury

Moral injury can be described as the phenomenon or syndrome that occurs "when we perpetrate, bear witness to, or fail to prevent an act that transgresses our deeply held moral beliefs."[7] The phenomenon was first assessed in military veterans who may have witnessed events or been required to act in ways that violated their values during war[8] and has been quantified using the Moral Injury Symptom Scale-Military Version.[9] Moral injury commonly manifests with psychological symptoms such as shame, grief, remorse, a sense of meaninglessness, and even a loss of faith or spirituality.[10]

Moral Injury in Health Care

Recently, moral injury has been assessed in health care, where morally injurious circumstances are common.[10,11] These circumstances include balancing conflicting priorities such as quality patient care, electronic health records tasks, productivity targets, insurance policies, and hospital interests.[7] In 2020, the Moral Injury Symptom Scale-Health Professionals (MISS-HP) was adapted from the military version to evaluate the degree of moral injury experienced among health care professionals.[10] In

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one study, 47.5% of health care professionals scored above the cutoff for clinically significant moral injury.[10] Moral injury in this population is associated with increased clinician burnout and medical errors.[11] Therefore, it is important to understand moral injury in health care professionals, including contributing factors such as climate change.

This Study

To our knowledge, moral injury has not yet been assessed in the context of climate change. The aim of this exploratory study was to evaluate climate change-related moral injury experienced by primary care providers and medical trainees. Given the dissonance between recognizing the health effects of climate change and personal contributions though profession and lifestyle,[5] we hypothesized that (1) primary care clinicians and medical trainees would have elevated levels of moral injury related to climate change, and (2) this moral injury would be correlated with climate change attitudes and awareness.

METHODS

Study Population and Setting

This unfunded, exploratory study was conducted within the University of Wisconsin Department of Family Medicine and Community Health (DFMCH). To expand the sample size and exploration of climate change-related moral injury, University of Wisconsin School of Medicine and Public Health (UWSMPH) medical and physician assistant (PA) students were included in addition DFMCH clinicians. Data were collected via a cross-sectional survey sent in June and July of 2023. All DFMCH clinicians with a valid email address – including physicians, advanced practice providers (APPs), and residents – received an email invitation via Qualtrics (Qualtrics) to participate. In total, 251 DFMCH clinicians were sent the survey. Because a complete list of student email addresses was unavailable, a mass email was sent to all active medical and PA students to solicit interest. Fifty-seven students expressed interest and were subsequently sent the survey. Participation was voluntary and responses were anonymous.

Survey Instrument and Delivery

The cross-sectional survey consisted of 4 sections and 23 items (Appendix A). The first section included a 3-item climate change attitude (CCA) assessment, a condensed version of a survey previously used to evaluate climate change attitudes and awareness.[12] Items were rated on a scale of 0 to 5; individual scores were summed for a total CCA score ranging from 0 to 15.

The second section contained the 10-item Moral Injury Symptom Scale for Climate Change (MISS-CC), adapted for use in this study from the previously validated MISS-HP.[10] The adaptation included adjustments or additions of minor phrases such as, "when it comes to planetary health" to help identify moral injury specifically related to climate change. The 10 items assessed feelings of betrayal, guilt, shame, moral concerns, loss of trust, loss of meaning, unforgiveness, self-condemnation, feeling punished, and loss of faith in the context of climate change. Responses used a 10-point Likert scale ranging from 1 (strongly disagree) to 10 (strongly agree). To prevent response bias, 6 items (questions [Q] 4-7, 11, 12) were worded negatively (higher values indicated higher moral injury), and 4 items (Q 8-10, 13) were worded positively (higher values indicated lower moral injury). After re-scoring the 4 positively worded questions, individual items were summed to get a total moral injury score ranging from 10 to 100. Participants with scores ≥ 36 were considered morally injured, consistent with previously established cutoffs.[10,11] The final question (Q14) assessed the significant distress and functional impairment at work, in relationships, or other areas of life caused by the moral injury indicated by the previous 10 questions. Responses used a 5-point Likert scale ranging from 1 (not at all) to 5 (extremely).

To assess dysphoria, the third section used the 2-item Patient Health Questionnaire (PHQ-2) and the 2-item Generalized Anxiety Disorder survey (GAD-2), a tool used in a previous study to evaluate the relationship between symptoms of anxiety and depression with attitudes and awareness of climate change.[12] Individual scores were summed for a general score ranging from 0 to 12. A threshold score of 5 identified individuals with dysphoria, indicating a positive screen (score ≥ 3) on either the PHQ-2 or GAD-2.[12,13] The final section collected participant demographics by role/profession, age, gender identity, race, and ethnicity, and whether participants had children.

The web-based survey remained open for 2 weeks, with up

Table. Participant Demographics

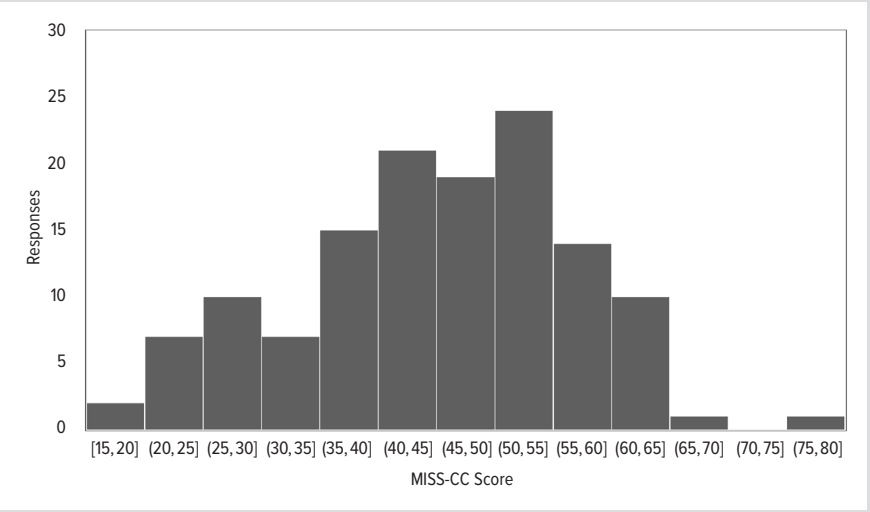
	No. of Participants (%)
Role	
Family medicine physicians	54 (41.2)
Family medicine resident physicians	12 (9.2)
Family medicine APPs	11 (8.4)
MD students	48 (36.6)
PA students	6 (4.6)
Age (years)	
26 and under	39 (29.8)
27–42	56 (42.7)
43–58	24 (18.3)
59 and older	12 (9.2)
Gender (self-identified)	
Men	50 (38.2)
Women	78 (59.5)
Nonbinary, other gender, or nondisclosed	3 (2.3)
Race and ethnicity (self-identified)	
White, non-Hispanic	96 (73.3)
Other races or ethnicities	34 (26.0)
Parental status	
Have children	59 (45.0)
Do not have children	70 (53.4)

to 4 email reminders. The study protocol was deemed exempt by the University of Wisconsin Minimal Risk Research Institutional Review Board (protocol 2023-0767).

Data Analysis

Descriptive statistics were used to analyze initial response results from various sections of the survey, including the CCA, MISS-CC, functional impairment or significant distress (Q14), and dysphoria. Individual item responses in the MISS-CC section were also evaluated using descriptive statistics. Pearson correlation determined relationships between CCA and MISS-CC scores. Due to skewed distributions, Spearman rank correlation was used to determine relationships between MISS-CC and general dysphoria or functional impairment. Subgroup analyses compared medical trainees and family medicine clinicians. For incomplete responses median values from the total population were imputed.

Figure 1. Moral Injury Symptom Scale for Climate Change (MISS-CC) Scores



Frequency histogram of the total score for the moral injury symptom scale for climate change (MISS-CC) of 131 surveyed participants. Scores at or above 36 were considered morally injured.

RESULTS

Response Rate and Demographics

Of 308 eligible participants, 131 completed the survey (42.5% response rate). Of these, 125 were entirely complete. Responses for 11 individual items were imputed. Sample demographics are shown in the Table.

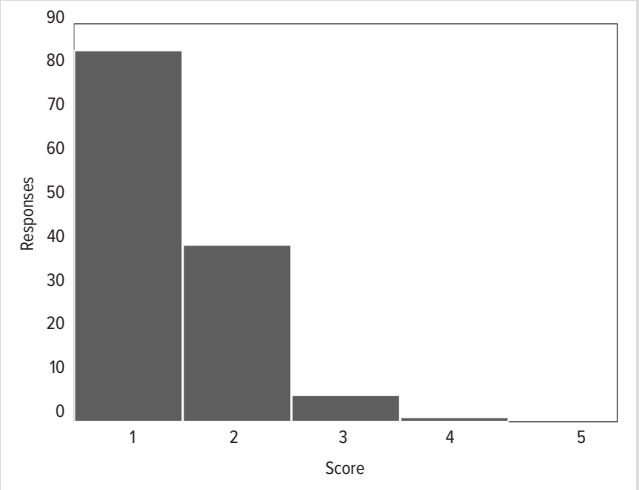
Moral Injury and Impairment

MISS-CC scores ranged from 15 to 76 (mean ± SD, 45.47 ± 11.77; median, 47) (Figure 1); 80.2% of participants scored at or above the moral injury threshold of 36. Differences across demographics were minimal. Medical trainees (MD and PA students) had a mean score of 45.81, compared to 45.22 for family medicine clinicians. Q14 scores (functional impairment) were skewed toward low impairment (Figure 2), ranging from 1 to 4 (mean ± SD, 1.42 ± 0.62; median, 1). Notably, 35.9% of participants reported some functional impairment (score ≥ 2), but only 5.3% reported moderate or worse impairment (score ≥ 3). A significant, moderate positive correlation (r = 0.463; $P < .0001$) was found between MISS-CC and functional impairment.

Individual MISS-CC Questions

Average individual MISS-CC item scores ranged from 2.3 (Q12, feeling punished) to 7.8 (Q13, loss of faith). Q13 scored noticeably higher than the other questions (Figure 3). While faith may decline due to climate change, the wording of this question may create artificially inflated values for participants who do not consider themselves religious or spiritual. When Q13 was excluded, 59.5% of individuals still scored above moral injury threshold compared to 80.2% when Q13 was included.

Figure 2. Functional Impairment on the Moral Injury Symptom Scale for Climate Change (MISS-CC)

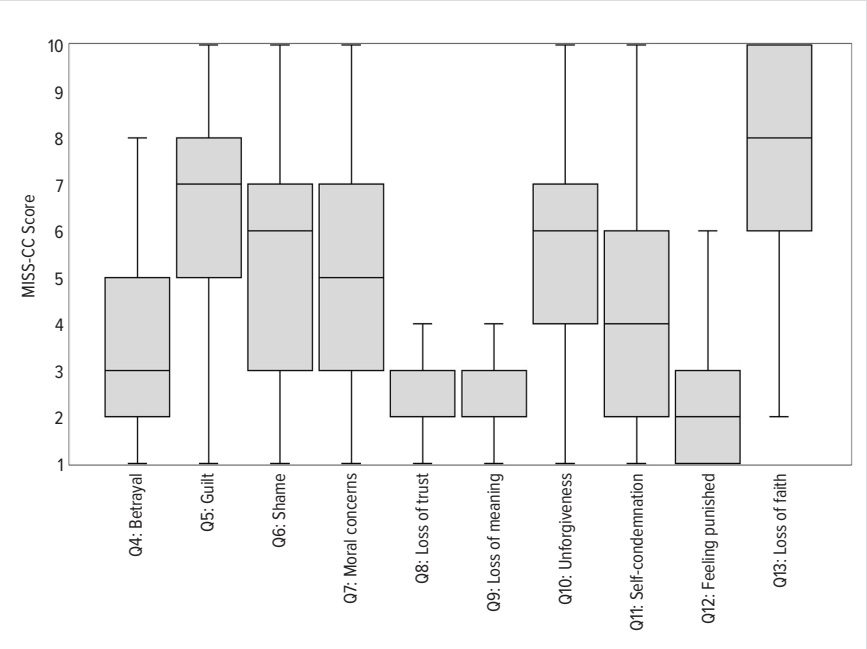


Frequency histogram of the 131 participants' scores for functional impairment or significant distress related to climate change related moral injury, as assessed by question 14 of the survey (Appendix A). Scores ranged from 1 (not at all impaired or distressed) to 4 (very functionally impaired or distressed).

Climate Change Attitude, Moral Injury and General Dysphoria

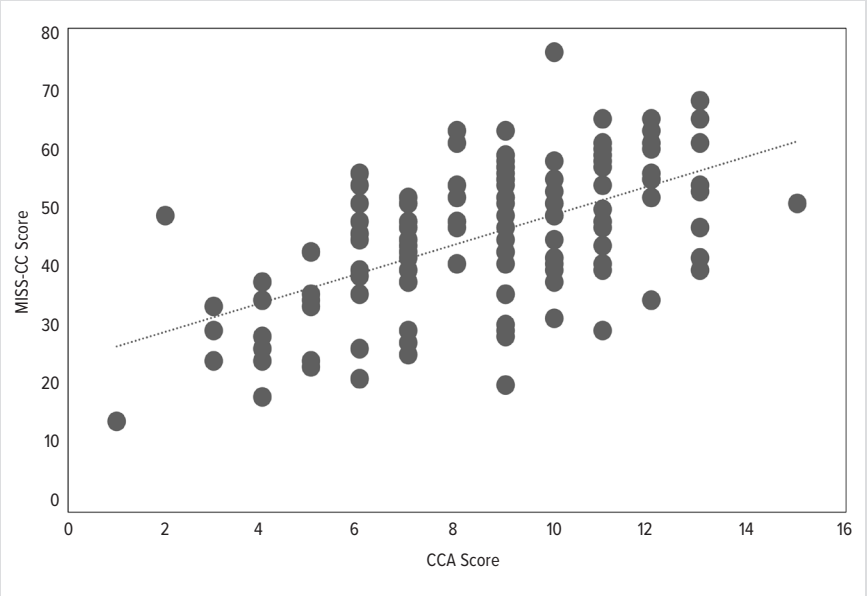
CCA scores ranged from 1 (low climate change awareness) to 15 (high awareness) (mean ± SD, 8.47 ± 2.73; median, 9). Pearson correlation revealed a significant, moderate positive correlation between CCA and MISS-CC scores (r = 0.561; $P < .0001$) (Figure 4). Subgroup analysis showed similar correlations for trainees (r = 0.502) and clinicians (r = 0.607). Dysphoria scores (PHQ-2 plus GAD-2) ranged from 0 and 8 (mean ± SD, 1.96 ± 2.04;

Figure 3. Individual Questions on the Moral Injury Symptom Scale for Climate Change (MISS-CC)



The box plots display the minimum, 1st quartile, median, 3rd quartile, and maximum for each individual question of the MISS-CC. The average response scores of individual questions were as follows: Q4 (betrayal), 3.6; Q5 (guilt), 6.3; Q6 (shame), 5.4; Q7 (moral concerns), 4.8; Q8 (loss of trust), 2.6; Q9 (loss of meaning), 2.5; Q10 (unforgiveness), 5.8; Q11 (self-condemnation), 4.3; Q12 (feeling punished), 2.3; Q13 (loss of faith), 7.8.

Figure 4. Correlation Between Climate Change Attitude (CCA) and Moral Injury Symptom Scale for Climate Change (MISS-CC)



Individual scores on the MISS-CC were plotted against CCA scores with associated linear trendline. A moderate correlation of r = 0.561 (P <.0001) was found between climate change attitude scores and MISS-CC scores.

median, 1); only 10.7% (n = 14) scored at or above the threshold of 5. No significant correlation was found between MISS-CC and dysphoria (r_S = 0.162; P = .0645).

DISCUSSION

In our sample of primary care clinicians and trainees, we found high rates of climate change-related moral injury (80.2%). Even with the exclusion of a potentially inflated item (Q13), 59.5% of participants remained above the threshold – higher than the 47.5% reported in the initial study evaluating general moral injury in health care professionals.[10] Despite this, functional impairment resulting from climate change-related moral injury was relatively low. Although 35.9% of participants showed some level of functional impairment or significant distress, only 5.3% indicated moderate or worse functional impairment or significant distress. In comparison, 23.9% of health care professionals showed moderate or worse functional impairment in previous studies evaluating moral injury in health care settings.[10,11] This suggests that while climate change creates a morally injurious environment, it may be less immediately impairing than the daily clinical challenges of modern health care. This may be due to the delayed consequences of climate change compared to direct clinical stressors.

Individual item analysis showed lower contributions to overall moral injury from factors such as feeling betrayed, losing trust in colleagues, or a loss of meaning in life or work. Participants maintained trust in those around them and a sense of what makes their lives and work meaningful. However, moral injury was driven by internal factors such as guilt, shame, feeling like a failure, violating one's own moral values, and unforgiveness of oneself in the context of climate change and planetary health. While Q13 (religious/spiritual faith) likely inflated total scores, the underlying moral injury remains substantial at nearly 60%.

Although we cannot infer causality

in this correlational analysis, the significant positive correlation between CCA and moral injury supports our hypothesis that greater awareness of climate change is associated with a higher degree of moral injury. We found an overall low level of general dysphoria (10.7%) among participants, which may reflect actual low levels of anxiety and/or depression or potential response bias from participants familiar with the PHQ-2 and GAD-2 tools. Whereas CCA was significantly correlated with dysphoria in a previous study,[12] we found no significant correlation between dysphoria scores and CCA or MISS-CC, suggesting that climate-related moral injury may be distinct from general psychological distress in this study population.

Our findings suggest that while academic primary care clinicians and medical trainees experience moral injury related to climate change, they remain professionally engaged, and previous work has shown they are interested in expanding their role in addressing the climate health crisis.[14] Engaging in roles such as patient educators on climate health, advocates for sound climate policy, and leaders in climate health response may provide a pathway for moral injury healing.

Limitations

There are notable limitations to this study. Although we achieved a reasonable response rate for an email survey, this study was conducted at a single academic institution in politically liberal-leaning county, limiting the generalizability. The voluntary nature of the survey introduces volunteer bias. However, there were a wide range of moral injury scores with a roughly normal distribution (Figure 1). Additionally, the MISS-CC tool has not yet undergone full psychometric analysis, nor has a definitive quantitative cutoff been identified for moral injury specific to this adapted survey. Finally, the survey was distributed during the 2023 Canadian wildfires, which caused unprecedented poor air quality in Wisconsin and may have influenced responses.

CONCLUSIONS

We conducted this study to explore moral injury in the context of climate change among primary care clinicians and medical trainees. Although further examination is needed in larger, more representative samples, a high degree of moral injury was found in our study population and was associated with increased awareness of climate change. Despite this, the study population continued to trust their colleagues, maintained a sense of meaning, and experienced relatively lower functional impairment resulting from this distress.

As previously noted, health care professionals – specifically primary care clinicians – are aware of climate change-related health impacts but remain unsure of their role in addressing this issue. Taken together, we believe that this suggests academic primary care clinicians and medical trainees may be motivated populations with room to grow as agents of change in climate change-related health efforts. More work is needed to explore the potential role and associated benefits – including moral injury healing – of primary care clinicians and medical trainees working as patient educators on climate-related health issues, advocates for sound climate policy, and leaders in health response.

Financial disclosures: None declared.

Funding/support: This project was carried out through the University of Wisconsin School of Medicine and Public Health Department of Family Medicine and Community Health's Summer Student Research and Clinical Assistantship Program which provided a small stipend to the research student for their work on this project. No additional funding was provided or used for this work.

Appendix: Available at www.wmjonline.org

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Assessing the Construct Validity of the Patient Health Questionnaire-9 in Measuring Severity of Major Depressive Disorder

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ABSTRACT

Introduction: Developed by Spitzer et al in 1999, the Patient Health Questionnaire (PHQ-9) is a 9-item, self-administered instrument used to screen for depression. This screening tool has been validated by more than 25 studies. However, although the PHQ-9 asks respondents to rate the frequency of symptoms, most validation studies focus on symptom severity. The objective of this study was to assess the construct validity of PHQ-9 for detecting the severity of depression, as defined by the Diagnostic and Statistical Manual of Mental Disorders.

Methods: In part 1 of this study, 1408 outpatients across 14 family practice clinics were asked whether they scored the PHQ-9 based on symptom frequency, symptom severity, or a combination of both. In part 2, 87 mental health clinicians were asked how they typically interpret PHQ-9 scores.

Results: Of the 87 clinician responses, 79.3%, reported interpreting PHQ-9 scores based on severity of depressive symptoms, 4.6% based on frequency, and 16.1% based on a combination of severity and frequency. In striking contrast, among the 1408 patient responses, only 10.7% reported completing it based solely on severity, and 28.6% reported completing it based on frequency alone. An additional 60.7% reported completing the PHQ-9 based on a combination of frequency and severity.

Conclusions: The findings of this study indicate that the language used in the PHQ-9 may be interpreted differently by patients and clinicians. These differences may lead to conflation of symptom frequency and severity, resulting in misinterpretation of the PHQ-9 scores. The authors recommend revisions to the language of this screening tool to determine whether such changes improve alignment between patient responses and clinician interpretation.

INTRODUCTION

The Patient Health Questionnaire (PHQ)[1] is a self-administered version of the Primary Care Evaluation of Mental Disorders (PRIME MD)[2] diagnostic instrument for common mental disorders. The PHQ-9[1] is the 9-item depression module from the full PHQ that assesses depressive symptoms based on criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM IV).[3] The instrument asks, "Over the last 2 weeks, how often have you been bothered by any of the following problems? Use 'X' to indicate your answer," and directs participants to rate each item as follows: "0" (not at all), "1" (several days), "2" (more than half the days), or "3" (nearly every day). It is widely used in the United States[1,4-7] and globally,[8-11] and is utilized extensively within the authors' affiliated ambulatory clinics.[12-14] Numerous studies have concluded that the PHQ-9 is a valid[1,4-8] and reliable[5,9,10,15-18] screening instrument for assessing depression severity across various patient populations and geographies. Many studies correlate PHQ-9 scores of 5, 10, 15, and 20 with mild, moderate, moderately severe, and severe depression, respectively.[4] A score of 10 or higher may warrant treatment.[4]

Jiraniramai et al[6] noted that the "PHQ-9 has been investigated for psychometric properties both by traditional classical test theory (CTT) and by item response theory, such as Rasch model analysis." Regarding construct validity – that is, whether the PHQ-9 precisely assesses what it is intended to measure – McCord and Provost[4] noted that "the high level of heterogeneity in just these 9

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items reflects one of the most significant problems with the categorical diagnostic paradigm…there are 18351 different patterns that produce exactly a score of 10…there are 101 different patterns with which two different patients can each earn a score of 10 without sharing a single symptom."

Although Levis et al[16] report that the "PHQ-9 is often used to estimate depression prevalence, it overestimates major depression prevalence substantially," they conclude that the heterogenic nature of presenting symptoms poses a statistical challenge in individual study analyses. Therefore, they recommend that "estimates of depression prevalence should be based on validated diagnostic interviews designed for determining case status; users should evaluate published reports of depression prevalence to ensure that they are based on methods intended to classify major depression."

The actual language of the PHQ-9 asks patients to rate the frequency of symptoms, not severity. In fact, symptom severity is not explored until the end of the questionnaire ("If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?"), with options ranging from "not difficult at all," to "extremely difficult." While symptom frequency over time may correlate with illness severity, these concepts are not interchangeable.

We hypothesized that this discrepancy may obscure the reliability and validity of the PHQ-9 as a tool for determining depression severity, potentially leading to overtreatment or undertreatment of depressive symptoms.

METHODS

Database Searches and Study Selection

A systematic literature search was designed and conducted by a medical librarian (RS), with input from the research team (HA, LF). The search strategy included Medical Subject Headings (MeSH) terms and keywords related to "Patient Health Questionnaire-9" or "PHQ-9" combined with "symptom assessment," "validity," or "systematic reviews." Searches were conducted using MEDLINE (Ovid), PsycINFO, and Scopus on July 27, 2021, using advanced search techniques relative to each database. Results were limited to English-language publication and managed in EndNote for duplicate removal. The complete search strategy is presented in the Appendix.

The Medical College of Wisconsin Human Research Protections Program approved all study procedures. Following Institutional Review Board (IRB) approval, informed consent forms and the survey (see Appendix) were distributed across 14 MCW/Froedtert outpatient clinics in the greater Milwaukee, Wisconsin, metropolitan area. These included 2 specialty behavioral health clinics and 12 primary care clinics.

Selection of Participants

From April 2022 through October 2022, patients visiting these clinics were asked to complete a voluntary, anonymous 1-question survey at check-out. After obtaining informed consent, research staff confirmed that participants had not completed the survey at a previous visit. Participants were asked if they had completed the PHQ-9 during that visit (an image of the PHQ-9 questionnaire was provided for reference). Participants were then asked, "When you answered the questions, did you score your symptoms based on severity of symptoms (how much you experience them); frequency of symptoms (how often you experience them); or both frequency and severity (a combination of how much and how often you experience them)."

For the clinician component of the study, we recruited participants via a national listserv of mental health clinicians. The post was an invitation to take a voluntary, anonymous 1-question survey that asked, "When you look at the scores of a PHQ-9, do you interpret the score as severity of depressive symptoms, as frequency of depressive symptoms, or as some combination of severity and frequency of depressive symptoms?"

Definition of Validity

The term "construct validity" is widely used and carries diverse connotations. The definition originates with Cronbach and Meehl,[19] who in 1955 discussed the challenges in quantifying construct validity and identified several contributing factors, including validation procedures, group differences, the nomological network, and the application of scientific methodology to complex testing. Campbell[20] posits that construct validity is crucial for understanding what a test measures and ensuring that it accurately reflects its theoretical construct. In a subsequent paper,[21] Campbell and Fiske differentiated between convergent validity (the degree to which theoretically related measures are actually related) and divergent validity (the degree to which a test does not correlate too highly with measures from which it should differ). Messick[22] emphasizes that valid inference in psychological assessment involves a comprehensive evaluation, including a unified concept of validity, theoretical rationale, and social consequences.

After considering these factors, we utilized the definition of validity provided by the Standards for Educational and Psychological Testing,[23] often considered the gold standard: "Validity is the degree to which accumulated evidence and theory support a specific interpretation of test scores for a given use of a test. If multiple interpretations of a test score for different uses are intended, validity evidence for each interpretation is needed."

RESULTS

Each project member collected survey responses from assigned clinics and entered them into a secure central data bank. Incomplete responses were excluded

Patient Survey

A total of 1408 participants who had filled out the PHQ-9 com-

Table 1. Patient Health Questionnaire-9 (PHQ-9) Scoring – Overall[a]

	N	%	95%CI
Severity	151	10.7	9.2–12.5
Frequency	402	28.6	26.2 – 31.0
Both	855	60.7	58.1 – 63.3
TOTAL	1408	100.0	

[a]Responses are to the question, "When you look at the scores of a PHQ-9, do you interpret the score as severity of depressive symptoms, as frequency of depressive symptoms, or as some combination of severity and frequency of depressive symptoms?

An examination by site (clinic) of the basis on which patients scored their symptoms showed significant variation between sites.

Table 2. Patient Health Questionnaire-9 (PHQ-9) Scoring Basis by Site

Site	Severity N (%)	Frequency N (%)	Both N (%)	Total N
Clinic A	22 (14.5)	40 (26.3)	90 (59.2)	152
Clinic B	40 (6.9)	156 (26.8)	387)66.4)	583
Clinic C	3 (7.0)	14 (32.6)	26 (60.5)	43
Clinic D	0 (0.0)	0 (0.0)	2 (100.0)	2
Clinic E	0 (0.0)	0 (0.0)	2 (100.0)	2
Clinic F	19 (22.1)	33 (38.4)	34 (39.5)	86
Clinic G	8 (9.2)	17 (19.5)	62 (71.3)	87
Clinic H	22 (27.8)	32 (40.5)	25 (31.6)	79
Clinic I	7 (8.6)	17 (21.0)	57 (70.4)	81
Clinic J	11 (6.2)	49 (27.5)	118 (66.3)	178
Clinic K	10 (16.9)	27 (45.8)	22 (37.3)	59
Clinic L	3 (21.4)	3 (21.4)	8 (57.1)	14
Clinic M	1 (4.8)	8 (38.1)	12 (57.1)	21
Clinic N	5 (23.8)	6 (28.6)	10 (47.6)	21
TOTAL	151 (10.7)	402 (28.6)	855 (60.7)	1408

There is a statistically significant association between Clinic and how patients scored their symptoms on the PHQ-9 (P <.001).

Table 3. Clinician Survey Responses[a]

	N	%	95% CI
Severity of depressive symptoms	69	79.3	69.3–87.3
Frequency of depressive symptoms	4	4.6	1.3–11.4
Some combination of severity and frequency of depressive symptoms	14	16.1	9.1–25.5
TOTAL	87	100.0	

[a]Responses are to the question, "When you look at the scores of a PHQ-9, do you interpret the score as severity of depressive symptoms, as frequency of depressive symptoms, or as some combination of severity and frequency of depressive symptoms?"

Table 4. Patient and Clinician Basis of Scoring and Interpreting PHQ-9[a]

	Patient N (%)	Clinician N (%)
Severity of symptoms	151 (10.7)	69 (79.3)
Frequency of symptoms	402 (28.6)	4 (4.6)
Some combination of severity and frequency of symptoms	855 (60.7)	14 (16.1)
Total	1408	87

[a]$\chi^2 = 307.3$; df = 2; P < .001 (chi-square test of independence).

pleted the follow-up survey. Three sites were excluded: Clinic O and Clinic P (each contributed only 2 completed surveys) and Clinic Q (because collaboration could not be established).

All follow-up surveys (n = 1408) were deemed valid. Overall, 10.7% of patients scored their symptoms based on severity, 28.6% based on frequency, and 60.7% based on a combination of both frequency and severity. We calculated 95% confidence intervals (CIs) for all proportions (Table 1). The proportion of patients scoring symptoms based on severity was 0.10 (95% CI, 0.09-0.12).

Additionally, the basis for scoring symptoms differed significantly by clinic (P < .001; Table 2).

Clinician Interpretations of PHQ-9 Scores

Of the100 clinicians surveys received, 99 were valid. Twelve clinicians reported that they did not use the PHQ-9. Of the 87 clinicians who reported using the instrument, 79% (95% CI, 69%-87%) interpreted PHQ-9 scores based as reflecting severity of depressive symptoms, 4% (95% CI, 1%-11%) as reflecting frequency, and 16% (95% CI, 9%-25%) as reflecting a combination of both severity and frequency (Table 3).

These results indicate a marked discrepancy: while up to 87% of clinicians interpreted PHQ-9 scores as reflecting symptom severity, up to 89% of patients scored their symptoms based on frequency (combining "frequency" and "both") rather than severity alone (Table 4).

DISCUSSION

In this study of 1408 outpatients, 151 participants (11%) reported completing the PHQ-9 based solely on symptom severity; 402 (28%) based on frequency, and 855 (60%) reported using a combination of both frequency and severity.

The language used in the PHQ-9 ("Over the last 2 weeks, how often have you been bothered by any of these problems") indicates that the tool measures frequency, not severity. However, studies examining the construct validity of the PHQ-9 have focused on the severity of symptoms, not the frequency. Even if PHQ-9 scores were shown to accurately reflect depression severity, this would suggest positive predictive value rather than construct validity. In other words, although the PHQ-9 explicitly asks about frequency, if the resulting score accurately reflects severity, it does so despite the instrument's wording, not because of it. Furthermore, only 11% of the participants in this study reported that the PHQ-9 facilitated their rating of the severity of their depression.

Contrary to prior studies that compared PHQ-9 with other depression questionnaires (eg, Beck's Depression Inventory,[24]Hamilton Depression Rating scale[25]), when we took a direct approach to examining construct validity – by asking patients whether they completed the PHQ-9 based on severity – only 12% of the 1408 participants indicated that they had. By comparison, 28% completed the PHQ-9 solely based on

frequency, and a majority (60%) reported using a combination of frequency and severity, a construct that remains subjectively defined by respondents.

These findings also raise concerns about the sensitivity and specificity of the PHQ-9 in detecting depression severity. Because clinicians tend to interpret PHQ scores as indicators of symptom severity, several clinical scenarios may arise. For example, if a patient completes the PHQ-9 based on frequency rather than severity, a low score may be inaccurately interpreted as indicating low severity, which may put the patient at risk of undertreatment. Conversely, if the patient completes the PHQ-9 based on frequency of symptoms, a high score may be interpreted as high severity, which may put the patient at risk of overtreatment or unnecessary treatment.

Based on these findings, we suggest that the language used in the PHQ-9 may be interpreted differently by patients versus clinicians. Although prior studies have demonstrated consistency between the PHQ-9 scores and other standard depression instruments, the construct validity of the PHQ-9—its ability to measure what it is intended to measure—may be improved. We propose revising the language of the PHQ-9 to explicitly assess severity rather than frequency (see Appendix). As Campbell and Fiske[21] state, construct validity should be strengthened rather than removed, as it provides a comprehensive framework for evaluating test validity. Accordingly, we recommend that a similar study be conducted using the revised questionnaire to assess whether construct validity improves.

It should be noted that any revised questionnaire should be used solely as a screening tool and must be accompanied by a comprehensive clinical evaluation, including consideration of DSM diagnostic criteria , such as exclusion of symptoms attributable to other effects/conditions. Use of a revised questionnaire as a standalone diagnostic tool could create many issues. For example, a patient who scores a "3" on Question 9 (suicidal ideation) and minimal scores on other items could receive a total score that underrepresents the seriousness of the situation.

Limitations

This study had several limitations. It was conducted only among adult outpatients, limiting its generalizability to other settings (eg, inpatient hospitals) or pediatric populations. Additionally, the study was confined to a specific geographic area (the greater Milwaukee metropolitan area), which may limit applicability to other geographic and cultural populations.

Although most participants reported completing the PHQ-9 based on a combination of frequency and severity, the survey asks respondents to elaborate on what they meant by this combination. As a result, these responses are subjective and open to a wide variation in interpretation. The study could have been strengthened by exploring participants' interpretations of this combined approach.

Finally, the finding that the basis on which patients scored their symptoms differed by clinic complicates interpretation of the overall proportions. Without additional data on clinic-level factors that could explain the differences, this association should be interpreted cautiously.

CONCLUSIONS

The findings of this study indicate that the language used in the PHQ-9 is interpreted differently by patients and clinicians. These differences may lead to conflation of symptom frequency and severity, potentially resulting in misinterpretation of PHQ-9 scores. The authors recommend revising the language of this screening tool and conducting further study to determine whether such revisions reduce the discrepancies identified in this analysis.

Financial disclosures: None declared.

Funding/support: None declared.

Appendix: Available at www.wmjonline.org.

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Severe Morbidity and Mortality From Coronavirus Disease 2019 in Hmong Individuals With Gout

Kari Falaas, MD; Michael Schnaus, MD; Elie Gertner, MD

ABSTRACT

Background: Given the disproportionate impact of coronavirus disease 2019 (COVID-19) on patients with comorbidities – including gout – and on diverse populations such as the Hmong community, it remains unclear whether a combination of these factors lead to more severe COVID-19 outcomes.

Methods: We reviewed the outcomes of 21 Hmong patients with coexisting gout and COVID-19 admitted to 2 tertiary care centers from March 1, 2020, through December 31, 2021.

Results: Seven patients required low-flow nasal cannula oxygen, 3 required high-flow nasal cannula, 1 required noninvasive ventilation, and 10 (48%) required mechanical ventilation. The 30-day mortality rate was 57% (n=12).

Discussion: The findings highlight a potentially disproportionate burden of severe COVID-19 outcomes among Hmong patients with gout. The high observed mortality raises questions about the role of comorbidities, vaccination disparities, and structural factors contributing to poor outcomes in this population.

BACKGROUND

The Coronavirus disease 2019 (COVID-19) pandemic brought unprecedented challenges to health care systems worldwide, impacting comorbidities and mortality rates and revealing disparities in disease outcomes among different populations. A large post-pandemic cross-sectional study determined that there were more than 1.38 million all-cause excess deaths (observed-to-expected ratio, 1.15 [95% CI, 1.12-1.18]), corresponding to approximately 23 million years of potential life lost.[1] COVID-19 also demonstrated a disproportionate burden on individuals with underlying comorbidities, such as rheumatologic diseases, cardiovascular conditions, and respiratory disorders. These comorbidities are associated with more severe illness and higher mortality rates among COVID-19 patients.[2]

An additional and often overlooked risk factor for severe COVID-19 disease outcomes is gout. Recent studies demonstrate that gout, as a comorbid condition, poses significant risk for severe COVID-19, including death, even when adjusted for other diseases and vaccination status.[3,4] In addition to comorbidities, diverse population groups faced unique challenges during the pandemic. The Hmong community, in particular, faced unique challenges. With strong representation throughout the Midwest, the Hmong community encountered multiple barriers, including access to health care, limited health literacy, and differing cultural approaches to medicine. In a 2020 report of COVID-19 deaths in Minnesota, Hmong Americans accounted for 49% of deaths within the Asian American community.[5]

In addition to being significantly affected by COVID-19, the Hmong population is also especially susceptible to hyperuricemia and gout. Previous studies have shown higher serum uric acid concentrations in the Hmong population, and genetic alleles linked to hyperuricemia are found more frequently among the Hmong individuals compared with non-Hmong patients.[6] Evidence suggests the Hmong population is at risk for developing gout almost a decade earlier than non-Hmong patients, despite similar rates of diabetes, hypertension, and mortality.[7]

Given the disproportionate impact of COVID-19 on patients with comorbidities including gout and the impact on diverse populations like the Hmong, it remains unclear if the combination of

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these factors leads to more severe outcomes. Therefore, a etrospective case series of Hmong patients with gout and severe COVID-19 was performed to evaluate how these combined factors affected clinical outcomes.

METHODS

In this retrospective chart review, 21 Hmong patients with a clinical diagnosis of gout and severe COVID-19 outcomes who presented at 2 tertiary care centers between March 1, 2020, and December 31, 2021, were identified. Hmong identity was determined by an open-ended self-identification question. An Institutional Review Board-approved COVID-19 registry was used to identify patients who were aged 18 years and older, had documented COVID-19 infection, and required oxygen. Of the 591 patients meeting this criteria, 54 patients had gout and 22 identified as Hmong. Twenty-one of these patients had a clinical diagnosis of gout and were included in the final case series. One patient was excluded due to self-reported gout without description of symptoms, prior uric acid levels, or treatment history. Descriptive statistics were used for analysis.

RESULTS

Of the 107 Hmong patients in the registry with COVID-19, 21 (20%) had gout and were included in this study. The average age was 62.9 years. Fourteen patients (63.6%) were male, with an average body mass index of 28.9. Most were unvaccinated (n = 19), one had received 1 dose of a COVID-19 vaccine, and one had received at least 2 doses. Nineteen of the 21 patients required an interpreter.

Gout was included on the problem list of all the patients; 11 met American College of Rheumatology (ACR) classification criteria. The other 10 patients were treated with allopurinol and had documented symptoms with elevated uric acid. Eighteen had uric acid levels recorded prior to admission; 15 were above 6 mg/dL. The average pre-admission uric acid level was 8.02 mg/dL. Six patients had a history of tophaceous gout, and 3 had uric acid nephrolithiasis. Fourteen were receiving allopurinol prior to admission. Other comorbidities included chronic lung disease (n = 4, 19.0%), chronic heart failure (n = 3, 14.2%), renal disease (n=5, 23.8%), and diabetes with end organ damage (n = 7, 33.3%). No patients had coexisting connective tissue diseases. Only 3 reported prior tobacco use or vaping history.

In the hospital, 66.7% of patients were febrile. Seven patients received low-flow nasal cannula oxygen, 3 required high-flow nasal cannula, 1 required noninvasive ventilation, and 10 (48%) required mechanical ventilation. The average duration of mechanical ventilation was 15.5 days (range, 2-34 days). Laboratory studies revealed the following maximum averages: D-dimer, 3.63 mg/L; C-reactive protein, 19.8 mg/L; lactate dehydrogenase (LDH), 602.8 U/L, and ferritin, 2550.8 ng/mL. The average length of stay was 12.1 days. Seventeen patients received steroids, 6 received remdesivir, and 1 received tocilizumab. Eleven patients transitioned to comfort care. The 30-day mortality for this cohort was 57% (n = 12).

DISCUSSION

In this limited case series, 10 of 21 Hmong patients with gout hospitalized for COVID-19 required intubation and were subsequently transitioned to comfort care, with a 30-day mortality rate of 57%. The reasons for these outcomes are likely a combination of physiological differences, cultural factors, and disparities in health care access and treatment.

Previous studies show that Hmong individuals tend to have elevated serum uric acid levels and increased rates of tophaceous gout and uric acid nephrolithiasis.[7,8] In this series, the average serum uric acid level was elevated (8.02 mg/dL), and nearly one-third of patients had clinical evidence of tophaceous gout. Gout is an independent risk factor for COVID-19-related mortality,[3,4] and hyperuricemia has been independently linked to the development of other metabolic diseases. A study of more than 860 000 people with gout found that women had an 88% higher risk of cardiovascular disease, while men had a 49% higher risk, compared to those without gout.[9] Given that cardiovascular disease and other comorbidities, such as older age, diabetes, and obesity, are strongly associated with worse COVID-19 outcomes, gout may contribute to increased COVID-19 severity indirectly through its relationship with these conditions.[2] In this series, 20% to 30% of patients had underlying chronic heart failure, chronic kidney disease, or diabetes, and only 1 patient was fully vaccinated. These factors likely contributed to the high mortality rate observed.

Communication barriers and differences in medical perspectives may also have played a role. Nineteen of the 21 patients required an interpreter. Language barriers can lead to communication disconnects and decrease quality of health care, particularly for the Hmong population, as many Western medical terms lack direct translations.[10,11] Additionally, Hmong individuals may hold differing views on chronic disease management compared to Western medicine, which can result in variable medication and dietary adherence.[12,13]

This study is hypothesis-generating due to its small sample size, lack of a control group, and retrospective design, which limit causal inference. The high mortality may reflect selection bias, as the analysis included only hospitalized patients, likely representing only those with more severe illness. The study was also reliant on a self-reported open-ended question that could lead to underreporting or misclassification. The absence of a comparator group limits the ability to determine whether outcomes differ significantly from other ethnic populations with similar clinical profiles. The high burden of comorbid conditions also likely contributed to the poor outcomes observed. Furthermore, lower vaccination rates within the Hmong community during the study period may have further increased vulnerability.

Rather than providing definitive conclusions, the findings highlight a potentially disproportionate burden of severe COVID-19 outcomes among Hmong patients with gout. This raises questions about the role of comorbidities, vaccination disparities, and structural factors that may contribute to poor outcomes in this population. Further investigation in larger, controlled studies is needed. Additionally, these findings emphasize the need for health care systems to improve chronic disease management, outreach, and education for diverse racial and ethnic groups affected by gout.

Financial disclosures: None declared.

Funding/support: None declared.

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Managing Access to Medical Specialists for the Uninsured: Specialty Access for the Uninsured Program

Katrina Gonzales, MD; Greg Stadter, MPH; Theresa Umhoefer Wittry, MD; Ann Christiansen, MPH

ABSTRACT

Background: Safety net clinics provide primary care to uninsured patients. However, receiving specialty care is more complex because most specialists are not employed by these clinics.

Methods: To improve specialty access, the Milwaukee Health Care Partnership created the Specialty Access for the Uninsured Program (SAUP). The program provides timely specialty care distributed equally across the 3 adult health systems in Milwaukee. This paper outlines the process and framework used to implement SAUP.

Results: Since SAUP implementation, 23 000 patients have been referred for specialty care, with a 91% appointment show rate.

Discussion: The current specialty access system is unsustainable. SAUP provides a framework to address inequalities in specialty care access.

Conclusions: The SAUP model demonstrates that a coordinated, equitable distribution of specialty referrals across health systems can improve access for uninsured populations. This collaborative framework offers a sustainable solution for other communities facing rising rates of uninsurance and the high costs of deferred care.

BACKGROUND

Uninsured people comprise approximately 8% of the US population and 7.12% of the Milwaukee County, Wisconsin, population.[1,2] There are numerous health implications associated with being uninsured. Compared with an insured, age-matched population, adults aged 51 to 61 years who lost insurance were 82% more likely to report a decline in overall health and had a 35% to 43% increased risk of death over the next 13 to 17 years.[3,4] Among those with chronic conditions, such as cardiovascular disease and diabetes, uninsured adults had a 65% higher risk of stroke and a 22% higher risk of myocardial infarction.[3]

Federally Qualified Health Centers (FQHCs) provide vital primary care to uninsured patients. With the creation of these clinics, access to primary care for the uninsured improved drastically.[5] However, a survey of 814 FQHCs inquiring about specialty access revealed that 25% of visits result in a specialty referral.[6] A referral for specialty care is defined as care that cannot be provided by the patient's primary medical home. Receiving specialty care is more complex because most specialists are not employed by FQHCs. In a national survey of FQHCs, 91% reported it is somewhat or very difficult to obtain off-site specialty care for their uninsured population.[7] Despite known health implications, high demand, and consistent difficulties obtaining specialty care, there is no federally funded safety net for specialty access for the uninsured.

The Milwaukee Health Care Partnership (MHCP), an unincorporated consortium, was launched in 2007.[8] The founders recognized that there was a high number of uninsured patients in Milwaukee and rising emergency department utilization at all major hospitals. MHCP members include the 3 adult health systems in Milwaukee County, 1 pediatric health system, safety net clinics, and city, county, and state governmental health agencies. To improve specialty access, the Specialty Access for the Uninsured Program (SAUP) was developed in 2012 by MHCP to provide timely, clinically appropriate specialty. Care is managed by primary care and is distributed equally across the 3 adult health systems in Milwaukee. This paper outlines the process and frame-

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work used to implement SAUP and shares program results to date.

Within the adult Milwaukee County population, 7.12% (66 049 people) are uninsured.[2] The uninsured are largely concentrated in 4 urban Milwaukee ZIP codes (53215, 53204, 53205, and 53206) where the proportions of residents living below the poverty level are 23%, 31.36%, 44.44%, and 39.56%, respectively.[9]

METHODS

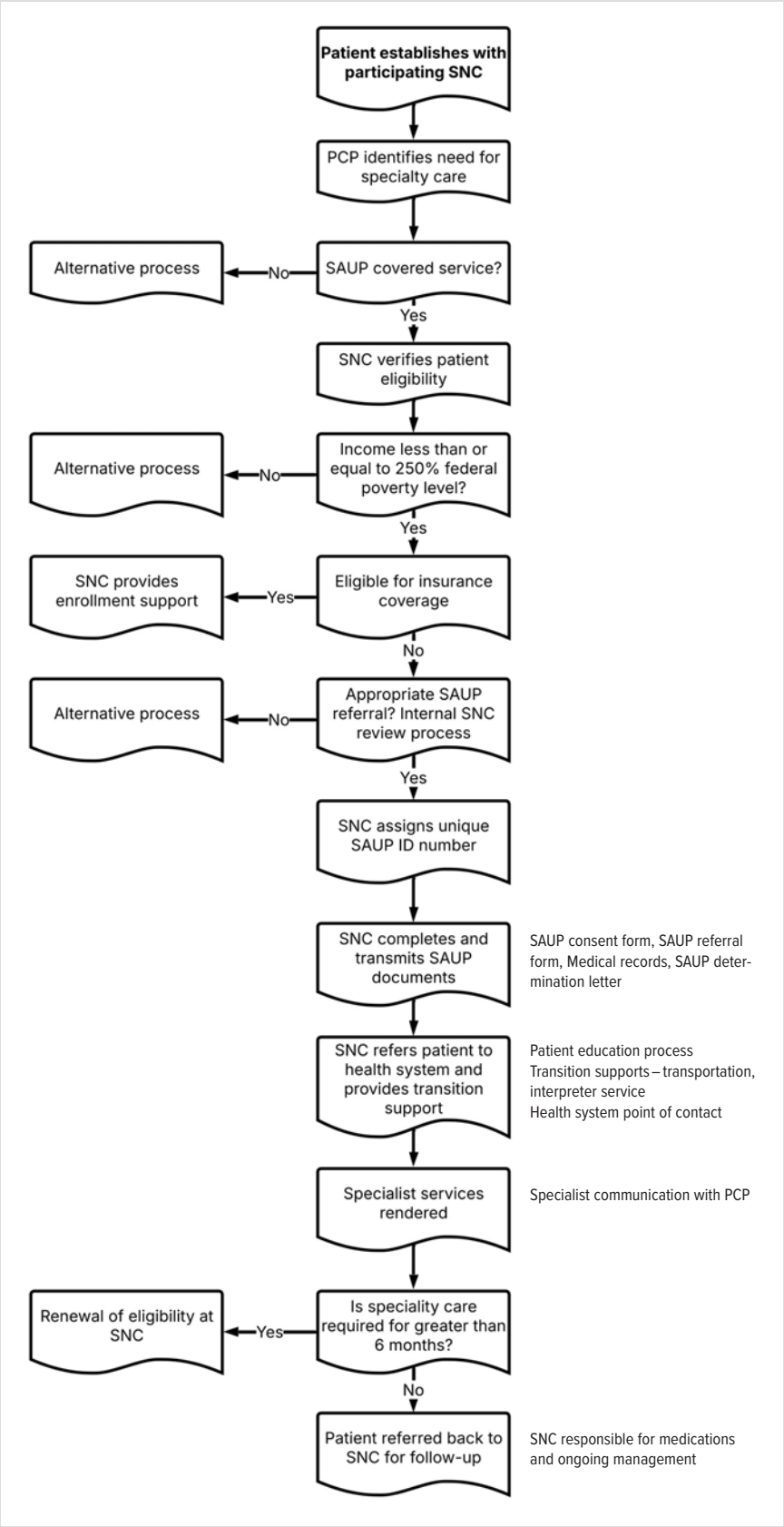
Implementing SAUP and Program Utilization

Before SAUP implementation, specialty care was obtained through clinicians' interpersonal connections and peer-to-peer consultations or by sending patients to the emergency departments for acute issues in hopes of an inpatient specialty consultation, resulting in significant delays in patient care.[10]

MHCP leaders were asked to develop a program for the management of uninsured patients who require a medical specialist. This process was delegated to the MHCP Clinical Council, consisting of member organizations' chief medical officers. The group designed a program to equitably distribute specialist care among the health systems and ensure referrals are clinically appropriate and managed by primary care. Care through the SAUP program is categorized as "charity care" by the participating health systems, allowing it to be provided at no cost to the patient.

SAUP was created with the agreement that patients would be equitably distributed among the participating health systems in Milwaukee: Aurora Health Care (part of Advocate Health), Froedert & ThedaCare, Inc, and Ascension Wisconsin. This agreement ensures the financial and operational risk for specialty care needs is not unduly placed on any health care system. This is achieved by assigning 1 health system as a partner to a safety net clinic. The safety net clinic network consists of various free clinics and 5 FQHCs in Milwaukee County. The Figure depicts the typical workflow of SAUP eligibility determination.

Figure. Workflow of Specialty Access for the Uninsured Program Eligibility Determination



Abbreviations: SNC, safety net clinic; PCP, primary care provider; SAUP, Specialty Access for the Uninsured Program.

SAUP Covered Services

Services covered by SAUP carry no out-of-pocket cost to the patient. These services mirror Wisconsin Medicaid guidelines, which include basic medical needs (laboratory work, diagnostic imaging, prescription drugs, and inpatient care). This comprises medically necessary outpatient and inpatient care, diagnostic tests and procedures ordered by specialists, specialty treatment, and certain preventive services. Restrictions of covered services are similar to Medicaid noncovered services, such as cosmetic procedures. SAUP differs from managed care organization initiatives in that case management is provided by safety net clinics rather than the payer directly.

RESULTS

Since the implementation of SAUP in 2012, 23 000 patients have been referred to the program for specialty care, with an overall show rate of 91%. The top specialties referred are orthopedics, ophthalmology, and cardiology. The Table details the yearly breakdown of referrals provided by health systems and safety net clinics.

Table. Number of Health System-Based Versus Safety Net Clinic-Based Specialty Care Referrals per Year Since Start of SAUP

Year	Health System-Based Specialty Care	Safety Net Clinic-Based Specialty Care
2012	605	0
2013	967	790
2014	862	1604
2015	1034	1953
2016	1299	1773
2017	950	1169
2018	1409	1280
2019	1395	741
2020	1124	313
2021	1312	260
2022	1317	417
2023	1549	349

Abbreviation: SAUP, Specialty Access for the Uninsured Program.

DISCUSSION

As noted by Iuga and McGuire, medication nonadherence creates a vicious cycle of subsequent poor health outcomes, increased service utilization, and higher health care costs that are ultimately passed on to the patient.[11] Nationally, the annual cost of medical nonadherence is estimated between $100 billion and $300 billion.[11] Furthermore, patients who defer care report that their health and quality of life decline compared with those who seek timely medical attention.[12] This decline is exemplified by a cohort study finding that lack of insurance was associated with an increased relative hazard for stroke and all-cause death, as well as an increased risk of undiagnosed and uncontrolled hypertension and undiagnosed hyperlipidemia.[13] The urgency of addressing these barriers is heightened by the "Medicaid unwinding"—the process of redetermining eligibility for millions of enrollees following the end of the COVID-19 Public Health Emergency. As individuals lose coverage, the demand for safety net specialty services is expected to rise. Without SAUP, this vicious cycle of nonadherence and declining health would likely occur in the Milwaukee County population.

The program features that have made SAUP successful could make similar programs sustainable in other communities. SAUP ensures that a single health system does not bear the financial burden of all uninsured patients through referral monitoring. SAUP also encourages patients to establish a long-term primary care medical home, with ongoing management between primary care and specialists. Finally, the safety net clinics utilize systems to verify that patients meet SAUP eligibility criteria, ensuring that all referrals are both financially and clinically appropriate. SAUP's commitment to these standards has contributed to SAUP's 12-year longevity and future sustainability from both a business and clinical perspective.

As illustrated in the Table, the significant increase in health system referrals in 2018 occurred because participating health systems removed annual referral caps. The Table also illustrates the decrease in care at safety net clinics (which are largely staffed by volunteers) due to many factors and accelerated by challenges associated with COVID-19. Referral rates have been relatively stable for the past 5 years.

SAUP Improvement Strategies

An area for SAUP improvement is interhealth system communication. Since many safety net clinics are funded through donations or, in the case of FQHCs, by meeting Health Resources and Services Administration benchmarks, many utilize paper charts or electronic health records outside of Epic (Epic Systems), while the health systems in Milwaukee all use Epic. This creates communication difficulties between the medical home and specialists. Improved health communication through the state-designated health information exchange system is one strategy deployed to exchange clinical information between the Epic and non-Epic organizations.

Another area of improvement for SAUP is embedding specialists at safety net clinics and encouraging them to hire their own specialists when feasible to maintain continuity at the medical home. However, there was a decline in safety net clinic specialists following the COVID-19 pandemic, and the number of specialists has not returned to prepandemic levels.

Telehealth is another opportunity for SAUP to extend specialist services. Some clinics have piloted programs where a primary care provider at a safety net clinic contacts a specialist via video in real time to determine if an in-person specialist visit is necessary. This has been particularly effective for some dermatological conditions.

Limitations

A limitation of SAUP being managed by MHCP, a neutral third-party organization, is that data collection and access to individual health system data is limited. Access to more robust clinical and financial data would strengthen the program's effectiveness from a clinical and economic standpoint. We were not able to perform an in-depth cost analysis regarding the amount saved by health care systems due to SAUP; this is a necessary step toward expanding the program.

CONCLUSIONS

With 8% of the US population remaining uninsured, the current system for accessing specialty care is unsustainable. The SAUP model provides a scalable framework for collaborative, equitable specialty care that mitigates the risks associated with deferred treatment. The authors hope these results will inspire other communities to implement similar managed specialty access programs for their uninsured and underinsured populations.

Financial disclosures: None declared.

Funding/support: None declared.

Acknowledgements: The authors would like to acknowledge the leaders and frontline staff at the 3 adult health systems and 11 safety net clinics that partner on SAUP to make the program successful.

Ethical approval and informed consent statement: Institutional Review Board approval was not required for this manuscript since no human subject information was accessed.

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Evaluating Uncommon Inflammatory Markers in Common Pediatric Bacterial Infections

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ABSTRACT

Background: Expected ranges for several inflammatory markers in children were poorly defined during the COVID-19 pandemic, making it difficult to distinguish common infections from multisystem inflammatory syndrome in children (MIS-C). We evaluated less commonly obtained inflammatory markers in children with common bacterial infections.

Methods: We completed a retrospective cohort study at a tertiary children's hospital from March 2018 through April 2023 of hospitalized patients >60 days to 21 years with cellulitis, community-acquired pneumonia, or urinary tract infection.

Results: A total of 973 patients were included (median age, 5.6 years; interquartile range, 1.9-12.2; 61% female). Most inflammatory markers were elevated across infections, whereas troponin levels remained within the reference range for all diagnoses.

Discussion: We report values for less commonly obtained inflammatory markers in children hospitalized with common bacterial infections. Normal troponin levels may help distinguish these infections from MIS-C, which more commonly involves cardiac inflammation. Further research is needed to define clinically useful cutoff values for inflammatory markers to aid decision-making in the setting of emerging disease processes.

INTRODUCTION

When evaluating febrile children during the COVID-19 pandemic, multisystem inflammatory syndrome in children (MIS-C) was often included in the differential diagnosis, for which no pathognomonic features are known.1,2 Many children, especially those requiring hospitalization, received a broad workup for MIS-C yet were ultimately diagnosed with a common illness that did not require extensive testing. Prior to the emergence of MIS-C, it was uncommon to routinely obtain inflammatory markers (IM) in the evaluation of febrile children. For example, in patients with urinary tract infections (UTIs), a urinalysis and urine culture are often sufficient for diagnosis. The diagnosis of community-acquired pneumonia (CAP) can often be made clinically or with a chest x-ray. In patients with cellulitis, laboratory testing is often not required.

Occasionally, laboratory tests including C-reactive protein (CRP), procalcitonin, a complete blood cell count (CBC), or erythrocyte sedimentation rate (ESR) can be helpful in stratifying disease severity or response to treatment; however, children admitted to a general hospital medicine service with these conditions typically do not require extensive laboratory testing. During the pandemic, however, given the overlapping features of these infections with MIS-C, many of these patients underwent a more extensive laboratory workup, which included less commonly obtained tests such as ferritin, D-dimer, troponin, and N-terminal pro-B-type natriuretic peptide (BNP), as specified in the MIS-C diagnostic algorithm. These laboratory values were often non-specifically elevated in both patients with MIS-C and those with

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Table. Inflammatory Markers by Diagnosis

	n eval	Cellulitis (n=403)	n eval	Pneumonia (n=158)	n eval	UTI (n=412)	n eval	MIS-C Data[2] (n=16)
C-reactive protein (mg/dL)	211		69		144		15	
Mean ± SD		5.0 ± 6.5		13.2 ± 12.6		12.5 ± 10.0		
Median (IQR)		2.9 (1.0-5.9)		8.3 (3.5-19.3)		8.6 (5.4-18.7)		11.2 (4.9-20.4)
95th percentile		19.9		39.2		34.3		
Reference range[a]		0-1		0-1		0-1		
Procalcitonin (ng/mL)	22		45		71		11	
Mean ± SD		5.7 ± 22.6		8.3 ± 24.5		12.5 ± 26.3		
Median (IQR)		0.11 (0.04-1.66)		1.1 (0.2-6.5)		3.0 (0.5-11.3)		1.02 (0.17-2.93)
95th percentile		91.4		29.1		63.9		
Reference range		< 0.11		< 0.11		< 0.11		
Erythrocyte sedimentation rate (mm/hr)	157		42		91		10	
Mean ± SD		23.5 ± 21.5		59.8 ± 33.8		53.8 ± 29.3		
Median (IQR)		15.0 (8.0-33.0)		68.5 (24.5-96.5)		55.0 (32.0-76.0)		55 (22-58)
95th percentile		75.2		101.0		101.0		
Reference range		0-20		0-20		0-20		
Ferritin (ng/mL)[b]	2		15		36		15	
Mean ± SD		33.7 ± 19.2		138.1 ± 167.4		141.8 ± 161.5		
Median (IQR)		33.7 (20.1-47.3)		120.0 (37.0-139.0)		102.0 (50.2-168.8)		538.4 (253.0-1293.5)
95th percentile		N/A		N/A		513.7		
Reference range		10-70		10-70		10-70		
BNP (pg/mL)[c]	3		10		37		16	
Mean ± SD		1090.0 ± 1367.1		1100.5 ± 2208.9		793.1 ± 1427.2		Elevated in 6/16
Median (IQR)		447.0 (163.0-2660.0)		168.0 (33.0-1039.3)		331.0 (107.0-614.5)		patients
95th percentile		N/A		N/A		5242.0		
Reference range		< 300		< 300		< 300		
D-Dimer (ug/mL)	6		17		36			
Mean ± SD		1.6 ± 0.8		1.7 ± 1.6		1.8 ± 1.3		Elevated in 12/16
Median (IQR)		1.5 (0.8-2.3)		1.3 (0.8-2.1)		1.5 (0.8-2.5)		patients
95th percentile		N/A		N/A		4.6		
Reference range		< 0.5		< 0.5		<0.5		
Troponin (ng/mL)	5		22		49			
Mean ± SD		0.006 ± 0.014		0.003 ± 0.009		0.003 ± 0.011		Elevated in 2/16
Median (IQR)		0.0 (0.0-0.016)		0.0 (0.0-0.0)		0.0 (0.0-0.0)		patients
95th percentile		N/A		0.03		0.03		
Reference range		< 0.035		< 0.035		< 0.035		

Abbreviations: IQR, interquartile range; UTI = urinary tract infection; BNP, N-terminal pro-B-type natriuretic peptide; N/A, not applicable; MIS-C, multisystem Inflammatory syndrome in children

[a]Reference ranges were obtained from our laboratory reference ranges reported in the electronic medical record. There may be slight variation based on age. The highest range was used.

[b]Ferritin (n = 2): 20.1 ng/mL and 47.3 ng/mL

[c]BNP (n = 3): 163 pg/mL, 447 pg/mL, and 2660 pg/mL.

historically common bacterial infections, and because expected ranges for many of these inflammatory markers in children with bacterial illnesses are unknown, interpretation was difficult.

To address this knowledge gap, we describe the values of several inflammatory markers observed in hospitalized pediatric patients with selected bacterial infections to assist clinical decision-making if clinicians are again faced with diagnostic ambiguity in the setting of emerging disease processes.

METHODS

A retrospective cohort study was conducted at a tertiary, freestanding children's hospital in the Midwest from March 2018 through April 2023. Patients > 60 days to 21 years who were discharged from the hospital medicine service with cellulitis, CAP, or UTI were included. Patients with MIS-C or a similar inflammatory syndrome were excluded. Laboratory values and reference ranges were extracted from the electronic health record (Epic Corp). Labs included CRP, procalcitonin, ESR, ferritin, BNP, D-dimer, and troponin. If multiple laboratory values were obtained during admission, only the first value was used for analysis. Data were reported as mean ± standard deviation (SD), median (interquartile range [IQR]), and 95th percentile. The Institutional Review Board at our institution waived the need for ethics approval and patient consent for the collection, analysis, and publication of the

retrospectively obtained and anonymized data for this noninterventional study.

RESULTS

A total of 973 patients were included: 403 with cellulitis, 158 with CAP, and 412 with UTI. Median (IQR) age was 5.6 years (1.9-12.2); 61% were female. The median (IQR) D-dimer (mg/dL) was 1.5 (0.8–2.3) in cellulitis, 1.3 (0.8–2.1) in CAP, and 1.5 (0.8–2.5) in UTI. The median ferritin (ng/mL) was 33.7 (20.1–47.3) in cellulitis, 120.0 (37.0–139.0) in CAP, and 102.0 (50.2–168.8) in UTI. BNP (pg/mL) demonstrated wider ranges, with a median value of 447 (163.0–2660.0) in cellulitis, 168.0 (33.0–1039.3) in CAP, and 331.0 (107.0–614.5) in UTI. Troponin levels were within the reference range for all diagnoses (Table 1).

DISCUSSION

Hospitalized pediatric patients with UTI, CAP, and cellulitis frequently demonstrated elevations in multiple inflammatory markers, making it difficult to differentiate these infections from other inflammatory syndromes such as MIS-C using laboratory evaluation alone. Prior literature suggests that elevated troponin levels occur more frequently in patients with MIS-C.1,2 Because cardiac inflammation and myocardial dysfunction are not typically associated with the infections we evaluated, troponin may be a helpful differentiator between these conditions.1,2

As the rest of the observed inflammatory markers are nonspecifically elevated across multiple conditions, utilizing data cutoff points may be of greater diagnostic utility when clinicians are uncertain how to interpret elevated values, although expected ranges for many of these tests remain poorly defined. Prior literature suggested a ferritin level of 228 ng/mL as a cutoff to differentiate patients with and without MIS-C, and our data support this finding, as ferritin levels in our cohort generally remained below this threshold.2 Similar laboratory thresholds have not been proposed for other inflammatory markers; however, we observed that the median BNP in our patients was similar to that reported in MIS-C, whereas the median D-dimer was lower than values observed in patients with MIS-C.1,2

Establishing cutoffs for these laboratory tests in pediatric patients may also play a role in future risk stratification. In critically ill pediatric populations, elevated ferritin, BNP, and D-dimer levels have been associated with increased morbidity and mortality, and some of these biomarkers have demonstrated diagnostic utility in selected infections.3-6 Further research is needed to optimize the clinical utility of these IMs in hospitalized pediatric patients. Such work is important to support diagnostic stewardship and high-value care by promoting judicious test use, accurate interpretation, and informed clinical decision-making.

Strengths of this project include a study design that is easily reproducible at other institutions, allowing expansion of these data in future studies. Limitations include the small sample size, limited range of infections represented, and retrospective design. Patients were not stratified by illness severity or the presence of cardiac complications. Further research is needed to better understand expected laboratory ranges of less commonly obtained inflammatory markers in hospitalized children to enhance clinical guidance and care delivery.

Financial disclosures: Kelly Graff is a consultant for and receives research support from BioFire Diagnostics, LLC; this company did not participate in this work.

Funding/support: Statistician time for this work was supported by the Medical College of Wisconsin Department of Pediatrics.

Acknowledgements: The authors wish to acknowledge Kelsey Porada, MA, for assistance with institutional review board submission and data formatting.

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Improvements in Infant Mortality From Congenital Cardiovascular Abnormalities Differ by Race in Wisconsin and the US, 1995-2022

Michael Rolfs, BS; Dirk Haselow, MD, PhD

ABSTRACT

Background: Infant mortality from congenital cardiovascular defects (CCDs) is the leading cause of death among individuals with birth defects.

Methods: A descriptive analysis of infant mortality due to CCDs in Wisconsin and the United States was performed using data from the Centers for Disease Control and Prevention's Wide-ranging ONline Database for Epidemiological Research (WONDER) from 1995 to 2022.

Results: Congenital cardiovascular defect-related infant mortality (CCDIM) declined during this period in the United States ($P < .0001$) and in Wisconsin ($P = .024$). In the United States, African American and American Indian or Alaska Native populations experienced higher rates than Asian or White populations. In Wisconsin, non-White populations experienced higher CCDIM rates than White populations.

Discussion: CCDIM in Wisconsin has declined over time. However, an excess of CCDIM in non-White populations persists compared with White populations. Because many risk factors for CCDIM are related to behavioral, environmental, and socioeconomic factors, these observed differences may represent opportunities for targeted prevention efforts.

BACKGROUND

Congenital cardiovascular defects (CCDs) are abnormalities in which the structure of the heart or major blood vessels does not form correctly. There are numerous specific types of CCDs, which, due to their relative individual rarity, are combined in this analysis. CCDs are the leading cause of infant mortality among persons with birth defects in the United States, causing about 40% of infant deaths among children with any congenital abnormalities.[1] They affect 8 to 9 per 1000 live births in the United States,[2] and from 2006 to 2015, infant mortality from CCDs was estimated to be 0.34 per 1000 live births.[3]

Risk factors for CCDs are complex and multifaceted. Both genetic factors and environmental factors—such as smoking during pregnancy, pregestational diabetes, poverty, obesity, and maternal age—have been associated with an increased risk of CCDs.[4]

Racial/ethnic disparities in CCDs have been observed in previous studies. A high-risk racial or ethnic status is likely a surrogate marker for socioeconomic factors mediating environmental and behavioral risks. Although true genetic factors likely exist, they are expected to account for only a minority of the increased risk.[5]

Congenital cardiovascular defect–related infant mortality (CCDIM) decreased by 24% from 1999 to 2006 in the United States.[6] This decline may be attributable to improved health care quality as well as enhanced newborn screening resulting in earlier identification and treatment. These improvements are strongly associated with well-resourced settings. In comparison, less well-resourced settings outside the United States have not seen comparable improvement in CCDIM.

We conducted this study to assess whether deaths from CCDs are changing over time in Wisconsin and whether these trends differ by race.

METHODS

We conducted a descriptive epidemiologic study using data from the Centers for Disease Control and Prevention's (CDC) Wide-ranging ONline Database for Epidemiological Research (WONDER) online data repository (wonder.cdc.gov) using the search term "congenital malformations of the circulatory system."

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CDC WONDER includes 5 separate queryable infant mortality databases covering the years 1995 through 2022. Numbers of infant deaths (defined as death in the first 12 months of life) and total births were assembled, along with CCDIM data and racial designation for each year for both the United States and Wisconsin. These data were concatenated into a single analytic database covering 1995-2022. Stratum-specific death rates per 1000 births were calculated in Excel (Microsoft Corp). Excel was also used to generate tables and figures and to calculate linear regression statistics and *P* values for differences in means.

Due to CDC WONDER confidentiality rules relating to small numbers, races other than White, Black or African American, American Indian or Alaskan Native, or Asian or Pacific Islander were not included in this analysis, even for national-level data. Similarly, when assembling Wisconsin data, the data source suppressed race-specific CCD data for all races except White due to small numbers. As a result, all non-White races were grouped into a single category for Wisconsin analyses.

During 1995 to 2022, racial designations varied across the 5 CDC WONDER datasets. To make them directly comparable, persons listed as Chinese, Filipino, or Other Asian race coded in 1995 to 2002 and 2019 to 2022 were recoded as Asian or Pacific Islander for this analysis.

Figure 1. Infant Deaths From Congenital Cardiovascular Abnormalities in the US by Race, 1995–2022

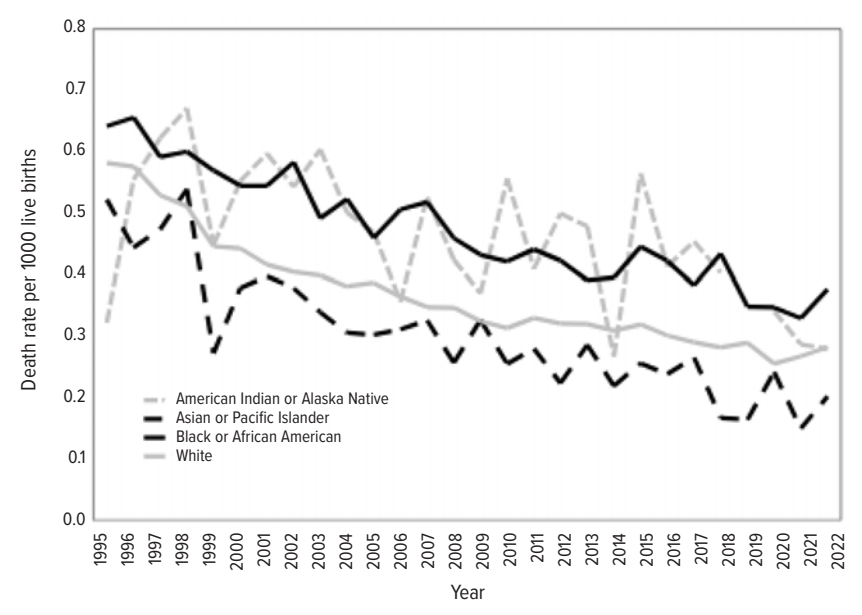
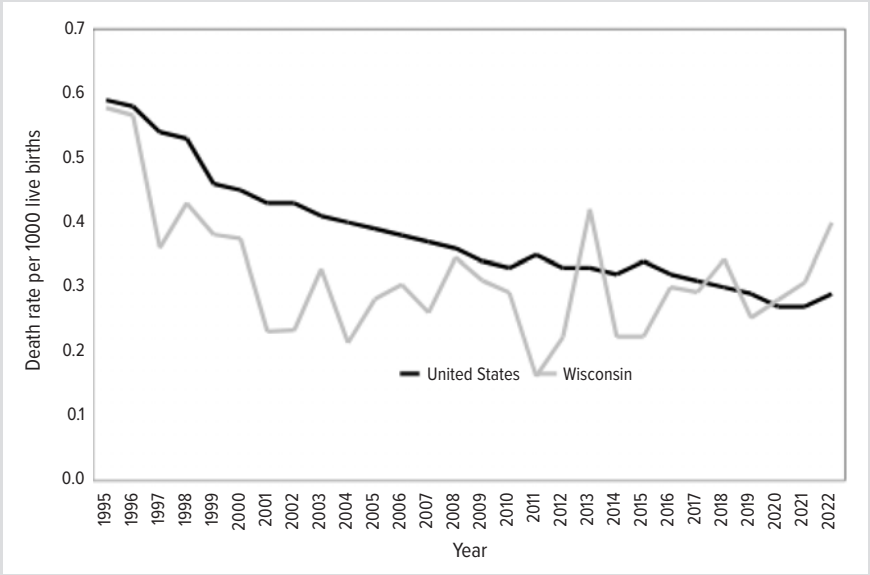


Figure 2. Infant Deaths From Congenital Cardiovascular Abnormalities, Wisconsin and the US, 1995–2022



RESULTS

Rates of CCDIM in the United States have decreased in all racial groups from 1995 to 2022 (Figure 1, $P<.0001$ for linear trend in all cases). Black or African American and American Indian or Alaskan Native populations had the highest rates. Black or African American individuals had higher rates than White individuals ($P<.00001$), and White individuals had higher rates than Asian or Pacific Islander individuals ($P=.007$).

Rates of CCDIM have decreased in both the United States (P for linear trend $<.0001$) and in Wisconsin ($P=.024$ for linear trend) during 1995 to 2022 (Figure 2). Overall, Wisconsin's rates were lower than national rates (P for linear trend $=.0001$ for linear trend), but from 2012 through 2022, rates became more similar ($P=.35$ for differences in means).

Figure 3 depicts trends in CCDIM in White versus non-White populations in Wisconsin. There is substantial variability in both lines, particularly among non-White individuals, reflecting small numbers. This variability limits the ability to make strong temporal inferences. Nevertheless, across the entire study period, White individuals consistently had lower rates than non-White individuals ($P=.0004$).

DISCUSSION

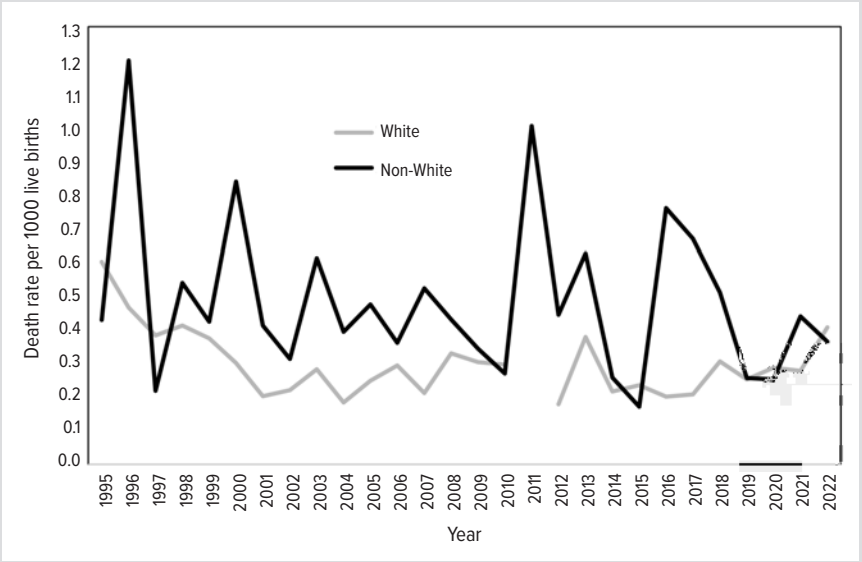
This study is a secondary analysis of publicly available data and is therefore subject to limitations related to missing and, most notably, suppressed data. The analysis is inherently limited in breadth and scope owing to limited data granularity. Specifically, due to

CDC WONDER data suppression rules, the analysis could not include important socioeconomic variables such as income, maternal education, marital status, maternal age, timing of prenatal care, gestational age, and infant birthweight. In addition, racial specificity among non-White populations was suppressed in the Wisconsin-specific analyses.

Future investigations could improve upon this work through a collaborative effort involving multiple birth defect registries. Such registries could include the aforementioned variables and provide greater granularity to the results.

It is encouraging that CCDIM has decreased in both the United States and Wisconsin during 1995 to 2022. Nationally, Black or African American individuals experienced higher CCDIM rates than White individuals, whereas Asian or Pacific Islander individuals experienced lower rates. Despite notable year-to-year variability, Wisconsin data also demonstrate higher CCDIM rates among non-White populations compared with White populations. This pattern reflects broader national trends in all-cause infant mortality, which varies by race. Although the persistence of racial disparities in CCDIM is not unexpected, it is encouraging that the magnitude of these disparities has narrowed over time. Nonetheless, continued efforts are needed to eliminate racial disparities in CCDIM.

Figure 3. Infant Deaths From Congenital Cardiovascular Abnormalities in Wisconsin, White vs Non-White Race, 1995–2022



The etiology of most CCDs remains poorly understood.[1] However, a range of social determinants of health may help explain racial disparities in CCDIM, as they have been shown to exert greater influence on health outcomes than genetic factors or access to care alone.[7] Factors negatively associated with infant mortality among African American women include lower rates of prenatal care utilization, smoking, not completing high school, and maternal age younger than 18 years.[7] Infants born to mothers with pregestational diabetes (type 1 or type 2) have a fivefold higher risk of CCD,[8] and diabetes prevalence is closely linked to racial, ethnic, and socioeconomic inequity. Exposures such as cigarette smoke, wood smoke, and low socioeconomic status during pregnancy have also been associated with increased CCD severity.[9]

Collectively, these social and environmental factors have been associated with later CCD diagnosis (postnatal vs prenatal), higher incidence, increased hospital readmission, poor neurodevelopmental outcomes, and death.[10] The racial disparities in CCDIM observed in this study may therefore reflect the cumulative impact of social determinants of health and structural inequities, including differences in health care infrastructure across communities. Public health professionals and clinicians may be well served to focus on prevention efforts on these social factors to reduce both racial disparities and overall CCDIM rates.

Financial disclosures: None declared.

Funding/support: None declared.

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Criteria to Assess Health Equity Implications of Research Articles in a Family Medicine Residency Journal Club

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ABSTRACT

Background: The purpose of this study was to evaluate a novel process for appraising the health equity implications of research articles.

Methods: We added 4 questions assessing health equity implications to existing resident journal club rubrics. We assessed family medicine resident attitudes toward and confidence in assessing health equity implications using surveys and focus groups at baseline and 6 months after implementing the additional questions.

Results: Average confidence in evaluating health equity implications of research articles increased between baseline surveys (n=33) and follow-up surveys (n=12; mean change, 0.7; range, 1-4).

Discussion: Incorporating additional journal club questions increased resident confidence in critically appraising the health equity implications of research articles.

BACKGROUND

The Accreditation Council for Graduate Medical Education (ACGME) requires that family medicine residency curricula address social needs and health disparities.[1] Current efforts to meet this requirement take a variety of forms, including quality improvement projects and didactic seminars.[2] However, initiatives have not traditionally taught residents to evaluate how study design and discussion of findings in research articles address social needs and health disparities.

Journal clubs are a staple of graduate medical education and are widely used to teach epidemiology, biostatistics, and critical appraisal of research articles. These skills prepare trainees to ask relevant questions, assess research quality, and apply appropriate knowledge to clinical practice.[3] Critically appraising research articles can also include assessing whether study design and associated findings impact health outcomes across distinct communities (eg, those facing systemic barriers to health equity). Systematic evaluation of the health equity relevance and implications of research articles is essential to understanding how evidence may apply across diverse populations. Currently, there are no known validated tools for the critical appraisal of health equity implications in research articles.

To address this knowledge gap, this study assessed a novel approach to appraising health equity implications during article evaluation. This approach added 4 questions to 4 existing sections of an established resident journal club evaluation rubric (ie, guiding questions to facilitate critical assessment of research articles). The additional questions direct residents to consider: (1) how the researchers included members of the target community in the study design; (2) whether study participants are representative of the target population; (3) the conceptualization and understanding of race as a social–rather than biological–construct, and (4) the use of inclusive language.[4] These 4 areas of focus were developed based on a literature review and expert consultation with health equity researchers and teachers.[2,5,6]

We measured the impact of the additional questions on resident attitudes toward and confidence in evaluating the health equity implications of research articles.

METHODS

We conducted this pilot study with family medicine residents at the University of Wisconsin Department of Family Medicine and

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Box. Questions Added to Journal Club Evaluation Rubric

1. Do the authors describe engaging or partnering with the community they are studying as part of their research? If so, at what stage of the research process (eg, developing the research question, study design, data collection, data analysis, sharing results, etc.)?
2. Is the study sample representative of the study's target population? Do the authors report sample characteristics including age, gender, race, ethnicity, disability, sexual orientation, gender identity, and socioeconomic status? If the sample is not representative, do the authors address this in the limitations section of the paper?
3. Do the authors report outcomes based on race? Do they discuss race as a biological factor? Do they account for social determinants of health or racism as an alternate cause of the outcomes?
4. Are there any instances of noninclusive language used to describe people or groups of people (eg, "Caucasian" instead of White, "non-White" instead of reporting specific racial or ethnic groups, etc)?

Community Health (DFMCH) (16 residents per post-graduate year [PGY]) during the 2023-2024 academic year (Figure 1). This study was exempt from review by the university's Institutional Review Board.

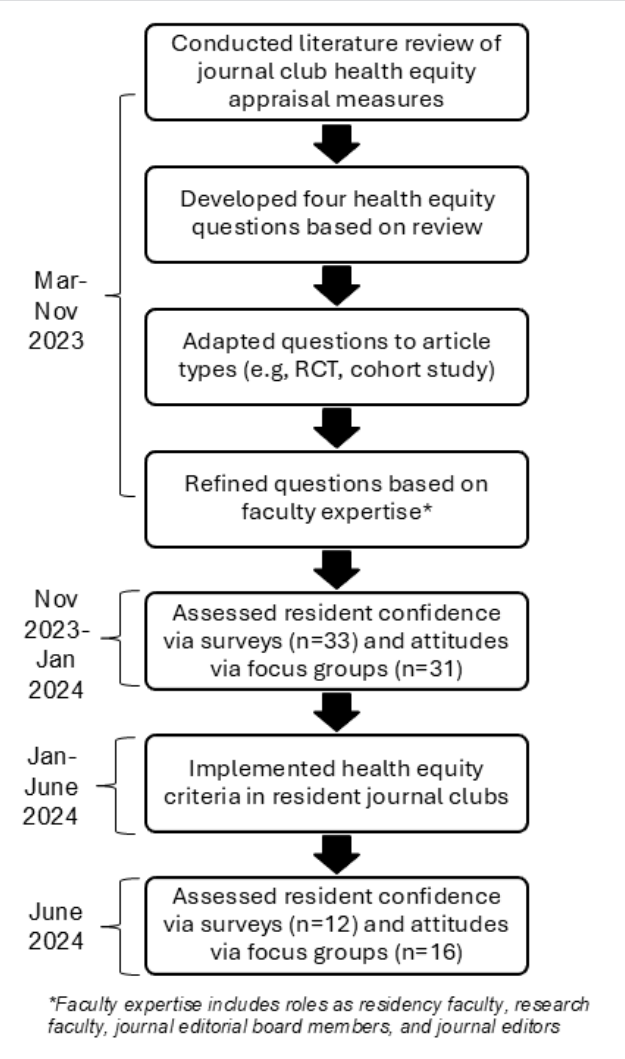
As part of the residency curriculum, each resident leads a 1-hour journal club to review a research article relevant to their clinical practice. Residents use article evaluation rubrics with guiding questions prepared by residency program faculty to assess relevance, validity, study population, study design, study conduct, and results.

We reviewed existing literature to develop 4 questions to guide learners in evaluating health equity implications of research articles by applying a health equity lens framework.[7] We refined these questions based on author expertise as residency faculty, researchers, journal editorial board members, and journal editors (Box). We added 1 question to each of the 4 main sections of the article evaluation rubric to encourage consideration of health equity throughout (Appendix). We then adapted questions for application across the various study designs routinely discussed in journal club (eg, cohort, randomized controlled trial, systematic review).

Prior to implementing these new questions, we used baseline surveys and focus groups conducted between November 2023 and January 2024. Surveys measured the importance and frequency of, and confidence in, evaluating the health equity implications of research articles using a Likert scale from 1 ("not at all") to 4 ("very").

We implemented the new rubric questions in January 2024 and conducted follow-up surveys and focus groups before the end of the academic year in June 2024. Baseline and follow-up surveys and focus groups were administered to the same cohort of DFMCH residents. We compared differences in mean survey responses and identified key themes from the focus groups.

Figure. Timeline of Pilot Study Activities



Abbreviations: RCT, randomized controlled trial.

RESULTS

Baseline Results

The 2 baseline focus groups included PGY-1s (n = 14) and a combined group of PGY-2s and PGY-3s (n = 15). Prior to the intervention, most residents agreed that health equity implications are important to understand when evaluating research articles. However, they lacked confidence in appraisal skills and were concerned about the potential additional time commitment required because of the new questions.

Table 1 describes resident response to baseline survey questions. Prior to the intervention, residents (n = 33; 69% response rate) completed baseline surveys. While 97% of respondents reported that it was important or very important to consider health equity factors when evaluating a research paper, only 27% reported doing so. Only 18% were confident or very confident in their ability to evaluate how a study's approach incorporates health equity, and 15% reported they were confident or very confident in their ability to evaluate the implications of findings on health equity.

Follow-up Results

The 2 follow-up focus groups included PGY-1s (n = 9) and PGY-2s/

PGY-3s (n = 7). Participants expressed overall positive reactions to the new questions. Identified themes included: (1) the questions were valuable in helping residents think about health equity systematically, and (2) the new questions integrated well with the existing rubrics without adding a time burden. Participants reported that the new questions offered a framework for measuring impact on health equity.

Twelve residents completed follow-up surveys, showing significant increases in mean confidence to evaluate how a study's approach incorporated health equity (baseline mean [SD], 2.1 [0.7] vs follow-up mean [SD], 2.8 [0.6]; $P = .004$) (Table). Similarly, there was a significant increase in mean confidence to evaluate the impact of findings on health equity (baseline mean [SD], 1.9 [0.7] vs follow-up mean [SD], 2.5 [0.5]; $P = .002$) (Table).

Table. Mean Responses to Attitudes About and Confidence in Assessing the Health Equity Implications of Journal Articles Before and After Implementing New Evaluation Rubric Questions

	Before n = 33 Mean (SD)	After n = 12 Mean (SD)	Change in Mean
How important is it to pay attention to health equity factors when evaluating a research paper?	3.5 (0.6)	3.8 (0.5)	+0.3
How often do you think about health equity when reading a research paper?	2.3 (0.6)	2.9 (0.7)	+0.6[a]
How confident are you in your ability to evaluate how a study's approach incorporated health equity?	2.1 (0.7)	2.8 (0.6)	+0.7[a]
How confident are you in your ability to evaluate the impact of a research study's findings on health equity?	1.9 (0.7)	2.5 (0.5)	+0.6[a]

Scores ranged from 1 to 4 with higher scores reflecting greater importance, frequency, or confidence.

[a]Statistically significant change in the mean value with $P < .05$.

DISCUSSION

In this pilot study, we established that the ability to assess the health equity implications of research articles is important to family medicine residents. With the addition of guiding questions to journal club rubrics, residents reported increased frequency and average confidence in their ability to assess health equity implications. These results suggest that such questions are acceptable to residents and feasible to implement. Because validated tools do not exist for this purpose, our findings can support other residency programs seeking to improve health equity education, training, and resources.

This work builds on previous efforts to advance the assessment of health equity in research practices (eg, randomized trials,[8] implementation research[9]). Within academic medicine, activities that promote health equity—such as building relationships and developing research questions with community partners and building diverse and inclusive work environments—have often been considered auxiliary to the work expected for academic promotion.[10] Integrating health equity into journal clubs emphasizes its relevance during medical education. Little research has examined how applying a health equity lens in journal clubs can improve understanding and the application of health equity within research. Previous attempts focused on topics related to diversity, equity, inclusion, or social determinants of health.[11,12] However, evaluating the potential implications of health equity within scholarly articles is a novel training activity for graduate medical education.

Limitations of this study include a small sample size, single-institution setting, and a lack of validated questions. Additionally, the response rate was low after the intervention despite multiple reminders. The same group of residents was invited to participate in focus groups before and after the intervention, but participation varied. By the end of the study, all PGY-3 residents had completed residency and were more difficult to contact.

Future work includes conducting a Delphi study with health equity research experts to develop consensus on criteria for medical residents and other learners to consider as they critically appraise the health equity implications of research articles. Subsequently, this research may be extended to other residency programs and disciplines. These additions to existing journal club curricula may help advance Family Medicine ACGME's efforts to address social needs and disparities.

Financial disclosures: None declared.

Funding/support: This project was made possible by the UW–Madison Institute for Clinical & Translational Research with support from NIH-NCATS Clinical and Translational Science Award (CTSA) 1UL1TR002373, funds through a grant from the Wisconsin Partnership Program at the University of Wisconsin School of Medicine and Public Health Program, Wisconsin Partnership Program (WPP 5129), and departmental grants through the University of Wisconsin School of Medicine and Public Health Department of Family Medicine and Community Health.

Appendix: Available at www.wmjonline.org

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A Case of Autoimmune Thyroiditis Presenting as Apraxia

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ABSTRACT

Introduction: Autoimmune thyroiditis, commonly referred to as Hashimoto's thyroiditis, is the leading cause of hypothyroidism in iodine-sufficient regions. Neurologic manifestations are uncommon.

Case Description: A 20-year-old female with no significant medical history presented with aphasia and episodes of nonsensical speech. Initial workup was unremarkable, and she was discharged. She subsequently returned with recurrent neurologic symptoms, including apraxia and headache. Further evaluation revealed an elevated thyroid-stimulating hormone (TSH) level and markedly elevated antithyroid peroxidase (anti-TPO) antibodies. A diagnosis of autoimmune thyroiditis was made, and treatment with levothyroxine led to improvement in symptoms.

Discussion: Autoimmune thyroiditis can have atypical presentations, particularly in younger individuals. Genetic predisposition and family history may increase susceptibility. Early recognition is critical in identifying cases such as Hashimoto's encephalopathy, which may resolve completely with appropriate treatment.

Conclusions: We present a case of autoimmune thyroiditis that manifested solely with neurological symptoms. It is crucial to consider hypothyroidism when treating complex, undifferentiated patients.

INTRODUCTION

Autoimmune thyroiditis (AIT), traditionally referred to as Hashimoto's thyroiditis, is the most common autoimmune thyroid disorder and the leading cause of hypothyroidism in iodine-sufficient areas.[1] AIT occurs in approximately 0.3 to 1.5 cases per 1000 persons annually, with a frequency 4- to 10-fold higher in women than in men.[1] The cause of AIT remains unknown; however, the primary risk factor, as with many autoimmune conditions, is thought to be a combination of genetic susceptibility and environmental triggers that result in loss of immunological tolerance. Treatment includes levothyroxine, although case reports have shown that residual symptoms may persist for years despite initiation of treatment.[2]

CASE PRESENTATION

A 20-year-old female with no past medical history presented to an outside emergency department (ED) after an episode of gross aphasia, during which her speech was nonsensical when present. Four days prior to presentation, she developed myalgias, malaise, and congestion that waxed and waned over several days. Physical examination was notable for dysarthria; otherwise, findings were normal. Initial laboratory results, including a basic metabolic panel and complete blood cell count (CBC), are shown in the Table. Her Electrocardiography (ECG) demonstrated normal sinus rhythm. Noncontrast computerized tomography of the head revealed no acute intracranial abnormality.

Medical decision-making at the outside hospital indicated that, in the absence of laboratory or imaging abnormalities, her aphasic episode was most consistent with a panic attack. Psychiatry was not consulted; ED staff made the diagnosis. She was discharged home without further intervention.

The patient returned to our ED the next day with headache and apraxia, in addition to continued episodes of aphasia. Repeat laboratory results are shown in the Table. Due to concerns for encephalitis, a lumbar puncture was performed (see Table). Additional history obtained during this encounter revealed that she had spent the summer working as a camp counselor and had

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experienced a rash during her recent illness that spanned the bilateral upper and lower extremities while sparing the palms of her hands and the soles of her feet; therefore, Lyme serologies were obtained (see Table). CBC showed no leukocytosis, arguing against infection, and the basic metabolic panel revealed no metabolic abnormalities. Cerebrospinal fluid (CSF) cultures and nucleic acid amplification testing were negative for all organisms tested. CSF cell count and glucose were within normal limits, reducing the likelihood of meningitis. Borrelia burgdorferi antibodies were negative, making Lyme disease unlikely. She was discharged with a working diagnosis of an unknown headache disorder.

She returned to the ED the following day after additional episodes of impaired cognition and another apraxic episode during which she was unable to dress herself. She had also developed a bilateral headache, nausea, and vomiting. Neurologic exam was normal; however, neurology was consulted given ongoing neurologic symptoms. Neurology recommended adding paraneoplastic studies and N-methyl-D-aspartate (NMDA) receptor antibody testing to the previously collected CSF, as the workup to date had been unrevealing. Brain magnetic resonance imaging and magnetic resonance venography were obtained and demonstrated no acute intracranial abnormality (Figure). Repeat laboratory testing was suggestive of AIT (Table).

Additional history revealed a family history of hypothyroidism in her mother and both maternal and paternal grandmother; her maternal grandmother also had Sjögren syndrome. Notably, the patient denied changes in weight or appetite, constipation, or cold intolerance.

Electroencephalography, obtained on admission per neurology recommendation, revealed mild diffuse background slowing, consistent with hypothyroidism. Based on her elevated thyroid-stimulating hormone (TSH; 28.3 µIU/mL), low thyroxine (T4; 0.76 ng/dL), and markedly elevated antithyroid peroxidase antibodies (>600 IU/mL), a diagnosis of AIT was made, and levothyroxine therapy was initiated. Given the patient's neurological symptoms, she met diagnostic criteria for Hashimoto's encephalopathy (Box). She was referred for outpatient follow-up with endocrinology.

Review of the patient's medical record 6 months later showed that levothyroxine dosing had been titrated in response to fluctuating TSH levels, ultimately reaching 100 µg daily, with complete resolution of neurologic symptoms. Steroids were not administered, as her symptoms had improved with levothyroxine alone. A timeline of her hospital presentations is provided in the Table.

Table. Timeline of Hospital Presentations and Laboratory Results

Date	Visit
Day 0	Presented to an outside emergency department for an episode of aphasia. Work-up normal, discharged with diagnosis of panic attack.
Day 1	Presented after another episode of headache, apraxia, and aphasia. Repeat lab testing, with addition of Lyme serology, lumbar puncture, and MRI brain are unremarkable. Discharged with working diagnosis of unknown headache disorder.
Day 2	Presented with continuing episodes of impaired cognition and apraxia. Thyroid testing suggestive of autoimmune thyroiditis. EEG with findings consistent with hypothyroidism. Diagnosis of Hashimoto's encephalopathy made.

Abbreviations: MRI, magnetic resonance imaging; EEG, electroencephalography.

Box. Diagnostic criteria for Hashimoto's encephalopathy[6]

Diagnosis can be made when all six of the following criteria have been met:

1. Encephalopathy with seizures, myoclonus, hallucinations, or stroke-like episodes
2. Subclinical or mild overt thyroid disease (usually hypothyroidism)
3. Normal Brain magnetic resonance imaging or with nonspecific abnormalities
4. Presence of serum thyroid (thyroid peroxidase, thyroglobulin) antibodies
5. Absence of well-characterized neuronal antibodies in serum and cerebrospinal fluid
6. Reasonable exclusion of alternative causes

DISCUSSION

Autoimmune thyroiditis (AIT) is a rare autoimmune disorder with diverse and sometimes confusing clinical presentations. While the exact cause remains unknown, genetic susceptibility is supported by epidemiologic data, with siblings of affected patients demonstrating a significantly increased risk. AIT is more common in monozygotic twins (29%-55%) than in dizygotic twins.[1]

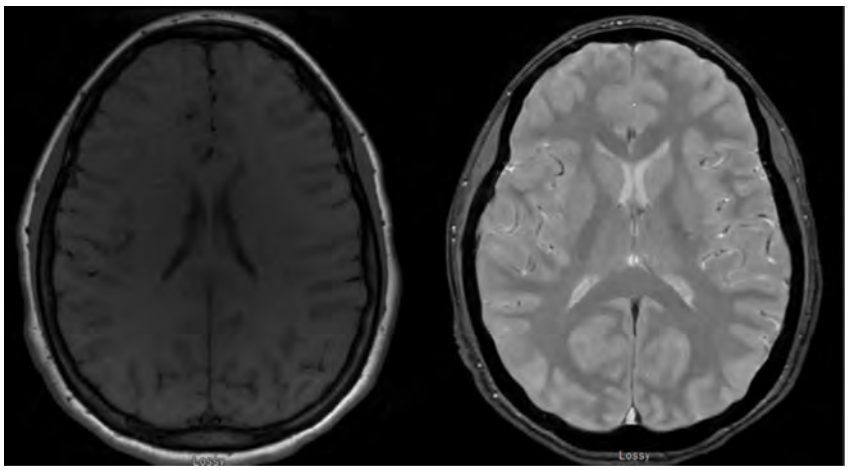
AIT involves both humoral (B cell-mediated) and cellular (T cell-mediated) processes. Pathogenesis includes a breakdown in immune tolerance, resulting in production of autoantibodies against thyroid peroxidase (anti-TPO) and thyroglobulin (anti-Tg), both of which are essential for thyroid hormone synthesis.[1] Antibodies against the TSH receptor may also be present in a subset of patients and can be stimulating, blocking, or neutral.[3] These autoantibodies, along with T cell–mediated cytotoxicity, contribute to the progressive follicular destruction. CD8+ cytotoxic T cells induce apoptosis of thyroid epithelial cells, while CD4+ helper T cells release pro-inflammatory cytokines (eg, IL-2, IFN-γ, TNF-β), exacerbating tissue damage. Genetic predisposition and environmental factors, such as viral infections and excessive iodine intake, further modulate disease progression.[4]

As thyroid tissue is destroyed, thyroid hormone production declines, leading to increased pituitary TSH secretion. Over time, the gland undergoes fibrosis and atrophy, resulting in progressive hypothyroidism.[4] Understanding the pathophysiology is critical for guiding diagnostic evaluation and therapy, including thyroid function monitoring and hormone replacement.

Patients with AIT typically present with hypothyroidism and/or goiter.[5] Clinical manifestations vary by disease stage, with early disease primarily presenting as asymptomatic. Goiter may also be present early. In goitrous AIT, also known as classic Hashimoto

disease, patients have a diffusely enlarged, firm thyroid gland that often has an irregular surface.[5] Thyroid enlargement typically ranges from minimal to massive, but in most cases the thyroid weighs approximately 2 to 3 times normal.[5] Although a feeling of neck tightness is common, thyroid pain and tenderness are rare.[5] In atrophic AIT, patients present without goiter.[5] Rarely, transitory hyperthyroidism (Hashitoxicosis) may occur due to follicular rupture of hormone-containing thyroid tissue, manifesting with symptoms such as irritability, heat intolerance, and diarrhea before progression to hypothyroidism.[7]

Figure. Unremarkable Magnetic Resonance Imaging of the Brain Without Contrast (Left) and Unremarkable Magnetic Resonance Venography of the Brain Without Contrast (Right).



As disease progresses, the thyroid may become normal-sized or small if extensive fibrosis has occurred, and patients may show signs of hypothyroidism.[5] Common symptoms include fatigue, lethargy, dry skin, cold sensitivity, muscle cramps, constipation, and voice changes. Less common manifestations, typically associated with severe or late-stage disease, include sleep apnea, pituitary hyperplasia, myxedema, and carpal tunnel syndrome.[7]

Diagnostic evaluation of AIT includes thyroid function tests and thyroid antibody testing. Thyroid function results vary by stage, with early disease showing transient hyperthyroidism (low TSH, high free T3, high free T4), progressive disease showing subclinical hypothyroidism (mildly elevated TSH, normal free T3/T4), and late-stage disease showing overt hypothyroidism (high TSH, low free T3, low free T4). Thyroid antibody testing is diagnostic, with antithyroid anti-TPO antibodies present in up to 95% of patients and anti-Tg antibodies in 60% to 80% of patients.[8]

The gold standard treatment symptomatic autoimmune hypothyroidism is daily, lifelong oral levothyroxine (L-T4), which addresses hormonal deficiency rather than disease pathogenesis.[7] Dosing is individualized to normalize serum TSH and typically averages 1.6 to 1.8 kg/day.[7] With appropriate therapy and lifelong monitoring, patients typically experience favorable outcomes with adequate symptom management.

A rare complication of AIT is Hashimoto's encephalopathy, an uncommon neurological syndrome with widely variable clinical features, including cognitive impairment, myoclonus, ataxia, seizures, and psychosis.[9] The condition affects approximately 2 per 100 000 individuals.[10] In a review of approximately 3000 patients with positive thyroid antibodies, only 5% met the criteria for Hashimoto's encephalopathy.[11] Diagnostic criteria include encephalopathy with seizures, myoclonus, hallucinations, or stroke-like episodes; dysthyroid state (typically hypothyroidism); normal or nonspecific brain MRI findings; presence of serum thyroid antibodies; absence of well-characterized neuronal antibodies in serum and CSF; and reasonable exclusion of alternative diagnoses (Figure).[6] Our patient met these criteria

Although steroid responsiveness is often observed and may support diagnosis, it is not established as part of the diagnostic criteria. Another case series and literature review described treatment with corticosteroids in combination with management the underlying dysthyroid state.[10] Given this patient's improvement with levothyroxine alone, steroids were deferred. Early recognition and treatment are essential, as timely intervention can significantly improve patient outcomes. Further research is needed to clarify pathogenesis and optimize management.

CONCLUSIONS

We report a rare case of Hashimoto's encephalopathy presenting solely with neurologic symptoms. This case highlights the importance of considering hypothyroidism in complex, undifferentiated presentations, as its presentation can vary widely. Awareness of AIT as a potential etiology for unexplained neurologic symptoms may facilitate earlier diagnosis and treatment, with levothyroxine leading to complete resolution of symptoms.

Financial disclosures: None declared.

Funding/support: None declared.

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Cervical Tuberculosis Lymphadenitis (Scrofula) in Wisconsin: Case Report, Pitfalls and Challenges

Carlos E. Figueroa Castro, MD, MS; April A. Shera, MD

ABSTRACT

Introduction: This case report presents a case of cervical tuberculous lymphadenitis (scrofula) in Wisconsin, illustrating the diagnostic challenges in a low-prevalence setting. It emphasizes the importance of including tuberculosis (TB) in the differential diagnosis of persistent cervical lymphadenopathy, particularly in patients with a history of latent TB infection.

Case Presentation: A 37-year-old woman presented with a persistent, painless left-sided neck mass without local warmth or erythema, characteristic of a cold abscess. Initial imaging demonstrated lymph node abnormalities, while multiple diagnostic tests were inconclusive. After misdiagnosis and unsuccessful treatments, she was eventually diagnosed with TB lymphadenitis. She completed a prolonged course of antituberculous therapy, followed by surgical intervention, with complete resolution of symptoms.

Discussion: This case underscores the need for a high index of suspicion for tuberculosis in patients with chronic cervical lymphadenopathy, even in regions with low TB prevalence. It also highlights the importance of thorough clinical and exposure history and the potential for diagnostic delay in atypical presentations, particularly when medical records are fragmented across health care systems.

INTRODUCTION

In the United States, a recent report by the Centers for Disease Control and Prevention revealed an increase in the incidence of tuberculosis (TB), with 9615 cases (2.9 per 100 000 persons) reported in 2023. This represents a 16% increase compared with 2022, reversing a 27-year decline following the COVID-19 pandemic.[1] Most cases (76%) occurred in people born outside the United States, including 34% among individuals of Asian descent. Multiple factors have contributed to this postpandemic increase, including diversion of staff and resources away from TB control programs. Extrapulmonary TB accounts for 30% of cases, most commonly affecting the lymph nodes.[2] Its proportion has increased over recent decades, from 15.7% in 1993 to 22.4% in 2019.[3] TB lymphadenitis, also known as scrofula, represents the most frequent form of extrapulmonary TB in the United States, accounting for approximately 25% of cases.[2] In areas with low incidence of TB including Wisconsin—where case rates have remained consistently below 1 per 100 000 population (Table)[4]—diagnosis of tuberculous lymphadenitis presents unique challenges. Nonspecific presenting symptoms, combined with the relative rarity of the condition, often lead to delayed diagnosis and inappropriate initial treatment.

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CASE PRESENTATION

A 37-year-old female of Southeast Asian ethnicity, born in the Philippines and who immigrated to the United States 11 years earlier, sought medical evaluation for a left-sided neck mass. The lump had gradually enlarged over 6 weeks, was approximately grape-sized, persistent, firm to touch, and mildly tender. The node was characteristically cold, without local warmth, erythema, pustule formation, or fever, consistent with a cold abscess. She denied cough, sputum production, emesis, nausea, diarrhea, hematuria, or lymphadenopathy at other sites. Her medical history included asthma, gestational diabetes, hypothyroidism treated with levothyroxine, and polycystic ovarian syndrome.

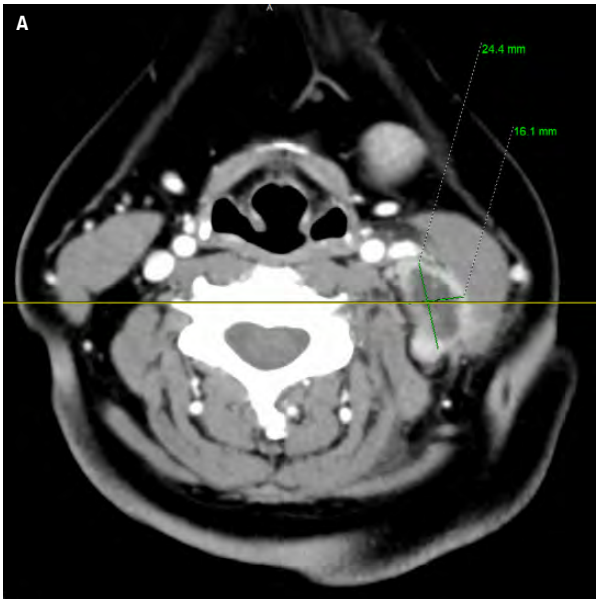
Table. Highest Incidence Rates of Tuberculosis in Wisconsin Counties in 2022[4]

County	Region	2022 Population by Region	Incidence per 100 000
Milwaukee	Southeastern	2 055 647	0.63
Dane	Southern	1 288 908	0.62
Marathon	Northern	497 642	0.60
Kenosha	Southeastern	2 055 647	0.19
Brown	Northeastern	1 287 166	0.15
Winnebago	Northeastern	1 287 166	0.15
Appleton	Northeastern	1 287 166	0.15
Greenfield	Southeastern	2 055 647	0.14
South Milwaukee	Southeastern	2 055 647	0.14
Monroe	Western	819 792	0.12

Physical examination revealed normal vital signs and firm, nonwarm enlarged lymph node (2 cm diameter) in the left anterolateral cervical region without local erythema. Chest examination was unremarkable, and no splenomegaly was noted. Laboratory testing revealed mild leukocytosis with neutrophil predominance (14 200 cells/µL; neutrophils, 93.7%), elevated erythrocyte sedimentation rate (41 mm/h), and C-reactive protein level of 1.66 mg/dL. HIV screening was negative. Neck ultrasound demonstrated hypoechoic, enlarged left-sided lymph nodes at level III (middle internal jugular, 1.1 cm), level IV (lower internal jugular, 0.9 cm), and level V (posterior triangle, 0.7 cm). Additional workup included negative Lyme serology, Epstein-Barr virus serology consistent with prior exposure, negative testing for acute cytomegalovirus infection, and a negative antistreptolysin O titer. Was treated with amoxicillin-clavulanic acid for 10 days but noted increased swelling and development of low-grade fever. Oral prednisone resulted in temporary clinical improvement, but symptoms returned after steroid completion.

Six weeks after initial presentation, the patient was admitted after CT imaging showed a lobulated, peripherally enhancing left level II (upper internal jugular) and level III lesion deep to the sternocleidomastoid muscle, concerning for suppurative adenitis, with prominent left cervical lymph nodes, some demonstrating central cystic change and necrosis (Figure 1A and 1B). No suspicious masses were identified in the nasopharyngeal soft tissues or thyroid. A right apical calcified granuloma was incidentally noted on the same CT scan, which included upper chest structures. She received vancomycin and piperacillin-tazobactam, followed by de-escalation to ampicillin-sulbactam. Percutaneous needle drainage by interventional radiology yielded thick purulent material. Standard bacterial cultures were negative; 16S ribosomal RNA testing was not performed. Fungal cultures were negative. Pathology evaluation revealed granulomatous inflammation with necrosis, without malignancy, and negative stains for acid-fast bacilli (AFB) and fungi. A mycobacterial culture was sent, but results were pending at discharge. She was discharged on clindamycin for 7 days but returned to the hospital with persistent symptoms despite antibiotic therapy.

Figure. Axial (A) and Coronal (B) Computed Tomography Scan of Neck With Intravenous Contrast With Lobulated Peripherally Enhancing Lesion Deep to the Sternocleidomastoid Muscle, and Left Cervical Lymph Nodes With Central Cystic Change and Necrosis



Further history revealed TB screening with a protein purified derivative (PPD) skin test during a job application 7 years before symptom onset. She described a large, tender, and red reaction, though documentation of induration and size was unavailable. A chest x-ray obtained at that time was normal. She was diagnosed with latent TB infection (LTBI), but treatment was not offered

after the reaction was attributed to prior bacille Calmette-Guérin (BCG) vaccination. She denied known contact with individuals with active tuberculosis.

Additional evaluation revealed negative *Bartonella* titers and normal chest x-ray. QuantiFERON TB testing was positive. Given concern for scrofula, a planned incisional biopsy was replaced with a repeat fine-needle aspiration performed 6 days after the initial procedure, again yielding purulent material. Pathologic evaluation showed acute inflammation and necrosis without malignancy. AFB stain was positive (3+). Cultures for common bacteria and fungi remained negative. Testing at the Wisconsin State Laboratory of Hygiene detected *Mycobacterium tuberculosis* complex DNA, with no evidence of *Mycobacterium avium-intracellulare* complex. Three sputum samples were negative for AFB and negative by nucleic acid amplification testing (Cepheid Xpert MTB/RIF assay). The aspirate culture eventually grew *M tuberculosis* after 6 weeks of incubation, but susceptibility results were available because of poor growth.

After diagnosis of cervical tuberculous lymphadenitis (scrofula), the patient began TB therapy in coordination with the local health department. The initial regimen included daily isoniazid, rifampin, ethambutol, and pyrazinamide for 8 weeks, followed by isoniazid and rifampin for 18 weeks, with vitamin B6 supplementation. Complications included pyrazinamide-associated hyperuricemia, managed with allopurinol and discontinuation of pyrazinamide after 6 weeks. Around this time, she developed purulent drainage, with cultures growing *Staphylococcus capitis,* initially treated with doxycycline and later switched to cephalexin because of diarrhea. Repeat imaging revealed enlargement of peripherally enhancing lesions, increased adjacent tracts, and similar enlargement of adjacent lymph nodes. A third ultrasound-guided aspiration was negative for bacteria, fungi, and AFB; mycobacterial cultures remained negative after 8 weeks. The initial phase of therapy with isoniazid, rifampin, and ethambutol was extended for 6 additional weeks after pyrazinamide discontinuation (total, 12 weeks), resulting in resolution of swelling and drainage. She completed a 6-month total course of isoniazid and rifampin.

Mild transaminitis was observed (maximum ALT, 46 U/L; AST, 59 U/L; references ranges ALT, 6-37 U/L; AST 111–33 U/L) and was monitored without therapy modification. Liver ultrasound demonstrated hepatic steatosis. Transaminitis resolved after completion of therapy.

Three weeks after treatment completion, the patient reported recurrent swelling. CT imaging showed a slight decrease in treated adenopathy in the left neck and reduced anteroposterior dimension of the low-attenuation collection medial to the left sternocleidomastoid muscle. Because of progressive swelling, she underwent excision of the left deep cervical lymph node and skin. Local culture grew methicillin-susceptible *Staphylococcus aureus* (MSSA) treated with trimethoprim-sulfamethoxazole for 10 days. Pathology showed granulomatous dermatitis with necrosis; AFB and fungal stains were negative, and AFB cultures remained negative after 8 weeks of incubation. At 12-month follow-up, the patient had complete healing of the surgical site with no swelling, tenderness, erythema, or drainage.

DISCUSSION

This case highlights several important aspects of the current understanding and management of TB lymphadenitis. Although scrofula remains one of the most common forms of extrapulmonary TB, its diagnosis and management continue to present challenges in both endemic and nonendemic settings. Diagnosis requires a high index of suspicion, as several infectious and noninfectious conditions may present similarly.[5] The patient's demographic and clinical features in our case align with current epidemiologic trends. A meta-analysis of head and neck TB (57 studies; 6950 cases) reported a predominance of cervical lymph node involvement (87.9%), followed by laryngeal (8.7%) and other sites (3.4%). Risk factors included age <40 years (83%), female sex (53.8%), HIV infection (31.3%), and foreign-born status (44.2%).[6] A retrospective study from Texas reported cervical lymph node involvement in 96.9% of cases; 52.7% were female, and 26.5% had both extrapulmonary and pulmonary TB (26.5%). Identified risk factors included positive HIV status, homelessness, excessive alcohol use, and drug use.[7]

Whether extrapulmonary TB is increasing overall remains unclear; however, older adults with weakened immune systems represent another important at-risk population, even when cancer initially seems more likely.[8] Our patient exemplified several recognized risk factors, including female sex, age younger than 40 years, and birth in a TB-endemic region. Her presentation as a classic cold abscess – firm, nontender swelling without warmth or erythema – is characteristic of TB lymphadenitis and should prompt suspicion for TB, particularly when appropriate risk factors are present.

This case also illustrates both the utility and limitations of current testing methods. While imaging studies helped delineate the extent of disease, definitive diagnosis required histopathological confirmation. Fine-needle aspiration cytology is a valuable first-line diagnostic tool, whereas excisional biopsy remains the gold standard, particularly when diagnosis is uncertain, alternative diagnosis such as neoplasm is suspected, or response to therapy is poor.[5] Despite the presence of granulomatous inflammation, negative AFB staining does not rule out TB. This may be explained by several factors, including the paucibacillary nature of some tuberculous lesions, sampling error, or prior broad-spectrum antibiotic exposure with partial activity against *Mycobacterium*. The sensitivity of AFB smear in extrapulmonary TB ranges from 0% to 40%, contributing to diagnostic delay. With respect to our patient's positive PPD history, current guidelines do not recommend discounting positive tuberculin skin

tests because of prior BCG vaccination, especially with reactions >15 mm. In such cases, interferon-gamma release assays are preferred because of higher specificity.[9] This represented a missed opportunity for LTBI treatment that might have prevented progression to active disease.

Treatment with standard 4-drug therapy under in coordination with the local health department reflects current TB treatment guidelines. Posttreatment recurrence of symptoms in this case could be related to a paradoxical reaction or postoperative complication, rather than treatment failure. Paradoxical reactions (transient worsening or appearance of new lesions despite appropriate therapy) can occur in 20% to 30% of cases and should not be misinterpreted as treatment failure.[5] Supporting factors include recurrence after therapy completion, granulomatous inflammation with persistently negative AFB stain and cultures for *Mycobacterium*, and lack of further recurrences while off anti-TB therapy. Isolation of MSSA may be related to inadequate initial source control or superimposed infection of the surgical site, may be influenced by the extensive nature of the disease and possibly worsened by the immunomodulatory effects early corticosteroid exposure. Extended therapy (9 months) is considered for extensive or complicated cases, although outcomes are generally favorable.[5] This case underscores the importance of screening for HIV, evaluating pulmonary involvement, reviewing TB history, and ensuring long-term follow-up.[10-12]

From a public health perspective, this case highlights challenges posed by fragmented medical records across different health care systems. Prior TB screening and occupational health records were unavailable to treating clinicians, potentially contributing to diagnostic delays. Improved cross-system health information exchange could facilitate earlier detection and appropriate management.

CONCLUSIONS

This case report emphasizes the need for a high index of suspicion for TB in patients with chronic cervical lymphadenopathy and "cold abscess" features, even in low-prevalence areas such as Wisconsin. It underscores the risk of diagnostic delay, the importance of comprehensive history-taking—including immigration and occupational screening—and the need for close monitoring during and after treatment. Clinicians should recognize the possibility of paradoxical reactions and the potential need for surgical intervention. Accurate interpretation of TB screening tests and appropriate follow-up of positive results remain essential in preventing progression from latent to active TB disease.

Financial disclosures: None delcared.

Funding/support: None delcared.

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A Challenging Case of Creutzfeldt-Jakob Disease Presenting as Stroke

Kassandra Ogbodu, BS; Morgan Lucero, BS; Pinky Jha, MD, MPH

ABSTRACT

Introduction: Early recognition of Creutzfeldt-Jakob disease relies on awareness of its clinical variability, particularly in patients with complex medical comorbidities.

Case Presentation: A 66-year-old woman presented with generalized weakness, tremor, double vision, and slurred speech. Initial imaging and laboratory studies were unremarkable, except for subtle magnetic resonance imaging findings suggestive of encephalitis. Despite treatment with methylprednisolone, her condition worsened. Repeat magnetic resonance imaging raised suspicion for Creutzfeldt-Jakob disease, which was confirmed by cerebrospinal fluid real-time quaking-induced conversion positivity and elevated total tau protein. She succumbed to the disease within a month.

Discussion: Creutzfeldt-Jakob disease is a rare, rapidly progressive prion disease that is often misdiagnosed due to nonspecific early symptoms. Extensive imaging and laboratory investigations may delay diagnosis, as seen in this case.

Conclusions: This case highlights the diagnostic challenges and rapid progression of Creutzfeldt-Jakob disease, emphasizing the need for early recognition and standardized intervention to improve patient care.

INTRODUCTION

Prion diseases are fatal, transmissible brain disorders that affect mammals and currently have no effective treatments.[1] These conditions are caused by an unusual mechanism in which the host's normal prion protein misfolds and aggregates into infectious structures known as prions, leading to progressive brain damage. This process, which can remain asymptomatic for years, is believed to underlie the most common human prion disorder, sporadic Creutzfeldt-Jakob disease (CJD).[2] CJD is clinically marked by rapidly worsening cognitive impairment and progression to akinetic mutinism, with pathologic features that include spongiform degeneration of the gray matter and accumulation of misfolded prion protein.[3] In humans, prion diseases are exceptionally rare, with an annual mortality rate estimated at 1 to 2 cases per million persons.[4] They can be categorized into 3 forms: sporadic, infection-acquired, and familial. Ongoing studies linking neurological symptoms to pathological findings, especially in atypical cases, are essential to improving our understanding of CJD pathogenesis.

CASE PRESENTATION

A 66-year-old woman presented to the emergency department (ED) with generalized weakness, tremor, diplopia, and slurred speech. Her medical history included multiple transient ischemic attacks (TIAs) in 2018 and 2023, hyperlipidemia, metabolic syndrome, anemia, benign paroxysmal positional vertigo, fibromyalgia, syringomyelia, degenerative disc disease, and depression. Following the TIA in 2018, she experienced mildly diminished sensation over the left side of her face and extremities, which resolved without permanent deficits. Previous TIAs had not resulted in lasting neurological symptoms.

Two months before this presentation, the patient had developed bilateral neuropathy in her hands and feet, which progressed proximally to her shoulders and buttocks. She also reported gait abnormalities characterized by a high-stepping pattern with intermittent crossing of the feet over the midline, as well as a slight right facial droop and increasing difficulty with balance and ambulation.

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On initial examination, she demonstrated abnormal finger-to-nose testing on the right, diminished right upper extremity strength, and slowed speech with intermittent stuttering. There was no resting tremor or distal sensory loss. Given concern for stroke, Neurology was consulted. Her National Institutes of Health Stroke Scale (NIHSS) score was 1 upon arrival and 0 during observation. Vital signs and the rest of the physical examination were stable. Initial workup, including complete blood cell count (CBC), basic metabolic panel (BMP), computed tomography (CT) of the head, and CT angiography (CTA) of the head and neck, was unremarkable. An electroencephalogram (EEG) revealed prominent slowing in the left cerebral hemisphere, prompting further investigation. Magnetic resonance imaging (MRI) of the brain showed mild signal changes in the right occipital lobe, left basal ganglia, and cingulate gyri, findings considered more suggestive of uncomplicated encephalitis or recent seizure activity rather than ischemia or prion disease (Figure 1). Given concern for an autoimmune etiology, the patient was started on a 5-day course of high-dose intravenous methylprednisolone.

Figure 1. Initial Magnetic Resonance Imaging Demonstrating Nonspecific and Subtle Abnormalities in the Right Occipital Lobe, Left Basal Ganglia and Cingulate Gyri

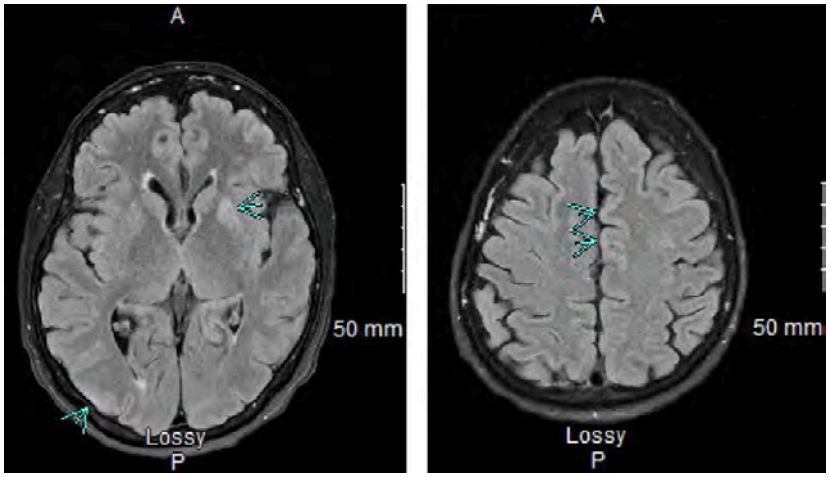
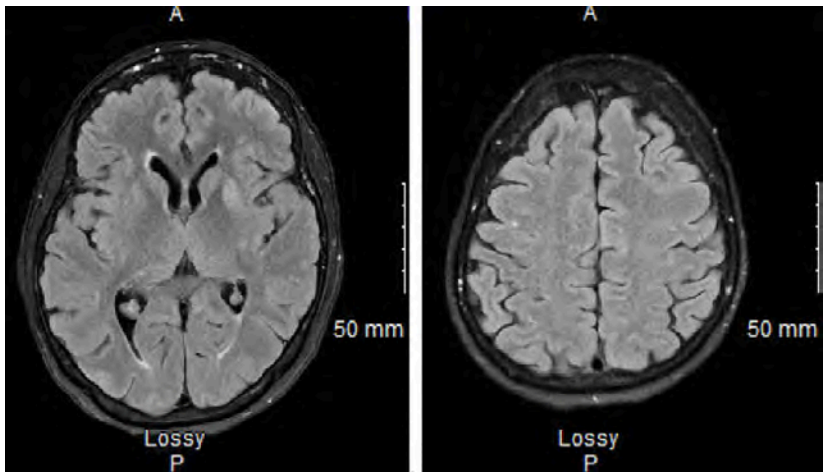


Figure 2. Repeat Magnetic Resonance Imaging Obtained Four Weeks Later Showing Progressive Cortical and Basal Ganglia Signal Abnormalities



Approximately 4 weeks later, her condition worsened despite treatment. She developed increasing ataxia, difficulty ambulating, and worsening balance issues. A repeat MRI demonstrated progressive signal abnormalities (Figure 2). Additional testing, including lumbar puncture, serum autoimmune/paraneoplastic panel, and cerebrospinal fluid (CSF) immunoglobulin G (IgG), returned unremarkable results. Due to the worsening clinical and radiological findings, suspicion for CJD increased, and further CSF testing for prion disease markers was ordered. At this point, the patient and her family elected to return home while awaiting results.

Subsequent CSF analysis revealed negative results for movement disorder markers; however, the real-time quaking-induced conversion (RT-QuIC) test was positive for prion disease, with a markedly elevated total tau protein level of 6422 pg/mL. These findings correspond to a greater than 98% likelihood of CJD. During a follow-up telemedicine visit 2 days after receipt of the tau protein results, the patient exhibited severe, rapidly progressive dementia, global ataxia, titubation of the head, and vocal tremor. Her condition continued to deteriorate, and she died 1 month after her initial ED presentation. The clinical presentation and diagnostic findings were consistent with a definitive diagnosis of sporadic CJD.

DISCUSSION

Creutzfeldt-Jakob disease (CJD) is a rare and uniformly fatal neurodegenerative disorder caused by prion proteins and characterized by rapid neurological decline. Early symptoms are often nonspecific or mimic other neurological conditions, frequently leading to misdiagnosis and delays in recognition. This report describes a case of sporadic CJD in a patient who initially presented with nonspecific, stroke-like neurological symptoms—including generalized weakness, tremor, diplopia, and slurred speech—that obscured the diagnosis and postponed appropriate management. This case

highlights the diagnostic challenges posed by atypical presentations when classical symptoms and imaging findings are absent and underscores the importance of early recognition of prion diseases for appropriate management.

This case demonstrates that CJD can present initially with features mimicking a cerebrovascular event, even though most patients present with ataxia and myoclonus, observed in approximately 90% of cases.[5] A review of the literature reveals only a limited number of reports describing CJD with this presentation (Table), emphasizing the importance of recognizing clinical presentations.

Table. Additional Case Reports Demonstrating Atypical Presentations Leading to Diagnostic Delays

Author Year	Patient Age	Presentation	MRI Findings	Diagnostic Modality
Kwon GT, et al[11] 2019	70	Rapid cognitive decline, aphasia, ataxia	Cortical ribboning on DWI without cerebral atrophy	CSF 14-3-3 protein; postmortem brain autopsy confirmed sCJD
Prodi, et al[12] 2020	59	Anomia, dyscalculia	Cortical diffuse restriction	RT-QuIC
Huang, et al[13] 2024	54	Severe and violent agitation	Restricted diffusion	14-3-3 and RT-QuIC; postmortem autopsy and Western blot

Abbreviations: MRI, magnetic resonance imaging; DWI, diffusion-weighted imaging; CSF, cerebrospinal fluid; sCJD, sporadic Creutzfeldt-Jakob disease; RT-QuIC, real-time quaking-induced conversion.

MRI remains the gold standard for in vivo diagnosis of CJD, with characteristic hyperintense lesions on diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) sequences, primarily affecting the corpus callosum, caudate nucleus, and superior parietal lobe.[6] However, this patient's initial MRI demonstrated only subtle and nonspecific alterations, none of which were diagnostic for CJD. Initial MRI findings may be subtle or absent; normal imaging does not exclude CJD. This underscores the need for clinical vigilance despite inconclusive imaging.

The diagnostic delay in this case series raises important considerations regarding current standards of care when CJD is included in the differential diagnosis. Early suspicion may prompt more aggressive diagnostic approaches, including CSF analysis. RT-QuIC, the most specific and sensitive test for prion disease, was positive in this case and, together with markedly elevated total tau protein levels, confirmed the diagnosis. RT-QuIC and other CSF biomarkers, including 14-3-3 protein and neurofilament light chain, are critical tools in cases where imaging findings are inconclusive.[7]

The clinical course of CJD is invariably rapid and fatal, with a median survival of 4 to 6 months after symptom onset.[8] In this case, the patient experienced rapid deterioration, progressing to severe dementia with global ataxia and titubation within weeks and ultimately dying 1 month after presentation. This course underscores the aggressive nature of prion diseases and the importance of timely diagnosis to support patient and family counseling and initiate palliative care. Palliative management focuses on symptom relief and quality of life. For example, myoclonus, a common symptom in CJD, can be managed with clonazepam or valproic acid.[9] Anxiety, agitation, and insomnia are common and may be managed with benzodiazepines or antipsychotic agents, depending on patient tolerance and symptoms.[10] Pain control is also essential and may require opioids, particularly in advanced stages of the disease. Nonpharmacological interventions, including physical therapy and assistive devices, may help reduce fall risk and maintain mobility early in the disease course.

A high index of suspicion should be maintained for any patient with rapidly progressive neurological decline. Our literature review identified several cases of CJD presenting with atypical symptoms, including manifesting resembling psychiatric illness (Table). These reports highlight the broad clinical spectrum of CJD and the potential for atypical symptoms to delay diagnosis and appropriate management.[11,12] Further research is needed to support earlier diagnosis and improved care for this fatal condition.

Although no interventions currently slow the progression of CJD, ongoing investigations into neuroprotective agents and antiprion therapies remain promising. Until effective treatments become available, early recognition and palliative care remain the cornerstone of CJD management. This report aims to raise awareness of an uncommon presentation of CJD and emphasizes the need for clinicians to consider prion disease in patients with rapidly progressive neurological or psychiatric symptoms.

CONCLUSIONS

This case emphasizes the diagnostic challenges associated with atypical presentations of CJD, particularly when symptoms mimic common conditions such as stroke. Early and accurate diagnosis is critical not only to facilitate appropriate patient and family counseling but also to avoid unnecessary and potentially harmful interventions. The diagnostic delay observed in this case highlights the importance of maintaining a high index of suspicion for CJD in patients with rapidly progressive neurological symptoms, even when initial imaging findings are nonspecific. Timely recognition allows patients and families to avoid prolonged diagnostic uncertainty and focus on palliative measures during the limited disease course.

Financial disclosures: None declared.

Funding/support: None declared.

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Drug-Induced Thrombocytopenia in an Immunosuppressed Renal Transplant Recipient: A Diagnostic and Therapeutic Challenge

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ABSTRACT

Introduction: Drug-induced thrombocytopenia (DITP) is a rare but life-threatening disorder, particularly in immunosuppressed patients; it can occur via immune and nonimmune mechanisms. β-lactam antibiotics are infrequently known to cause immune DITP.

Case Presentation: We present the case of a 30-year-old woman with a history of renal transplantation who developed severe thrombocytopenia while receiving ganciclovir for cytomegalovirus, and meropenem and cefoperazone/sulbactam for sepsis. Despite discontinuing ganciclovir, she developed thrombocytopenia, which worsened upon switching to cefoperazone. Her platelet count improved only after discontinuing both β-lactam antibiotics and the administration of eltrombopag.

Discussion: While ganciclovir is a well-known myelosuppressive agent, β-lactam antibiotics such as meropenem and cefoperazone have also been implicated in DITP, particularly via immune-mediated mechanisms. Similar case reports are limited, especially involving immunosuppressed patients requiring complex antimicrobial regimens.

Conclusions: Clinicians should monitor patients receiving antibiotics for DITP, particularly those on immunosuppressive therapy. This case underscores the need for close monitoring, early drug discontinuation, and consideration of thrombopoietin receptor agents in severe cases of DITP.

INTRODUCTION

Thrombocytopenia, defined as a platelet count of less than 150 000/μL, can result from multiple causes, including bone marrow suppression and increased platelet destruction. Drug-induced thrombocytopenia (DITP) is a well-known phenomenon[1] often associated with certain medications, particularly those affecting hematological function. This case describes a patient with DITP that persisted following discontinuation of the suspected agent. We aim to highlight the importance of monitoring platelet counts in patients receiving antibiotics with potential hematological toxicity and the significance of drug interactions in managing complex clinical scenarios involving immunosuppressed patients.

CASE PRESENTATION

A 30-year-old woman with a history of renal transplant 7 years prior was admitted to the hospital for recurrent diarrhea (8 to 10 daily episodes of watery, nonbloody stool), with the most recent episode 2 days prior. She had been hospitalized 2 weeks earlier for a similar complaint; at that time, the workup was negative except for cytomegalovirus (CMV) polymerase chain reaction (PCR) of 200 copies/mL. A colonoscopy performed nearly 6 months earlier was unremarkable. Following her previous discharge, she started oral valganciclovir. Additional medications included tacrolimus (1.5 mg twice daily), mycophenolate mofetil (500 mg twice daily), and oral prednisone (5 mg daily).

On physical examination, blood pressure was 90/50 mm Hg, heart rate was 100 beats per minute, and oxygen saturation was 98% on room air. Her weight was approximately 40 kg. She appeared hypovolemic with dry tongue and reduced skin turgor; jugular venous pressure was normal. The chest was clear to auscultation, heart sounds were normal, the abdomen was soft and nontender, and there was no peripheral edema.

Her initial laboratory tests showed a hemoglobin level of 10.0 g/dL, white blood cell count (WBC) count of 7700/μL, and a platelet count of 155 000/μL. Chemistry panel revealed

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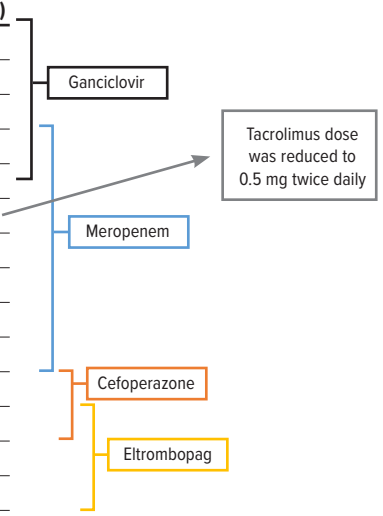
urea, 128 mg/dL; creatinine, 8.1 mg/dL; sodium, 132 mmol/L; potassium, 2.8 mmol/L, chloride, 112 mEq/L; and bicarbonate, 8 mEq/L. An extensive workup for diarrhea – including stool examination for *Clostridium difficile* toxin, *Cryptosporidium*, and *Isospora* – was negative. She received hydration with Ringer lactate containing bicarbonate and potassium supplementation and was switched to a renally adjusted dose of intravenous ganciclovir. Mycophenolate mofetil was discontinued.

Figure. Trend of Complete Blood Cell Count and Medication Use

Days Since Admission	Hemoglobin (g/dlL	WBC ($x10^3/\mu L$)	Platelets ($x10^3/\mu L$)
Day 1	10.6	7.7	155
Day 8	9.5	3.3	127
Day 10	7.8	2.4	140
Day 11	5.4	1	98
Day 12	7.4	1.1	71
Day 13	9.3	0.8	75
Day 14	9.9	0.5	60
Day 15	10.2	0.67	40
Day 16	9.8	0.69	35
Day 17	8.7	0.8	23
Patient was discharged at her request			
Day 20	9.1	6.5	6
Day 23	8.9	10.7	80
Day 25	8.3	6.8	80
Day 31			128



Hospital Course

The patient's electrolytes and acid-base balance were corrected over the next few days, and diarrhea improved after 6 days. Her creatinine level improved to 2.2 mg/dL. However, she developed a significant decline in WBC and platelet counts on hospital day 10, prompting discontinuation of ganciclovir. She received filgastrim for severe leukopenia; while the WBC count stabilized, the platelet count continued to decline (Figure). Filgastrim was discontinued after 7 days. A workup for alternate causes of bicytopenia – including repeat CMV PCR, parvovirus, Epstein Barr virus, blood and urine cultures, B12, folic acid, tacrolimus trough, beta-D-glucan, galactomannan, and a peripheral blood smear for schistocytes, lactate dehydrogenase, and haptoglobin – was inconclusive. However, urine culture grew *Escherichia coli*, and tacrolimus trough was elevated at 14.1 ng/mL, prompting a dose reduction. She was started on meropenem but her platelet count fell to 23 000/μL. She was then switched to cefoperazone/sulbactam and discharged at her request with follow-up in 3 days.

Cefoperazone/sulbactam was discontinued 3 days later when her platelet count reached 6000/μL. She was transfused with 1 apheresis unit of platelets and started on eltrombopag. Her platelet count subsequently improved to 80 000/μL (Figure). Eltrombopag was discontinued after 7 days, and the platelet count continued to rise to 128 000/μL. Renal function normalized during follow-up.

DISCUSSION

DITP is a rare side effect caused by drug-dependent antibodies that react with platelet membrane glycoproteins only when the implicated drug is present.[2] It typically occurs 1 to 2 weeks after beginning a new drug or suddenly after a single dose of a medication previously taken intermittently. However, severe thrombocytopenia can occur immediately after the first administration of antithrombotic agents such as abciximab, tirofiban, and eptifibatide. Recovery from DITP usually begins within 1 to 2 days of drug cessation and is typically complete within a week.1 Immune and nonimmune mechanisms can cause DITP, including impaired maturation or replication of megakaryocytes and reduced release of platelets from the bone marrow. Where an immune mechanism is involved, an increased rate of apoptosis or increased peripheral destruction of platelets is implicated, and antibodies specific to individual drug structures have been identified.[3]

Ganciclovir is associated with bone marrow suppression – including neutropenia and thrombocytopenia[4] – with reported thrombocytopenia rates of approximately 23%.[5] Despite stopping ganciclovir and later switching from meropenem to cefoperazone, this patient's platelet count reached a nadir of 6000/μL on hospital day 20. This extreme thrombocytopenia, occurring after discontinuation of the primary myelosuppressive agent, implicated the beta-lactam antibiotics as likely culprits in immune-mediated DITP. Platelet recovery occurred only after both meropenem and cefoperazone were discontinued. Alternative causes of thrombocytopenia, including CMV, Epstein Barr virus, parvovirus, and thrombotic microangiopathy (TMA), were ruled out. The patient was also on tacrolimus, which can cause thrombocytopenia primarily via thrombotic microangiopathy.[6,7] While the tacrolimus level was 14 mg/dL, the absence of clinical and laboratory features of TMA and recovery of platelets while remaining on a (reduced) dose of tacrolimus make it an unlikely cause.

DITP typically results from drug-dependent antibodies that recognize platelet glycoproteins only in the presence of the drug. These antibodies trigger platelet destruction through complement activation or phagocytosis. The diagnosis is supported by the time course of thrombocytopenia and its resolution

upon drug discontinuation.[1] In this patient, thrombocytopenia resolved after discontinuing all suspected drugs, supporting the diagnosis of DITP but making it difficult to pinpoint a single causative agent.

Six types of antibiotics have been identified according to their antibody-binding mechanisms.[2] While meropenem and cefoperazone/sulbactam have not been specifically classified into one of these 6 categories, they likely follow the "hapten-dependent" mechanism similar to other penicillins, where drugs covalently link to cell surface proteins to induce a drug-specific immune response.[2] DITP due to myelosuppression is also a possibility; however, the decrease of platelet production via myelosuppression tends to develop gradually and after at least 10 days of antimicrobial therapy. In contrast, immune-mediated thrombocytopenia could present earlier, primarily after 7 to 14 days.[8] Our patient developed DITP after 4 to 5 days after administration of the drug, suggesting an immune-mediated mechanism rather than myelosuppression.

Meropenem has been reported to cause DITP more frequently than other drugs; one study found that it caused thrombocytopenia in 37.81% of renally compromised patients.[9] It is also known cause of drug-induced pancytopenia and neutropenia.[10,11] Cefoperazone has also been documented to cause coagulation disorders: one study reported an incidence of 9.2% in patients receiving cefoperazone,[12] while another reported a DITP incidence of 2.4% in patients on cefoperazone.[13]

While in most cases of drug-induced thrombocytopenia, cessation of treatment is sufficient for reversal of a low platelet count, in our case, the patient was given eltrombopag to increase the platelet count. Eltrombopag is usually used to treat chronic immune thrombocytopenia;[14] however, its usefulness in treating chemotherapy-induced thrombocytopenia[15] suggests it may also be useful to treat patients with DITP, as seen in our case.

CONCLUSIONS

This case highlights the importance of recognizing DITP, particularly in immunosuppressed patients receiving multiple medications. Beta-lactam antibiotics can induce severe immune-mediated thrombocytopenia in rare instances. Prompt identification and discontinuation of the offending agent are crucial. Additionally, the use of eltrombopag in severe DITP warrants further exploration as a potential therapeutic intervention.

Financial disclosures: None declared.

Funding/support: None declared.

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Granular Cell Tumor: A Rare Suprasellar Tumor

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ABSTRACT

Introduction: Granular cell tumors of the neurohypophysis are rare, benign neoplasms originating from pituicytes that often pose diagnostic challenges due to their resemblance to other sellar lesions.

Case Presentation: We report the case of a 26-year-old man with a 2-year history of headache, polyuria, and hypopituitarism. Magnetic resonance imaging revealed a 21×23×30 mm suprasellar mass compressing the optic chiasm and hypothalamus. Hormonal evaluation showed hypogonadotropic hypogonadism, central hypothyroidism, and arginine vasopressin deficiency. The patient underwent partial tumor resection. Histopathology confirmed a grade I granular cell tumor, positive for thyroid transcription factor 1, S100, and vimentin.

Discussion: Granular cell tumors are slow-growing lesions with nonspecific clinical and radiologic features. Diagnosis relies on histologic and immunohistochemical findings. Complete resection is often limited by tumor vascularity and proximity to vital structures.

Conclusions: Granular cell tumors should be considered in the differential diagnosis of suprasellar tumors. Early recognition and multidisciplinary management may improve patient outcomes.

INTRODUCTION

Neurohypophysial granular cell tumors (GCTs) are rare, benign neoplasms that belong—together with pituicytoma and spindle cell oncocytoma—to the family of low-grade neoplasms with common immunostaining for thyroid transcription factor 1 (TTF-1).[1,2] These tumors are considered to have a common origin from the pituicytes of the posterior pituitary or infundibulum.[2]

GCTs are slow-growing and cause compressive symptoms over time. They usually present as a solid mass located in the suprasellar region, arising from the infundibulum or, less frequently, from the neurohypophysis.[3] They are composed of polygonal monomorphic cells with abundant granular cytoplasm, which is ultrastructurally filled with lysosomes, without evidence of atypia.[4]

Preoperative diagnosis is often challenging due to similarities with other sellar lesions, such as pituitary adenoma, meningioma, pituicytoma, and spindle cell oncocytoma.[5,6] The prognosis is determined mainly by extent of surgical resection; however, surgical treatment is frequently hampered by factors such as tumor size, proximity to the optic chiasm, and high vascularization, leading to a significant recurrence rate.[7]

The objective of this report is to describe the case of an adult male patient with GCT to highlight its clinical, radiologic, and histopathologic characteristics.

CASE PRESENTATION

A 26-year-old male patient of Peruvian nationality, with no

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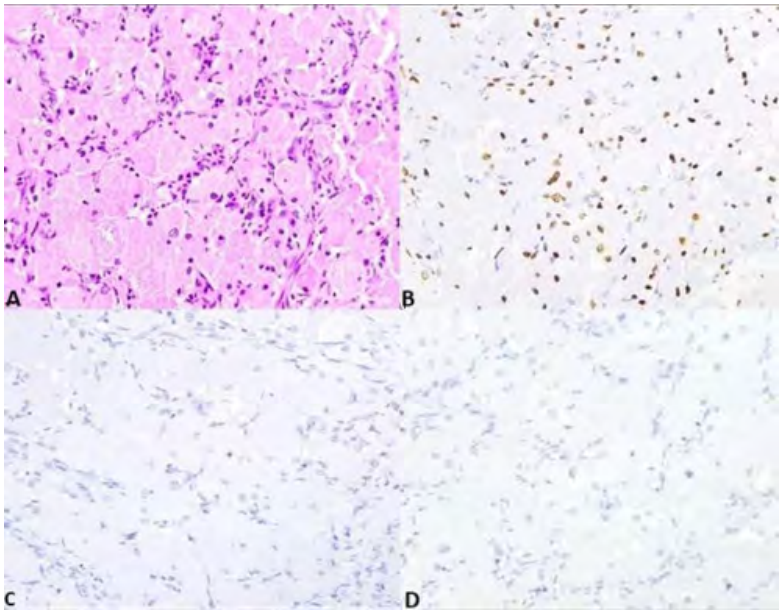
medical history or relevant family history, presented with a 2-year history of oppressive retro-orbital headache with increasing intensity from moderate to severe (pain score 9/10) over the last year. Symptoms were partially relieved by tramadol 50 mg orally once daily and were associated with decreased visual acuity, nausea, and sporadic vomiting. Based on these symptoms, at the recommendation of his private physician, the patient underwent a contrast-enhanced brain magnetic resonance imaging (MRI), which suggested a probable craniopharyngioma.

Given the clinical presentation, the patient was hospitalized in the neuroendocrinology service. Medical history revealed polyuria (5 L/day), polydipsia, nocturia, asthenia, and cold intolerance for 5 months. Physical examination revealed an axillary temperature of 37 °C, heart rate of 80 beats per minute, respiratory rate of 20 breaths per minute, a body mass index of 21 kg/m^2 (eutrophic). Confrontational campimetry showed no abnormalities in the right eye and inferior temporal quadrantanopia in the left eye. The remainder of the examination was unremarkable.

Figure. Photomicrographs of a Suprasellar Tumor at 400× Magnification



(A) Hematoxylin-eosin staining shows eosinophilic polygonal cells with granular cytoplasm, small nuclei, and inconspicuous nucleoli. (B) Immunohistochemistry at 400× shows nuclear positivity for thyroid transcription factor 1. (C) Immunostaining is negative for chromogranin. (D) Immunostaining is negative for synaptophysin.

MRI of the pituitary gland with contrast showed a solid lesion, isointense in T1, T2 and fluid-attenuated inversion recovery (FLAIR), with moderate contrast enhancement and lobulated contours, involving the optic chiasm without extension to the optic nerve or tract. It measured 21 x 23 x 30 mm (transverse x longitudinal x anteroposterior) and occupied part of the interpeduncular and prepontine cistern, affecting structures of the hypothalamic region without involvement of the infundibulum or pituitary gland.

Hormonal testing (Table) revealed an insulin-like growth factor 1 level at the lower limit of normal (116 ng/mL), hypogonadotropic hypogonadism (total testosterone 28 ng/dL; luteinizing hormone 0.66 U/L; follicle-stimulating hormone < 0.66 U/L), central hypothyroidism (thyroid-stimulating hormone [TSH] 2.04 µU/mL, free T4 0.6 ng/dL), normal prolactin (9.5 ng/mL), normal basal cortisol (15 µg/dL), supporting a diagnosis of hypopituitarism. Furthermore, due to the hypernatremia (Na 150 mmol/L) associated with polydipsia and polyuria, arginine vasopressin deficiency (AVP-D) was presumed.

Based on the clinical and radiologic findings, a decision was made to perform a frontotemporal craniotomy using a combined subfrontal, transzygomatic, transsylvian, and translamina terminalis approach for biopsy and limited tumor resection for diagnostic purposes. Hormone replacement therapy was initiated with levothyroxine 100 µg orally once daily and desmopressin intranasally (2 sprays daily). Subsequently, testosterone enanthate 200 mg intramuscularly every 15 days was added, with improvement in symptoms and good tolerance.

Table. Biochemical Tests Requested During Hospitalization and After Surgery

Biochemical Tests	Admission	3 Months Postsurgery	Ref Range
Sodium (mmol/L)	150	132	135 – 150
Potassium (mmol/L)	4.4	4	3.5 – 5.0
Creatinine (mg/dL)	0.6	—	0.7 – 1.3
Alpha-pheoprotein (ng/dL)	< 2	—	1.09 – 8.04
Urine density	1030	1030	1005 – 1030
Prolactin (ng/dl)	9.4	8.9	< 20
Cortisol (µg/dL)	15.4	7.7	5 – 25
FSH (mIU/mL)	< 0.66	—	1.5 – 12.4
Luteinizing hormone (IU/L)	0.63	—	1.8 – 8.6
Total testosterone (ng/dL)	28.5	—	132 – 813
Free thyroxine (ng/dL)	0.6	0.7	0.6 – 1.12
TSH (µIU/mL)	1.5	—	0.4 – 5.5
IGF-1 (ng/mL)	90.1	—	116 – 358

Abbreviations: FSH, follicle-stimulating hormone; TSH, thyroid-stimulating hormone; IGF-1, insulin-like growth factor 1.

Histopathological examination showed neural tissue with focal gliosis and granular cell tumor. Immunohistochemistry revealed a Ki-67 proliferation index of 1%; p53, negative; glial fibrillary acidic protein (GFAP), negative; chromogranin, negative; synap-

tophysin, negative; S100, positive; vimentin, positive; and TTF-1, positive (Figure).

These findings were consistent with suprasellar GCT, World Health Organization grade I. During follow-up 3 months after surgery, the patient presented with sporadic nausea and vomiting and hyponatremia (Na 132 mmol/L) associated with low borderline cortisol (7 µg/dL). These findings suggested adrenal insufficiency, and oral prednisone 5 mg/day was initiated.

Because tumor resection was minimal and primarily diagnostic, the patient is currently awaiting definitive surgery for complete resection and continues outpatient follow-up by the endocrinology service.

DISCUSSION

Granular cell tumors were first described in 1893 by Boyce and Beadles[8] and represent less than 0.5% of all sellar tumors. Most are benign, with a malignant transformation rate of approximately 2%.[9] Fewer than 70 symptomatic cases have been reported in the literature,4 making the present case notable for its florid clinical presentation.

Women are more commonly affected than men (2:1), with peak incidence occurring in the fifth decade of life,[10] However, the present case involves a 26-year-old male patient.

Symptoms associated with GCT include gradual onset of visual disturbances in up to 90% of cases, headache, and endocrine dysfunction (eg, amenorrhea, galactorrhea, infertility, impotence, and weight fluctuations) in approximately 50% of cases. Hormonal disturbances such as hypopituitarism and hyperprolactinemia are frequently observed.[7] In this case, the patient presented primarily with moderate to severe headache accompanied by sporadic nausea, vomiting, visual impairment, and partial hypopituitarism (hypogonadotrophic hypogonadism and central hypothyroidism) with normoprolactinemia.

In addition, due to polyuria (5 L/day), nocturia, and hypernatremia (150 mmol/L), AVP-D was suspected. A water deprivation test was not performed given the clinical context, and copeptin or AVP assays were unavailable.

Radiologic findings are nonspecific and resemble those of other central nervous system lesions, such as meningioma, adenoma, chordoma, or teratoma.[11,12] MRI typically shows an isointense tumor mass on T1 and slightly hypointense on T2, with homogeneous contrast enhancement,[12] consistent with this case.

Definitive diagnosis is typically established by histological examination following surgical excision.[13] In this patient, diagnosis relied on histopathology, as clinical, laboratory and imaging findings were inconclusive.

Histologically, GCTs consist of spindle-shaped and polygonal cells with granular eosinophilic cytoplasm. They are typically positive for certain markers including PAS, S100, CD68, vimentin, and TTF-1, and negative for GFAP and pituitary hormones.[14] These features distinguish them from other oncocytic tumors of the sellar region, such as pituicytoma and spindle-shaped oncocytoma.[14] Expression of TTF-1, S100, and SOX10 supports the diagnosis, which relies on both immunoprofile and cellular morphology.

Surgical removal is the primary treatment, but complete resection is often difficult due to tumor firmness, vascularity, and adherence to adjacent structures.[7] Therefore, partial resection with preservation of adjacent brain structures is more common.[7] In this case, only biopsy and partial resection were performed due to proximity to the optic chiasm and invasion into the third ventricle.

The use of radiotherapy with primary or adjuvant treatment is controversial and not routinely recommended. It may be considered in aggressive, progressive, or inoperable recurrent disease.[15] In this patient, radiotherapy is being considered as further surgery carries a high risk of hypothalamic injury.

However, the diagnosis of AVP-D remains uncertain. Although hypernatremia supports central diabetes insipidus, previously reported elevated urine density values are inconsistent with this diagnosis, as AVP-D typically presents with hypotonic polyuria. The absence of confirmatory testing (water deprivation or copeptin measurement) limits diagnostic certainty.

Prognosis depends largely on surgical excision, and no metastases have been reported to date.[14] An interesting indicator in GCTs is the Ki-67 index; paradoxically, tumors with Ki-67 < 3% have shown growth, whereas higher values remained stable in 1 cohort studied.[12] This patient had a Ki-67 value < 3%, warranting close follow-up due to potential tumor growth.

CONCLUSIONS

Granular cell tumors are a rare but important cause of suprasellar tumors and should be considered in the differential diagnosis of sellar lesions. Early diagnosis, supported by radiologic and immunohistochemical findings, is essential for optimal surgical management. Despite their benign nature, partial resection may be challenging due to proximity to critical structures, increasing the risk of recurrence. Appropriate and timely management may improve patient outcomes.

Financial disclosures: None declared.

Funding/support: None declared.

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The Influence of Falsely Low HbA1c Levels in Diabetes Patients With Hereditary Hemorrhagic Telangiectasia: The Need for Alternative Diagnostic Approaches

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ABSTRACT

Introduction: Hereditary hemorrhagic telangiectasia (HHT) causes various age-related symptoms, including epistaxis, telangiectasia, and anemia. These symptoms often require a variety of treatments, including iron supplementation and blood transfusions. The resulting anemia can lead to atypical presentations of comorbidities, such as diabetes.

Case Presentation: A 46-year-old Hispanic woman with a history of HHT presented for diabetes evaluation due to asymptomatic, elevated nonfasting blood glucose despite normal hemoglobin A1c (HbA1c) levels. Following initiation of continuous glucose monitoring and metformin (500 mg twice daily), her blood glucose levels improved significantly.

Discussion: Patients with HHT are more likely to develop iron deficiency anemia and anemia secondary to chronic blood loss, rendering HbA1c levels unreliable for diagnosing diabetes.

Conclusions: Clinicians should consider the impact of HHT-related anemia when monitoring patients for diabetes. Alternative diagnostic methods are necessary to prevent delays in diagnosis and treatment.

INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT) (Renu-Osler-Weber syndrome) is an autosomal dominant vascular disorder affecting approximately 1 in every 5000 individuals.[1,2] The disease is characterized by vascular malformations primarily involving the skin, mucous membranes of the nose and gastrointestinal (GI) tract, and visceral organs such as the brain, liver, and lungs.[2] The most common symptoms include epistaxis and telangiectasia, which both have an age-related presentation.[2] Due to delayed symptom presentation and the rarity of the disease, diagnostic delay of HHT is common, averaging nearly 3 decades after disease onset.[1]

A major complication of HHT is anemia, including iron deficiency anemia and anemia due to chronic blood loss.[1] While the total burden of anemia among patients with HHT is unknown, the condition typically worsens with delayed diagnosis.[1,3] Patients frequently require chronic oral and intravenous iron replacement therapy and, in severe cases, blood transfusions.[3] Both anemia and blood transfusions can significantly impact hemoglobin A1c (HbA1c) levels, making the presentation of diabetes atypical and difficult to diagnose.[4] This case report highlights a patient with HHT, chronic blood loss anemia, and a delayed diagnosis of diabetes, illustrating the importance of exploring alternative diagnostic methods in patients with unique clinical presentations, including HHT.

CASE PRESENTATION

A 46-year-old Hispanic woman with a personal and family history of HHT since childhood, transfusion-dependent anemia secondary to chronic blood loss, and seropositive systemic lupus erythematosus (SLE) presented with asymptomatic elevated nonfasting blood glucose levels. At initial presentation, she was taking ferrous sulfate (325 mg every other day) for anemia due to chronic blood loss and iron deficiency anemia diagnosed in childhood. She had also begun receiving iron infusions 4 to 5 years prior.

On initial visit, the patient's vital signs and comprehensive physical examination, including a foot exam, were unremark

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able. Laboratory tests revealed a slightly elevated HbA1c level of 6.0%, increased from 4.5% and 4.0% recorded 10 months and 12 months earlier, respectively. An anti-islet cell antibody test was negative, and the urine microalbumin level was elevated at 23.5 mg/L, leading to a diagnosis of suspected type 2 diabetes. She was prescribed continuous glucose monitoring (CGM) (Freestyle Libre 3 Sensor Plus) and started on metformin, 500 mg twice daily. The CGM was recommended due to the inaccuracy of previous HbA1c readings. The patient was instructed to collect at least 2 weeks of glucose data for review at the next visit.

At the 1-month follow-up, the patient's blood glucose levels had improved significantly. Prior to metformin initiation, glucose levels ranged from 74 to 208 mg/dL; these stabilized to 142 to 151 mg/dL after 2 weeks of therapy. Continued dietary and activity modifications were advised, along with collecting 10 to 14 more days of CGM data and follow-up in 3 months.

DISCUSSION

Due to the angiodysplasia and arteriovenous malformations, anemia from iron deficiency and chronic blood loss is common in patients with HHT.[5] A 2018 study identified the prevalence of anemia among patients with HHT at 50%, with an average age at diagnosis of 38 years.[3] In contrast, the estimated global prevalence of anemia in 2010 was 32%.[3] Thus, it is crucial for physicians to continually monitor HHT patients for anemia and its confounding effect on other comorbidities.

Patients with HHT and anemia due to chronic blood loss may require both iron and blood transfusions. This can affect the formation and levels of HbA1c, resulting in missed diabetes diagnoses.[4,6] HbA1c is formed through the irreversible, nonenzymatic glycation of hemoglobin.[6] This process depends on the glucose concentrations present in red blood cells (RBCs), and levels are impacted by many factors, including the length of RBC lifespan.[6] In 2010, the American Diabetes Association (ADA) established an HbA1c level of 6.5% or higher as indicative of diabetes; since then, HbA1c has been heavily relied upon for diabetes diagnoses.[4]

Despite its widespread use, HbA1c is not an ideal disease indicator for all patients. Amenia has a significant impact on HbA1c levels due to its effect on RBC lifespan and treatment requiring frequent blood transfusions.[7] Any condition that shortens the lifespan of RBCs will result in a decreased HbA1c level, making this value ineffective for diabetes screening.[4] Furthermore, blood transfusions have been shown to lower HbA1c levels more significantly in patients with diabetes than in the general population.[8] Thus, it is crucial to recognize the impact that both HHT and chronic blood loss anemia have on patient HbA1c levels and utilize alternative methods for proper diabetes diagnosis and treatment.

In this case, once it was determined that the patient had undiagnosed diabetes of unspecified type, CGM was utilized. CGM is an increasingly reliable and efficacious alternative for diagnosing and monitoring diabetes.[9] These devices monitor interstitial glucose levels as frequently as every 5 minutes.[9] The frequency and accuracy of these values allow physicians to fine-tune treatment strategies more effectively than self-monitoring of blood glucose.[9] CGM is not typically a primary diagnostic tool due to the inconvenience of insertion and sometimes frequent calibration required.[10] Access to CGM is also limited by insurance coverage, which often requires a prior diagnosis of type 1 diabetes, a significant history of home glucose monitoring, or established insulin therapy.[11] However, when HbA1c is unreliable, CGM can provide the necessary data for proper diagnosis and management.[9] Beyond CGM, fructosamine assays may also be utilized to monitor glycemic control in these patients.[12]

Most people with type 2 diabetes experience diagnostic delays of 4 to 7 years following the onset of hyperglycemia.[13] A 2018 study found that of 18 356 adults studied with an elevated HbA1c level, 30.2% remained undiagnosed 1 year later.[13] This study also noted that individuals with lower initial HbA1c levels or prediabetes were more likely to remain undiagnosed.[13] While patients are frequently asymptomatic during this period, delays represent a lost opportunity to prevent complications.[13] Particularly when looking at delays in treating high blood pressure secondary to new type 2 diabetes diagnosis, it was found that even a 1-year delay can result in a significant increase in lifetime diabetes complications, including amputation, congestive heart failure, end-stage renal disease, ischemic heart disease, myocardial infarction, and stroke.[14]

CONCLUSIONS

It is crucial for physicians with patients with conditions that make HbA1c levels unreliable to monitor potential diabetes development using alternative methods. To prevent diagnostic delays and reduce long-term complications, clinicians should treat the individual clinical presentation rather than relying solely on standard diagnostic criteria.

Financial disclosures: None declared.

Funding/support: None declared.

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A Case of Low-Dose Ceftriaxone-Induced Liver Injury in an Adult

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ABSTRACT

Introduction: Ceftriaxone is a commonly used third-generation cephalosporin; however, rare cases of drug-induced liver injury have been reported. Atypical hepatic responses in adults at standard doses warrant clinical attention.

Case Presentation: A 48-year-old woman with a history of nephrolithiasis, cholecystectomy, and Roux-en-Y gastric bypass presented with abdominal pain. After receiving a 1-g dose of ceftriaxone, she developed significant liver enzyme elevation aspartate aminotransferase 725 U/L, alanine aminotransferase 455 U/L, and alkaline phosphatase 319 U/L). Evaluation for viral and autoimmune causes was negative. A chart review revealed prior similar episodes linked to ceftriaxone use.

Discussion: Ceftriaxone-induced hepatitis is more frequently reported in pediatric populations and typically associated with higher doses. Adult cases with such marked liver function test elevations are rarely documented.

Conclusions: This case highlights an unusual adult presentation of ceftriaxone-induced hepatitis. Clinicians should consider ceftriaxone as a potential cause of liver injury, even at standard doses, particularly in patients with a history of adverse reactions.

INTRODUCTION

Drug-induced liver injury (DILI) is a significant adverse reaction to antibiotic therapy, accounting for more than 50% of acute liver failure cases.[1] DILI is a complex diagnostic challenge because it mimics various hepatic disorders. Among antibiotics, ceftriaxone—a third-generation cephalosporin—is favored for its efficacy against a broad range of bacterial infections. Although ceftriaxone is generally well tolerated, it has been linked to liver toxicity, ranging from mild, transient enzyme elevations to severe hepatocellular injury and acute liver failure.[2]

Ceftriaxone is excreted in both the urine and bile, with hepatic excretion playing a significant role in its metabolism. The drug's hepatic processing involves the biliary system, where alterations can lead to cholestasis and biliary sludge, factors implicated in hepatic injury.[3] Moreover, ceftriaxone's high plasma protein binding and its ability to displace bilirubin from albumin may exacerbate liver stress, particularly in patients predisposed to bilirubin accumulation.[4]

The pathophysiology of ceftriaxone-induced DILI is complex and not fully understood but is thought to involve direct hepatocyte toxicity and immune-mediated mechanisms.[5] Given that DILI is often idiosyncratic and not dose-related, it poses significant diagnostic challenges. Ceftriaxone-induced liver injury may present as an asymptomatic elevation in liver enzymes; severe cases can manifest with jaundice, coagulopathy, and hepatic encephalopathy. Diagnosis relies on excluding other causes of hepatic dysfunction through a detailed drug history, serologic testing, imaging, and, in some cases, liver biopsy.[6]

This report discusses the case of a 48-year-old female with a history of recurrent urological issues and multiple abdominal surgeries who exhibited significant liver enzyme elevations following ceftriaxone administration.

CASE PRESENTATION

A 48-year-old woman with a history of recurrent nephrolithiasis requiring stent placement and stone extraction, status post-cholecystectomy and Roux-en-Y gastric bypass, presented to the emer-

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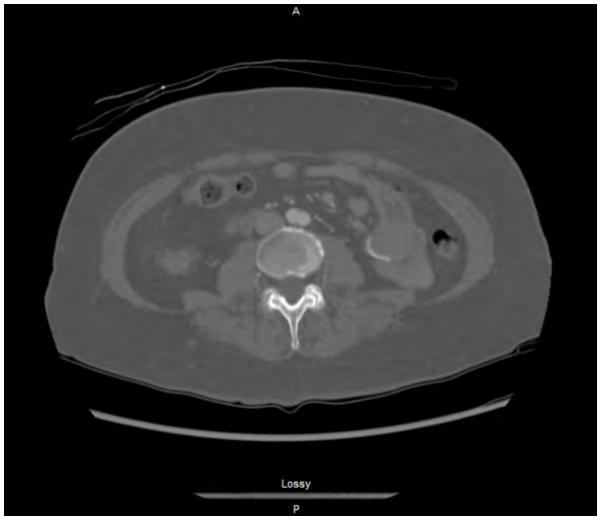
Table. Liver Function Test Trends Over Hospitalization

Laboratory Test	Day 1	Day 2	Day 3	Day 8	Reference Range
Aspartate aminotransferase (U/L)	725	537	187	53	10–40
Alanine aminotransferase (U/L)	455	671	436	123	7–56
Alkaline phosphatase (U/L)	319	343	287	165	44–147

Figure. Axial Contrast-enhanced Computed Tomography of the Abdomen on the Day of Admission Demonstrating a Short Segment Intussusception at the Jejunojejunal Anastomosis



gency department (ED) with abdominal pain. Initial computed tomography (CT) showed focal intussusception at the jejunojejunal anastomosis without associated small bowel obstruction. A follow-up CT scan showed resolution of the intussusception without intervention, confirming its transient nature. Given her symptoms, urinalysis was ordered on admission; results revealed nitrites and bacteria, prompting administration of 1 g of ceftriaxone.

On the same day, liver function tests (LFTs) showed aspartate aminotransferase (AST) 725 U/L, alanine aminotransferase (ALT) 455 U/L, and alkaline phosphatase (ALP) 319 U/L. Because of these elevations and a 2-day history of right upper quadrant and right lower quadrant pain radiating to the back, along with subjective fevers and chills, an extensive chronic liver disease workup was initiated. Results were unremarkable for alpha-1 antitrypsin, mitochondrial antibody IgG, ceruloplasmin, antinuclear antibody (ANA), hepatitis B core antibody, hepatitis B core antibody (IgG and IgM), hepatitis B surface antibody, hepatitis E antibody IgG, and hepatitis C antibody. Magnetic resonance cholangiopancreatography (MRCP) reported no focal liver lesions, normal liver size, patent hepatic and portal veins, and no biliary duct dilation. Infectious, autoimmune, and structural hepatic disorders were effectively ruled out, strengthening the case for ceftriaxone-induced liver injury as the most plausible diagnosis.

A chart review revealed multiple hospitalizations since 2019. Each visit involved ceftriaxone administration (1 g or 2 g) due to recurrent urinary tract infections (UTIs) or pyelonephritis, followed by transiently elevated liver enzymes that normalized within weeks after ceftriaxone cessation. Given the pattern and lack of alternative explanations, ceftriaxone was implicated as the likely cause. The patient's LFTs improved over 48 hours, and she was discharged with outpatient follow-up (Figure).

The transient nature of the intussusception, in the absence of bowel obstruction or ischemia, suggested it was an incidental finding. Subsequent imaging confirmed resolution without intervention, supporting an alternative etiology for the patient's presentation. Serial LFTs during hospitalization are summarized in the Table, demonstrating a progressive decline in hepatic enzymes following cessation of ceftriaxone. AST levels decreased from 725 U/L on admission to 53 U/L by day 8, while ALT declined from a peak of 671 U/L on day 2 to 123 U/L by day 8. ALP also trended downward, decreasing from 343 U/L on day 2 to 165 U/L by day 8. The decline in transaminases without additional therapeutic intervention supports ceftriaxone as the likely causative agent. Total bilirubin remained within the normal range throughout hospitalization. The international normalized ratio (INR) was 1.0 on day 3, and creatinine levels remained stable (0.52-1.07 mg/dL). Hepatitis B/C serologies, ANA, and ceruloplasmin were negative at admission, further supporting the exclusion of alternative etiologies.

DISCUSSION

Ceftriaxone-induced liver injury is a rare but clinically significant adverse drug reaction that necessitates careful consideration, particularly in patients with recurrent antibiotic exposure. While DILI is often a diagnosis of exclusion, certain characteristics of ceftriaxone-induced hepatotoxicity set it apart from other drug-related liver injuries. The underlying mechanism has been linked to both direct hepatocyte toxicity and immune-mediated responses.[6] This dual mechanism may explain why some patients exhibit transient enzyme elevations while others, as in this case, experience pronounced hepatocellular damage.

One distinguishing feature of this case is the hepatocellular pattern of liver injury, which contrasts with the more commonly reported cholestatic, or mixed-type injury associated with ceftriaxone. Previous studies have documented that ceftriaxone-induced hepatotoxicity is often associated with biliary pseudolithiasis and sludge formation, leading to a predominantly cholestatic injury pattern.[7] In a study by Yoshida et al, CT imaging of patients receiving ceftriaxone revealed sludge formation in the biliary tree, which correlated with liver function abnormalities.[7] However,

imaging in our patient showed no evidence of biliary obstruction or sludge, suggesting that ceftriaxone may cause hepatotoxicity through alternative pathways.

In patients with altered gastrointestinal anatomy, such as those who have undergone Roux-en-Y gastric bypass, ascending cholangitis must be considered in the differential diagnosis for liver enzyme abnormalities. The patient's symptoms of abdominal pain, subjective fevers, and chills raise concern for this; however, several findings argue against cholangitis in this case. The patient did not have leukocytosis, hypotension, or jaundice; her bilirubin and INR remained within normal limits, and imaging showed no biliary dilatation or sludge. While MRCP may have limited sensitivity in detecting biliary abnormalities in patients with Roux-en-Y anatomy,[8] the clinical and laboratory data in this case did not support acute infectious cholangitis.

Notably, our patient developed significant transaminitis following a single 1-g dose. While high-dose ceftriaxone (≥ 4 g/day) has been more frequently associated with liver injury,[9] our case highlights an atypical reaction occurring at a standard therapeutic dose, suggesting an idiosyncratic response. A recent study by Hayahide et al found that higher doses increased the risk of liver enzyme elevations, particularly in patients with impaired hepatic reserve.[1]

While ischemic hepatitis due to sepsis or shock can lead to acute transaminase elevations, our patient did not consistently demonstrate clinical or laboratory evidence of systemic hypoperfusion. In prior ED visits, liver enzyme elevations were observed shortly after ceftriaxone administration despite the absence of overt hypotension or significant leukocytosis (eg, blood pressure 155/80 mm Hg, heart rate 130 beat per minute, temperature 101 °F, and white blood cell count 6000–10 000/μL followed by AST 185 U/L, ALT 254 U/L, and ALP 190 U/L within 24 hours). The reproducibility of enzyme elevations in close temporal relation to ceftriaxone use without consistent signs of systemic illness makes ischemic hepatitis less likely. Coupled with the exclusion of other hepatic etiologies, this pattern supports a diagnosis of drug-induced liver injury. These observations align with prior reports highlighting the idiosyncratic nature of antibiotic-related hepatotoxicity, including ceftriaxone.[4]

Age and sex also have been identified as potential risk factors for DILI, with older patients and females being at greater risk.[5] Lucena et al found that older patients were more likely to develop cholestatic liver injury, while younger patients more frequently exhibited hepatocellular injury patterns.[5] Our patient's profile aligns with this trend, underscoring the importance of patient-specific factors in predicting susceptibility.

The prognosis of ceftriaxone-induced liver injury varies widely. In most cases, liver function abnormalities resolve following drug discontinuation, as observed in our patient. However, severe DILI cases can progress to acute liver failure requiring transplantation.[10] Reuben et al reported that antibiotics, including cephalosporins, were among the leading culprits of acute liver failure.[10] Although our patient experienced full recovery within weeks, the potential for severe outcomes highlights the need for vigilance in monitoring hepatic function during ceftriaxone therapy, even at low doses.

Additionally, the rapid improvement in liver enzyme levels over a few days is atypical for DILI, which more commonly resolves over weeks.[1,5] However, previous episodes in this patient followed a similar pattern of transient transaminitis that normalized without intervention after ceftriaxone cessation. The reproducibility of these episodes across multiple hospitalizations lends credence to an idiosyncratic hepatotoxic response to ceftriaxone. While rechallenge testing is not ethically justifiable, a future episode with baseline normal LFTs followed by ceftriaxone administration and subsequent enzyme spikes could offer stronger causal evidence.

Labeling ceftriaxone as an allergen must also be weighed carefully. Ceftriaxone is a cornerstone in managing several infections, and its exclusion may lead to the use of broader-spectrum or less effective agents, such as vancomycin or fluoroquinolones, which carry additional risks.[10] Documentation of suspected ceftriaxone-induced hepatotoxicity should include details on the severity and reversibility of prior reactions to inform future prescribing decisions. Inappropriate or unverified allergy labeling has been linked to worse antimicrobial stewardship outcomes and higher rates of resistant infections.[11]

Finally, consultation with a bariatric surgeon not involved in the patient's care could provide further insight into whether the patient's Roux-en-Y anatomy could predispose her to atypical biliary complications. While such input was not obtained during this case, it may represent a valuable addition to future evaluations of similar presentations.

CONLCUSIONS

This case underscores the importance of considering drug-induced liver injury, even at standard doses of commonly used antibiotics like ceftriaxone. In patients with Roux-en-Y anatomy, alternative causes such as ascending cholangitis must be considered; however, the reproducible elevation and subsequent normalization of liver enzymes support a diagnosis of idiosyncratic ceftriaxone-induced liver injury. These recurring episodes emphasize that a thorough review of patient history is vital to identifying DILI risk factors. Clinicians should maintain a high index of suspicion for antibiotic-induced hepatotoxicity and carefully weigh the risks of prematurely documenting antibiotic allergy labels, which may compromise future care. Broader multidisciplinary evaluation, including surgical expertise, may further improve diagnostic accuracy in complex postoperative patients.

Financial disclosures: None declared.

Funding/support: None declared.

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Phlegmasia Cerulea Dolens With Compartment Syndrome

Aryan Shiari, MD; Ryan Bailey, MD; Jason Beckerman, MD

ABSTRACT

Introduction: Phlegmasia cerulea dolens (PCD) is a rare, severe form of deep vein thrombosis (DVT) characterized by extensive venous thrombosis and significant venous congestion, leading to swelling, cyanosis, and severe pain. Unlike typical DVT, PCD causes secondary arterial compromise via small arteriole collapse, resulting in critical limb ischemia and potential venous gangrene. This compromise, coupled with increased compartment pressures and fluid sequestration, makes PCD a true emergency requiring immediate intervention to prevent irreversible damage and limb loss.

Case Presentation: A 58-year-old woman with a complex medical history presented with severe left hip and lumbar pain following trauma. Examination revealed a swollen, cold, cyanotic, and painful left leg with weak pulses indicating compromised blood flow. Computed tomography confirmed extensive DVT from the left common iliac to the tibial veins, consistent with PCD and concerning for compartment syndrome. Given the critical presentation, fasciotomy was performed without obtaining compartment pressure measurements. The patient received anticoagulation and underwent inferior vena cava filter placement, attempted thrombectomy, and subsequent fasciotomy. Despite these measures, persistent ischemia necessitated a left above-the-knee amputation. Incidental cholangiocarcinoma was subsequently diagnosed, likely contributing to her thrombotic condition.

Conclusions: This case highlights the need for prompt diagnosis and intervention in PCD and its progression to compartment syndrome. Underlying malignancy can complicate the clinical course, necessitating a multidisciplinary approach to care. Immediate anticoagulation, thrombus removal, and supportive measures are essential in preventing further complications and improving outcomes.

INTRODUCTION

Phlegmasia cerulea dolens (PCD) is a severe and rare form of deep vein thrombosis (DVT) characterized by extensive venous thrombosis, significant swelling, cyanosis, and pain. This condition arises from venous obstruction, which increases interstitial pressure, compromises arterial inflow, and leads to ischemia. Notably, a well-documented link exists between venous thromboembolism (VTE) and occult cancer; VTE can be the first sign of undiagnosed malignancy. This heightened risk is due to the hypercoagulable state induced by cancer, involving the release of procoagulant factors, inflammatory cytokines, and tumor-shed microparticles that promote thrombosis.[1]

Distinguishing between unprovoked and provoked VTE is essential for management. Unprovoked VTE occurs without an obvious precipitating factor, while provoked VTE is associated with identifiable risk factors such as trauma. This distinction is important as it can guide the clinical approach to screening for hidden malignancies. When considering conditions like compartment syndrome and phlegmasia, it is important to note that phlegmasia is largely associated with severe venous thrombosis, potentially leading to arterial ischemia due to extensive venous congestion. In contrast, compartment syndrome typically results from trauma and is marked by increased pressure within a closed muscle compartment, which can compromise circulation and cause tissue ischemia.[2,3] In severe cases, PCD can progress to compartment syndrome--a surgical emergency requiring immediate intervention to prevent irreversible damage. PCD represents one

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Figure 1. Patient's Legs

Leg was swollen, cold to the touch, cyanotic, and exhibited severe pain and paresthesia.

Figure 2. Contrast-enhanced Axial Computed Tomography Through the Pelvis at the Level of the External Iliac Vessels

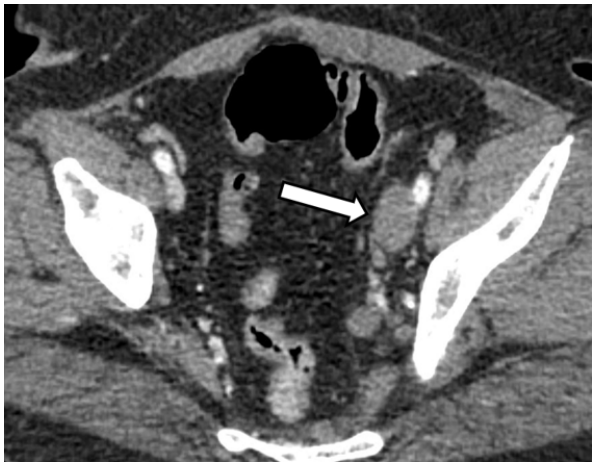
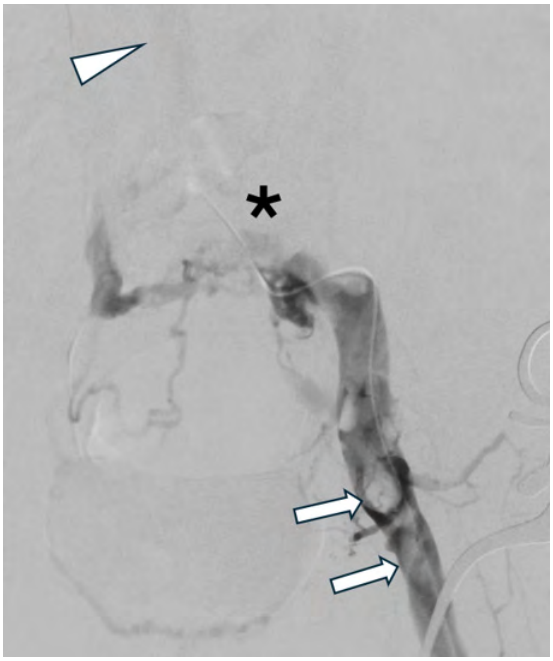


Image demonstrates marked asymmetric enlargement and nonenhancement of the left external iliac vein (arrow) consistent with deep venous thrombosis.

Figure 3. Digital Subtraction Angiography Performed With Catheter Access via Left Superficial Femoral Vein



Angiography demonstrates multiple filling defects in the common femoral and external iliac veins (arrows) with occlusion of the common iliac vein (asterisk) and faint opacification of the IVC (arrowhead) via pelvic collaterals.

of the most severe complications in the spectrum of DVT, where prompt recognition is crucial to prevent progression to compartment syndrome and irreversible ischemic damage.

CASE REPORT

A 58-year-old woman with a complex medical history including diabetes, neuropathy, obesity-related limited mobility (body mass index 44), hypertension, chronic obstructive pulmonary disease, depression, borderline personality disorder, generalized anxiety disorder, chronic pain syndrome, and posttraumatic stress disorder presented with severe left hip and lumbar pain. Symptoms began after her 300-pound son accidentally fell on her 24 hours earlier. There was no evidence of hematoma or rhabdomyolysis from this initial injury. The patient had limited prior medical care and reported no recent hospitalizations, previous surgeries, or chronic pain medication use. Following the trauma, she was advised to rest and limit physical activity to manage her symptoms.

Clinical Examination

Upon examination, the patient's left leg was swollen, cold to the touch, and cyanotic, with severe pain and paresthesia (Figure 1). Pulses in the left lower extremity were weak, indicating compromised blood flow. Her initial creatine kinase (CK) level was 958 U/L.

Investigations

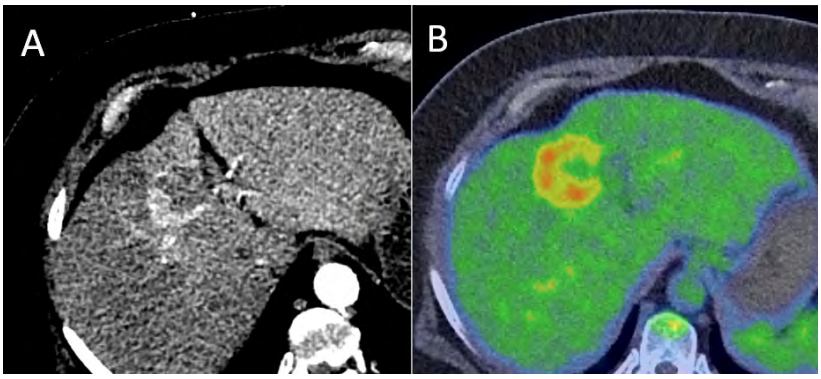
Computed tomography (CT) confirmed a substantial DVT extending from the left common iliac to the tibial veins. A contrast-enhanced axial CT through the pelvis demonstrated marked asymmetric enlargement and nonenhancement of the left external iliac vein, consistent with DVT (Figure 2).

As part of the trauma evaluation, abdominal and pelvic CT revealed a peripherally enhancing mass in the right hepatic lobe

with associated capsular retraction and probable slight peripheral biliary dilation (Figure 4A). The CA 19-9 level was normal at 15 U/mL.

Digital subtraction angiography via the left superficial femoral vein demonstrated multiple filling defects in the common femoral and external iliac veins, occlusion of the common iliac vein, and faint opacification of the inferior vena cava (IVC) via pelvic collaterals (Figure 3). These findings led to a clinical diagnosis of PCD with a high suspicion of compartment syndrome. Although intercompartmental pressure measurement is an important diagnostic tool, the acute presentation necessitated immediate intervention, making it a secondary consideration.

Figure 4. Contrast-enhanced Computed Tomography and Fluorodeoxyglucose (FDG) Positron Emission Tomography-CT (PET-CT) Findings of Cholangiocarcinoma



A. Contrast-enhanced CT through the level of the liver demonstrates the arterially enhancing lesion (arrow) in the right hepatic lobe. B. FDG PET-CT demonstrates increased FDG uptake within the peripheral enhancing component of the biopsy-proven cholangiocarcinoma. Decreased central FDG uptake is consistent with central necrosis and fibrotic changes typical of cholangiocarcinoma.

Treatment

Intravenous heparin was initiated, and the patient underwent sequential IVC filter placement, attempted thrombectomy, and subsequent fasciotomy. Despite these surgical interventions, her left lower extremity remained immobile, with minimally detectable posterior tibial pulses and absent dorsalis pedis pulses on Doppler examination. Her CK levels continued to rise, reaching 11 427 U/L within 24 hours of admission. Due to unsuccessful nonoperative management and progressive ischemia, the decision was made to proceed with a left above-knee amputation.

Pathology and Oncological Findings

Pathological examination of the amputated limb revealed organizing thrombus within the posterior tibial, popliteal, and femoral veins. Post-procedure, the patient's clinical condition stabilized, and CK levels normalized within 48 hours. She remained hemodynamically stable, and further workup was initiated to determine if the causative event was trauma or underlying malignancy.

CT-guided biopsy of the right hepatic mass revealed a well-differentiated carcinoma with clear cell features associated with dense fibrosis. The tissue sample exhibited positive staining for cytokeratin 7 (CK7), OSCAR keratin, albumin in situ hybridization (ISH), and Ki-67 (indicating increased cellular proliferation), and negative staining for CD10, CDX2, CK5/6, CK20, estrogen receptor (ER), GATA3, MelA, PAX8, S100, TTF1, Hep Par-1, and arginase. The immunohistochemical profile was consistent with cholangiocarcinoma.

With malignancy confirmed, the thrombotic condition was likely provoked by the underlying malignancy and subsequent trauma, highlighting the complexity of the patient's medical condition. Further diagnostic workup with positron emission tomography (PET)/CT imaging revealed no evidence of metastasis. Following multidisciplinary tumor board discussion and consultation with the patient, the decision was made to treat the cholangiocarcinoma with radiation therapy alone (Figure 4B). She was not a surgical candidate due to comorbidities and performance status, as noted by the general surgery and medical oncology teams. She also had experienced significant deconditioning since admission. Interventional radiology (IR) assessed the possibility of ablating the primary cholangiocarcinoma lesion but concluded that they could not achieve a full ablation, making IR procedures unsuitable. Finally, the patient expressed a strong preference against chemotherapy, citing concerns about potential side effects and its impact on quality of life. Thus, it was determined that palliative radiation therapy would offer the most benefit by alleviating symptoms and improving quality of life. She preferred this choice, focusing on palliation rather than curative intent.

DISCUSSION

The management of PCD and its progression to compartment syndrome in this case underscores the complex clinical decision-making required in such critical conditions. Although rare, PCD carries significant risks due to complications, including venous gangrene, pulmonary embolism, and circulatory shock, with mortality rates ranging from 20% to 40%. Additionally, the high risk of amputation, affecting up to 50% of cases, highlights the need for urgent intervention to prevent severe ischemia and tissue necrosis.[4-6]

In this case, the progression from PCD to compartment syndrome was primarily attributed to a malignancy-induced prothrombotic state further exacerbated by trauma. Immediate anticoagulation with intravenous unfractionated heparin (UFH) was initiated to prevent further thrombus propagation. This step is crucial in managing PCD; the activated partial thromboplastin

time (aPTT) ratio should be maintained between 1.5 and 2.5 times the control value to achieve therapeutic levels, following standard guidelines.[7,8]

Thrombus removal was a central component of the management strategy, especially given the limb-threatening nature of the condition. Catheter-directed thrombolysis (CDT) and mechanical thrombectomy were employed as key interventions. An IVC filter was placed prior to mechanical thrombectomy to prevent distant embolization, a decision supported by studies demonstrating the effectiveness of retrievable IVC filters in capturing emboli during CDT, thereby reducing the risk of iatrogenic pulmonary embolism. For instance, Lee et al reported successful emboli capture in 31.4% of patients undergoing CDT, with no pulmonary embolism cases in those with filters.[9] Similarly, the FILTER-PEVI trial highlighted a significant reduction in iatrogenic pulmonary embolism risk with IVC filter placement during percutaneous endovenous intervention.[10] However, the potential bleeding risks associated with IVC filters must be weighed carefully.

Endovascular interventions, such as single-stage endovascular thrombectomy combined with iliac vein stenting, provide a minimally invasive approach with high technical success and symptom relief, particularly relevant when PCD is due to iliac vein lesions. In scenarios where compartment syndrome developed and pressures remained elevated despite restoring venous outflow, a fasciotomy was considered necessary. While it relieves pressure, fasciotomy carries significant risks, including blood loss--especially when combined with thrombolytic therapy and anticoagulation.[8,11,12] Therefore, it is reserved for situations where other interventions fail to reduce compartment pressures.

In cases such as the one presented, where endovascular interventions and mechanical thrombectomy, along with anticoagulation therapy and fasciotomy, fail to salvage the limb, the severity of the condition often leads to irreversible ischemic damage. In such severe cases, where all attempts to restore adequate circulation and reduce compartment pressures fail, amputation becomes necessary to prevent further systemic complications and to preserve the patient's overall health.[4,5,13] This outcome underscores the importance of early recognition and aggressive management of PCD, although even with optimal care, limb loss can still be unavoidable in the most severe presentations. Supportive measures, including fluid resuscitation, leg elevation, and effective pain management, are essential components of the treatment plan. Continuous monitoring for signs of compartment syndrome—including severe pain, paresthesia, and motor deficits—is crucial to ensure timely intervention and prevent long-term complications.[14]

CONCLUSIONS

This case of PCD progressing to compartment syndrome highlights the importance of rapid diagnosis and intervention in managing severe venous thrombosis. Despite the complexity of the patient's condition, exacerbated by underlying malignancy and trauma, this case illustrates the necessity of a multidisciplinary approach in such emergencies. While immediate interventions, including anticoagulation, thrombus removal, and supportive measures, are essential to prevent further complications, limb salvage is not always possible. The need for amputation in this patient reflects the severe nature of PCD and its potential for irreversible damage. This case also reinforces the need for vigilance in patients with underlying malignancies, as they are at increased risk for thrombotic events, necessitating a proactive and coordinated approach to care.

Financial disclosures: None declared.

Funding/support: None declared.

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Should We Consider the Use of Buprenorphine for Pain Management in Nonsurgical Candidates With End-stage Osteoarthritis? A Case Report

Thomas Licata, DO; Adam Clements, DO

ABSTRACT

Introduction: Buprenorphine is a partial μ-opioid receptor agonist, an antagonist at the κ-opioid receptor, and a partial agonist at the δ-opioid receptor.

Case Presentation: This case report highlights the successful management of patient with advanced osteoarthritis who was not a surgical candidate, using transdermal buprenorphine, which provided significant improvement in quality of life and functional status.

Discussion: This case report describes the use of buprenorphine as a potentially safer analgesic option and aims to reduce stigma associated with its use in both medical and nonmedical communities.

INTRODUCTION

Buprenorphine is a partial μ-opioid receptor agonist (MOR), an antagonist at the κ-opioid receptor, and a partial agonist at the δ-opioid receptor. Buprenorphine has demonstrated safer clinical outcomes when compared with full MOR agonists, especially regarding respiratory depression, even at increasing doses.[1] Prior clinical trials and meta-analyses suggest improved pain control with buprenorphine compared with full-agonist opioids while simultaneously reducing the risk of respiratory depression. In some situations, buprenorphine may be prescribed for outpatient use in 3 common formulations: buccal (daily), transdermal patch (weekly), and subdermal depot injection (monthly). It is also available for intravenous (IV) use in hospitalized patients. Typically, subdermal formulations have higher bioavailability, whereas buccal films provide a more rapid onset of action. However, given its continuous medication delivery, many patients benefit from the transdermal patch.

CASE PRESENTATION

We present the case of a 60-year-old man without significant past medical or surgical history who was seen initially for a routine wellness exam for evaluation of chronic bilateral hip pain that had begun to impact his quality of life and limit his function in his construction job. He reported longstanding intermittent pain for several years but had not sought care previously, and the pain was responsive to as-needed acetaminophen and ibuprofen. He was open to trying physical therapy but was concerned that his pain would be too severe to participate meaningfully. During this visit, he was also agreeable to scheduling his first colonoscopy after previously deferring, motivated by a close friend's diagnosis of colorectal cancer.

Physical therapy did not improve his pain after several sessions, prompting re-evaluation. X-rays of the hips and pelvis were interpreted as "bilateral end-stage osteoarthritis of the hips; consider orthopedic referral." He was agreeable to referral, as he could no longer meet functional demands at work. He was seen by orthopedics within a week. Given the extent of osteoarthritis, elective unilateral hip arthroplasty was scheduled in 2 months with contralateral hip arthroplasty planned within 4 to 6 months. His pain was still manageable with over-the-counter (OTC) acetaminophen and ibuprofen.

Between his initial orthopedic visit and scheduled surgeries, the patient underwent screening colonoscopy, during which he experienced a colonic perforation requiring hemicolectomy with colos-

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tomy formation. He was no longer considered a surgical candidate for hip arthroplasty at that time and planned to delay surgery until several months after colonic anastomosis. Pain from the colonic perforation and osteoarthritis was no longer controlled with OTC medications, and he requested assistance with pain management but remained adamantly opposed to opioid therapy due to personal observations of opioid addiction in several close friends and family members.

Approximately 1 month after the colonic perforation, the patient developed severe, crushing chest pain radiating to the left shoulder. He presented to the emergency department and was found to have elevated troponin levels, a nonischemic-appearing electrocardiogram (ECG), and echocardiography showing global hypokinesis. He was taken emergently to the cardiac catheterization laboratory and subsequently had 2 stents placed in the left anterior descending artery, with a diagnosis of non-ST-elevation myocardial infarction. Three months later, repeat echocardiography demonstrated a reduced ejection fraction of 25%, and he was started on guideline-directed medical therapy.

After his colon surgery, his myocardial infarction, and new ischemic cardiomyopathy, he was no longer deemed a safe candidate for elective hip arthroplasty even 1-year later, despite partial recovery of ejection fraction (40%-45%). He was no longer able to work due to pain, worsening depression, and passive suicidal ideation in the setting of these life events. Duloxetine and gabapentin were added to regimen with some benefit. He required a 4-point walker due to pain-related gait instability. He remained resistant to opioid therapy but felt he was reaching a breaking point.

We introduced buprenorphine, a partial opioid agonist, as a treatment option for chronic pain. He agreed to trial transdermal patches, applied directly over the site of maximal pain, typically his right hip. He started at 5 µg/h, the lowest US Food and Drug Administration (FDA)-approved dose. He reported a slight improvement in pain and quality of life. Over several months, he was titrated up to 20 µg/h (maximum FDA-approved dose), with patches applied weekly. As his function improved, he no longer required a walker. He reported improved quality of life, particularly related to improved mental health, including resolution of suicidal ideations. Although his goals were to return to construction in some capacity, to discontinue pharmacologic analgesia, and to have surgery, he was unable to return to manual labor but transitioned to a lower-impact desk job.

Over several months, the patient was medically optimized while maintaining adequate analgesia with transdermal buprenorphine. He was able to meaningfully participate in physical therapy and cardiac rehabilitation to the point that he underwent bilateral hip arthroplasty. With resolution of his pain, he discontinued buprenorphine postoperatively and returned to a productive lifestyle with improved quality of life.

DISCUSSION

This case illustrated successful management of advanced osteoarthritis using buprenorphine, a partial opioid agonist, and aims to increase awareness of its appropriate use while reducing stigma associated with this medication compared with full agonist opioids (eg, oxycodone, hydromorphone). Although commonly used for opioid use disorder, buprenorphine also has a role in chronic pain, particularly when the pain is not readily reversible. Guidance from the Veterans Health Administration supports its use to facilitate functional improvement rather than focusing solely on pain scores.[2] Patients with a reversible cause of pain should not be maintained on lifelong therapy of buprenorphine and should be tapered once the underlying condition is addressed.

Before initiating opioid therapy in patients with chronic or longstanding pain, conservative measures—such as scheduled OTC analgesics, physical or occupational therapy, and behavioral health approaches—should be attempted. Many patients achieve relief with lifestyle modifications and do not require pharmaceutical analgesia. Buprenorphine may be considered within a multimodal analgesic approach but should not be first line unless the patient also has concurrent OUD.

Questions remain regarding optimal dose and route of administration. Generally, the lowest effective dose should be used. Route of administration should be chosen to optimize ease of use, safety, and adherence. For example, sublingual films administered multiple times daily may be appropriate for some patients, whereas once-weekly transdermal patch may better align with others' preferences and lifestyles. Before starting any form of analgesia, the patient's functional goals and treatment options should be discussed, as complete pain elimination is not always achievable and typically is not the goal.

Buprenorphine is associated with adverse effects. Postmarketing data most commonly reported nausea, vomiting, opioid-induced constipation (OIC), and skin irritation at the application site. These effects are typically more prominent during therapy initiation and dose titration phases.[3] The side effects of nausea and vomiting often subside as the dose reaches a steady state. OIC may be mitigated with increased water intake and water-soluble fiber (eg, psyllium), and oral laxatives, such as polyethylene glycol. In more severe cases, peripherally acting µ-opioid receptor antagonists (eg, methylnaltrexone), may be considered.[4] The patch does not need be applied directly over the site of pain, and rotation of application sites can minimize irritation. In this case, a placebo effect cannot be excluded.

It is worth noting that differences in dosing availability exist between the United States and Europe. In the United States, the maximum transdermal dose is 20 µg/h, whereas in Europe, doses may reach 100 µg/h.[5,6] Limited evidence regarding higher-dose safety raises questions about whether current US dosing limits may restrict analgesic efficacy.

CONCLUSIONS

Buprenorphine is a partial opioid agonist that may be considered for nonoperative management of osteoarthritis. The treatment goal is to provide enough analgesia to optimize function, reduce suffering, and improve quality of life, rather than complete eradication of pain. This case highlights a potential role for buprenorphine in chronic pain management and may help increase clinician comfort with its use. Although commonly prescribed for OUD, buprenorphine has broader applications in patients with chronic pain of various etiologies.

Financial disclosures: None delcared.

Funding/support: None delcared.

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Starvation Ketosis Versus Euglycemic Diabetic Ketoacidosis in Pregnancy: A Case Report Highlighting the Diagnostic Overlap

Divya sai Vunnam, MD; Samantha E. Moore, RD; Ram D. Pathak, MD

ABSTRACT

Introduction: Starvation ketosis in pregnancy, though rare, is increasingly recognized, underscoring the need for a better understanding of its pathophysiology. Prolonged fasting or inadequate carbohydrate intake leads to elevated ketone levels, which can adversely affect maternal and fetal health. Early diagnosis via ketone monitoring and clinical assessments, is essential. The clinical presentation and laboratory profile of starvation ketosis overlap with euglycemic diabetic ketoacidosis (DKA), often creating a diagnostic dilemma.

Case Presentation: A 28-year-old female with gestational diabetes presented at 37 weeks of gestation with a 3-day history of nausea, vomiting, and abdominal pain. She had been unable to eat for 60 hours, consuming only small sips of water. Laboratory workup revealed high-anion gap metabolic acidosis with elevated β-hydroxybutyrate. Other causes of high-anion gap metabolic acidosis were ruled out, leading to a diagnosis of starvation ketosis versus euglycemic DKA. The patient was treated with dextrose supplementation to meet caloric needs, along with an insulin infusion. As her nausea improved, she tolerated an oral diet and was gradually weaned off intravenous dextrose. She recovered well and delivered a healthy infant at 38 weeks of gestation via spontaneous vaginal delivery.

Discussion: During starvation, the body transitions from glucose to lipid metabolism, producing ketone bodies as an alternative energy source. While ketoacidosis typically develops after 10 to 14 days in nonpregnant individuals, pregnancy-induced insulin resistance increases susceptibility, allowing ketoacidosis to develop within 24 hours, particularly in the third trimester.

Conclusions: Treatment of starvation ketosis in pregnancy involves aggressive caloric replacement through dextrose infusions and insulin supplementation. Early intervention and maintaining a high index of clinical suspicion are crucial to prevent adverse complications for both mother and fetus.

INTRODUCTION

Ketoacidosis during pregnancy can be manifested as both diabetic ketoacidosis (DKA) and starvation ketosis. Starvation ketosis in pregnancy is a metabolic state that occurs when the body shifts from using glucose to ketone bodies as a primary energy source due to prolonged fasting or inadequate caloric intake.[1] During pregnancy, maternal metabolism undergoes significant adaptations to support fetal growth, including increased insulin resistance and enhanced fat metabolism. These changes predispose pregnant individuals to ketosis and metabolic acidosis during periods of caloric deprivation, which can adversely affect maternal and fetal health. Euglycemic DKA is a close differential diagnosis for starvation ketosis.[1]

We report a case of ketoacidosis in late pregnancy that presents such a conundrum. The patient was successfully managed with dextrose and insulin infusions. The intricate underlying biochemical interactions and hormonal changes that predispose pregnant females to this condition are discussed.

CASE PRESENTATION

A 28-year-old female with a history of gestational diabetes presented at 37 weeks of gestation with nausea, vomiting, and abdominal pain of 3 days' duration. During this time, she was unable to eat for 60 hours and only consumed only small sips of water. She was diagnosed with gestational diabetes at 34 weeks and was started on 4 units of insulin aspart before supper. Her

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home blood glucose levels usually ranged from 90 to 150 mg/dL. Upon admission, she was in acidosis, with a pH of 7.22 (reference range, 7.32–7.42), bicarbonate level of 9 mmol/L (reference range, 21–33mmol/L), anion gap of 17 mmol/L (reference range, 2–16 mmol/L), and β-hydroxybutyrate level of 5.11 mmol/L (reference range, 0.00–0.39 mmol/L).

In the context of gestational diabetes with high-anion gap metabolic acidosis, the differential diagnoses included DKA, starvation ketoacidosis, and alcoholic ketoacidosis. The patient's glycated hemoglobin (HbA1C) was 5.3%. DKA was considered less likely due to normal blood glucose levels and the absence of sodium-glucose cotransporter 2 (SGLT2) inhibitor use. Nevertheless, given the history of gestational diabetes, euglycemic DKA of pregnancy was also considered. She reported no alcohol consumption in the prior 3 days, and serum ethanol levels were undetectable; thus, alcoholic ketoacidosis was unlikely.

A septic workup, including white blood cell count, lactic acid level, and inflammatory markers, yielded normal results. The patient denied exposure to chemicals such as antifreeze or excessive use of acetaminophen. Serum methanol, acetaminophen, and isopropyl alcohol levels were undetectable.

Starvation ketoacidosis was considered the more likely diagnosis due to the patient's prolonged fasting and the high caloric requirements of the third trimester. In the first 24 hours, she received 4 L of 5% dextrose, equivalent to 200 g of dextrose (800 kcal). With glucose infusion, her blood glucose levels increased to 140 to 160 mg/dL. She was started on a regular insulin infusion at 50 units over 24 hours. However, she continued to experience nausea, which limited her ability to eat solid food. During the first 24 hours of hospitalization, her acidosis resolved (Table).

Because the patient received only 800 kcal despite 4 L of 5% dextrose, we changed the intravenous (IV) fluid to 10% dextrose on day 2. She received 5 L of 10% dextrose, equivalent to 500 g of dextrose (2000 kcal), and 97 units of regular insulin via infusion. Due to a substantial potassium deficit, she required approximately 200 mEq of potassium replacement, resulting in potassium levels ranging from 3.6 to 3.8 mEq/L. With adequate caloric supplementation after 24 hours, her β-hydroxybutyrate level normalized to 0.06 mmol/L and her anion gap decreased to 9 mmol/L.

The patient had a prepregnancy body mass index classified as obese. On admission, her weight was 160 lb (72.5 kg). Accounting for the additional calorie needs of the third trimester, her estimated caloric needs were 2268 to 2631 kcal per day.[2] During the first 24 hours, she consumed minimal liquids and no solid food. Her oral intake was less than 100 kcal in the initial 24 hours after admission. To meet the caloric requirements, she received continuous glucose and insulin infusions to avoid hyperglycemia.

By day 3, her condition improved with symptomatic relief and resolution of ketoacidosis. She was able to tolerate solid food but struggled to meet the caloric requirement of at least 2500 kcal/day. Consequently, she remained on 10% dextrose infusions targeting blood glucose levels around 100 mg/dl and was transitioned to a basal-bolus insulin regimen with 20 units of insulin glargine twice daily and supplemental insulin lispro every 4 hours. By day 4, she tolerated 3 meals a day and was discharged home with follow-up scheduled in 2 to 3 days. She later delivered a healthy female infant at 38 weeks of gestation through spontaneous vaginal delivery.

Table. Laboratory Values in the First 24 Hours of Admission

	At Admission	12 Hours	24 Hours
pH	7.22	7.31	
pCO_2 (mmHg)	27	23	
Serum bicarbonate (mg/dL)	9	12	15
Anion gap (mmol/L)	17	18	7
Glucose (mg/dL)	158	111	116
Beta hydroxy butyrate (mmol/L)	5.11	2.20	0.06
Lactate (mmol/L)	0.7		
Urine analysis	3+ ketones		
Potassium (mEq/L)	4.5	3.5	3.6

Abbreviations: pCO2, partial pressure of carbon dioxide

DISCUSSION

Understanding normal metabolism is crucial for grasping abnormalities associated with disease. When carbohydrate stores are adequate, glucose serves as the primary fuel for most tissues and is metabolized through glycolysis. Aerobic tissues metabolize pyruvate to acetyl-CoA, which enters the citric acid cycle for complete oxidation to carbon dioxide and water molecules. This is linked to the formation of adenosine triphosphate (ATP) in the process of oxidative phosphorylation. Glycolysis can also occur anaerobically (in the absence of oxygen), resulting in lactate as the end product.[3]

During starvation, the body transitions from carbohydrate to lipid metabolism for energy, conserving glucose for the central nervous system and red blood cells. This shift is regulated by low insulin and high epinephrine and norepinephrine levels, which stimulate the release of long-chain fatty acids and glycerol from peripheral fat stores by increasing intracellular cyclic adenosine monophosphate (cAMP) levels, leading to the phosphorylation and activation of hormone-sensitive lipase.[4]

These fatty acids are then transported into hepatocytes, where they undergo β-oxidation in the mitochondria to generate acetyl-CoA. When acetyl-CoA levels are elevated, they enter the ketogenic pathway, leading to the production of ketone bodies—acetoacetate and 3-hydroxybutyrate. These ketone bodies are released into the bloodstream and serve as an alternative energy source for various tissues, including the brain, thus maintaining energy homeostasis during prolonged fasting.[1]

In the nonpregnant population, this process typically occurs at moderate levels, preventing ketoacidosis. High ketone body concentrations stimulate insulin release (despite low glucose levels), increasing adipose tissue sensitivity to insulin's inhibitory effect on fatty acid release; furthermore, ketone bodies directly inhibit lipol-

ysis. Thus, it typically takes 10 to 14 days of starvation for ketoacidosis to develop in nonpregnant individuals. In contrast, during pregnancy, hormonal changes—including placental hormones such as glucagon-like peptides and human placental lactogen—cause relative insulin resistance. This makes pregnant individuals more prone to ketosis, especially in the third trimester, with ketoacidosis developing as early as 24 hours into starvation.[1] This vulnerability is underscored by the significantly increased energy demands of late-stage pregnancy. According to the Academy of Nutrition and Dietetics, women with a healthy prepregnancy weight require an average of 2200 to 2900 kcal/d.[2] While the first trimester typically does not require additional calories, the second and third trimesters necessitate an extra 340 and 450 kcal, respectively.[2] When these heightened metabolic requirements are unmet, even brief periods of fasting can rapidly precipitate ketosis.

Distinguishing between starvation ketoacidosis and euglycemic DKA in pregnancy is diagnostically challenging. Both conditions can present with elevated serum β-hydroxybutyrate, acetonemia, and ketonuria.[5-11] In the case described, prolonged fasting for 60 hours likely precipitated ketosis, which was exacerbated by the underlying insulin resistance of gestation, making euglycemic DKA the most plausible diagnosis. The rapid correction of acidosis with caloric replacement supports starvation ketoacidosis of pregnancy as the likely etiology.

Given the overlapping laboratory profiles and clinical features, differentiating starvation ketoacidosis from euglycemic DKA in pregnancy requires careful consideration of the illness trajectory and response to treatment. Acknowledging this diagnostic dilemma is crucial, as it underscores the need for heightened clinical suspicion and prompt treatment in pregnant patients presenting with ketoacidosis, regardless of their glycemic status. It is often difficult to clearly distinguish between the two conditions. Nevertheless, treatment with adequate calories, insulin supplementation to avoid hyperglycemia, and correction of electrolyte imbalance is the mainstay of management in both conditions.

CASE STUDIES

A review of the literature reveals previous case reports by JM Land,[6] Cecere et al,[7] Mahoney et al,[12] and Sinha et al,[13] which describe pregnant patients in their third trimester presenting with acidosis (pH 7.0-7.2). These patients were managed with IV fluids with or without 5% or 10% dextrose and, in some cases, sodium bicarbonate. Subsequently, they underwent emergent cesarean deliveries, resulting in either healthy deliveries or stillbirths. Additional case studies by Patel et al[8] and Frise et al[9] also report fluid resuscitation alone, following which their patients underwent emergent cesarean deliveries to prevent maternal and fetal complications.

In contrast, our patient was managed with caloric replacement using 10% dextrose, supplemented with insulin infusion to avoid hyperglycemia and electrolyte replacement. This approach effectively reversed ketoacidosis, leading to a healthy vaginal delivery at 38 weeks gestation without emergent surgical intervention. Chausse et al[10] also reported treating a 24-year-old patient with 10% dextrose and insulin, resulting in an uncomplicated vaginal delivery at 38 weeks. Karpate et al[11] described managing a patient with fixed-dose insulin as well, which led to the delivery of a healthy infant.

To our knowledge, there is no reported literature detailing the diagnostic overlap between starvation ketosis and euglycemic DKA. However, euglycemic DKA in pregnancy is well documented in multiple case reports by Yasin et al,[5] Karpate et al,[11] Jaber et al,[14] Chico et al,[15] and Wazir et al,[16] where patients were managed per DKA protocols. These patients usually had a history of type 1 or type 2 diabetes prior to pregnancy, and DKA was usually triggered by infections such as COVID- 19, urinary tract infection, or other intercurrent illness.

CONCLUSIONS

Starvation ketosis in pregnant women, particularly during the third trimester, is increasingly recognized due to hormonal changes that cause relative insulin resistance and heightened caloric needs. As demonstrated in this case, even brief periods of fasting can precipitate ketosis.

This case study highlights the importance of maintaining a high index of suspicion for starvation ketosis and the need for timely caloric replacement during pregnancy, typically through dextrose and insulin supplementation. If IV dextrose does not quickly reverse acidosis, clinicians should investigate other potential causes of high-anion gap metabolic acidosis. Ultimately, early recognition and appropriate nutritional management are vital to prevent life-threatening complications for both mother and fetus.

Financial disclosures: None declared.

Funding/support: None declared.

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Proceedings From the 2025 Medical College of Wisconsin Innovations in Healthcare Education Research Annual Conference

The following award-winning abstracts were presented during the 12th Annual Medical College of Wisconsin (MCW) Innovations in Healthcare Education Research (IHER) Annual Conference on September 16-18, 2025. Health care educators and researchers from MCW and other national institutions meet annually at IHER to present their research and innovative ideas and to learn from one another about the new and creative approaches to educating students and residents. The 3-day conference includes nationally recognized keynote speakers, panel sessions, workshops, roundtables, oral presentations, and posters that can be viewed at https://www.mcw.edu/IHER2025. Four hundred and fifty-six participants hailed from 31 states and 6 countries. The winning oral presentations and posters in the research and innovations categories are published below.

INNOVATIONS – ORAL PRESENTATION

Bridging the Gap: Advancing Medical Student Research and Scholarship with Medical Education Research and Scholarship Program

Rhett Reichard, PhD

Problem: Academic scholarship and research skills are essential in medical education and clinical practice, yet preclinical and clinical students often struggle to develop them due to time constraints, competing demands, and limited formal training. Additionally, many medical students have limited prior exposure to research, minimal understanding of its role in clinical practice and general unawareness of scholarly opportunities available to them. The MERAS program is structured to bridge these gaps. Through exposure to diverse examples of scholarship, MERAS remediates students' deficits in critical research and scholarship skills while fostering innovation, critical thinking, and academic inquiry. Aligned with Western Atlantic University School of Medicine's (WAUSM) core values, it prepares future physicians to advance medical education and integrate evidence-based practice.

Approach: At WAUSM, student scholarships include oral presentations on educational practices, reflections, and review articles. In collaboration with Student Affairs, medical educators and a librarian developed a 10-session live online program with longitudinal mentorship across all curricular years. These standalone, panel-style sessions promoted self-directed student learning in literature search, study design, curriculum development, and scholarly dissemination. Emphasizing innovation reports and reviews, the program linked health professions education to traditional and emerging publication formats. Sessions were recorded and archived on CANVAS enabling asynchronous access. Several students engaged in mentorship, resulting in the submission of 2 peer-reviewed scholarly works and demonstrating their developing competence in medical education research, critical thinking, and academic inquiry.

Lessons: The MERAS program exemplifies how aligning educational initiatives with institutional values can foster a dynamic culture of innovation, collaboration, and scholarship among medical students. By offering a flexible structure that allows participants to tailor their involvement based on individual interests, the program creates an engaging and multifaceted learning environment led by a diverse team of medical educators. Key lessons from MERAS include the efficiency of adapting proven frameworks, the transformative impact of faculty-student collaboration, and the importance of programs that inspire both academic output and innovative teaching practices. These experiences underscore the power of structured extracurricular programs to integrate research and teaching while fostering meaningful academic growth and creativity.

Significance: Scholarship and research skills are vital in medical education, yet students often face challenges acquiring them. The MERAS program fosters critical thinking, innovation, and academic excellence through a flexible, interest-driven approach that enhances student engagement in scholarly activities.

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RESEARCH – ORAL PRESENTATION

Generating Interactive Case Reports from Published Literature with a Large Language Model

Haelynn Gim, BA

Background: Published case reports represent a cornerstone of medical literature and are valuable educational resources,[1] but their static format limits engagement and interactivity. Artificial intelligence (AI) has the potential to generate and simulate interactive clinical scenarios with which learners can engage.[2,3] This project explores the feasibility of using AI, namely large language models (LLMs), to convert existing published case reports into interactive cases to enhance their educational utility.

Methods: We prompted OpenAI's GPT-4o to convert 5 published case reports with neuroinfectious diagnoses into case descriptions following a provided standardized template. These case descriptions were then uploaded to a custom internet interface, and 3 learners (2 medical students and 1 resident) interrogated them via free-text questioning regarding history, examination, and studies to arrive at a diagnosis and management plan. The LLM was prompted to play the patient and adhere to the case description for each of the 5 cases. All user questions and LLM-generated answers were then reviewed by a neurologist to determine medical appropriateness.

Results: Of 803 total LLM-generated answers, only 1 (0.1%) contained information that was not in alignment with the original case report; this was in response to a question about the time course of an illness, which was deemed to be unclear in the published case report upon human review. In 689 instances (85.8%), the LLM provided medically appropriate responses that aligned with the content of the case reports. The LLM declined to answer in 113 instances (14.1%). An example of such a response may occur following a request for "liver function tests" when none were presented in the case; the response may be "These results are not available."

Conclusions: In this pilot study, a LLM successfully converted published case reports into interactive cases that learners could engage with to arrive at diagnoses and plans. The LLM adhered closely to content within the case reports in its responses to learner inquiries. The risk of generating faulty information ("hallucinations"[4]) appears low, supporting the feasibility of employing AI to enhance the interactivity of case reports. Further research is needed to evaluate the effectiveness of this technology in supporting student learning and to facilitate its integration into everyday use within health care education.

Significance: LLMs offer a transformative approach to converting published case reports into interactive cases, creating a novel and engaging way for learners to explore and learn from medical literature.

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INNOVATIONS – POSTER PRESENTATION

A Novel Abbe-Vermilion Switch Flap for Near-Total Upper Lip Reconstruction

Laura Whitney, BS

Problem: Upper lip reconstruction presents unique challenges due to its intricate anatomy and critical functional and aesthetic roles. Traumatic injuries, such as those caused by dog bites, can result in substantial defects, leading to functional impairments and aesthetic deformities. Established techniques, such as the Abbe and vermilion switch flaps, offer effective solutions for specific lip subunit losses, but neither are ideal for complete upper lip reconstruction.

Approach: A 31-year-old female with a dog bite-induced near-total upper lip avulsion injury underwent staged reconstruction using a combination of the Abbe flap and a vermilion switch flap. Initially, the patient presented with severe soft tissue loss, including a complete absence of the upper lip's aesthetic subunits, such as the central tubercle, philtrum, and Cupid's bow. To address the extensive tissue loss, a novel combination Abbe- vermilion switch flap was designed. This combination flap consisted of a 1 cm-wide Abbe flap, designed to address the central philtral column, with incorporated bilateral vermilion switch flaps to simultaneously restore the vermilion and red lip tissues. The first stage of the reconstruction involved flap transposition, followed by a second-stage procedure after a 3-week delay for flap division and inset.

Lessons: At 2.5 months postoperation, the patient reported significant improvement in both upper lip function and appearance. The upper lip contour dramatically improved and oral competence was fully restored. Despite the presence of some hypertrophic scarring, the patient expressed high satisfaction with the results. Further interventions, such as intralesional steroid injections and nonsurgical resurfacing, were planned to address the residual scarring. Overall, this new technique was successful and demonstrated the potential of the combination Abbe-vermilion switch flap to revolutionize upper lip reconstruction.

Significance: This novel method of upper lip reconstruction successfully combines 2 well-established techniques and demonstrates the importance of personalized, innovative reconstructive strategies tailored to the unique needs of patients with complex facial trauma.

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INNOVATIONS – POSTER PRESENTATION

Bookending the Learner's Experience With the Donor Body: Pre- and Post-encounter Reflections

Robert V. Hill, PhD

Problem: Modern medical curricula face calls to incorporate humanistic practices early and

often in medical school training. We have incorporated a set of humanistic elements into our integrated structure lab curriculum, including a first-day exercise wherein learners link observations to hypotheses about the body donor's life. Students engage in dissections framed as patient care scenarios and participate in a narrative reflection on their first experience in the lab. In contrast with these meaningful early sessions (and despite an annual donor memorial service), students have lamented the absence of a ceremonial end to the year's laboratory sessions. Many found their final lab encounter to be anticlimactic—a missed opportunity for closure and to say goodbye to the body donor.

Approach: To address this gap, we adapted our final lab session to include a second reflection, effectively bookending the students' year-long experience with the body donor with reflections. For this new activity, dissection groups summarized both clinical and personal observations gathered through the year as documented in their donor's chart, akin to a medical record. Previously unknown details on the donors' causes of death and occupations in life were provided. Students discussed these materials in their dissection teams, reflecting on what they had learned over the year about their donor, their team, and themselves. They then shared their journey with the body donor in discussions with the larger group. The session provided a space for students to explore how their perspective has changed since starting medical school as a result of encounters with the body donor.

Lessons: In postsession surveys, a majority of learners agreed that the end-of-year reflection appropriately honored their body donor (94%) and their overall experience in the laboratory (91%). In addition, 90% believed that the session provided a satisfying conclusion to the year's work. Most respondents expressed appreciation for the opportunity to share impressions about their donor and to hear about other teams' donors. Timing of the session proved challenging, however: some students were scheduled to return to lab and present and disliked having to do so after the emotional reflection session. In general, students appreciated the opportunity to honor their donors and reflect on how far they had come since beginning medical school.

Significance: Recent research at the intersection of medicine and philosophy has criticized the "medical gaze," an objectifying view of patients that focuses on their disease as separate from their personal identity. Our reflection activities represent an opportunity to cultivate humanism in medical education.

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RESEARCH—POSTER PRESENTATION

Assessing Online PRP Injection Information: Can ChatGPT Serve as a Reliable Evaluator?

Rushabh Shah, BS

Background: The internet has become a primary source of medical information for patients; however, much of the content available in sports medicine remains unverified, lacking standardized quality assessment.[1,2] Given the increasing role of artificial intelligence (AI) in health care, we sought to evaluate whether ChatGPT could reliably evaluate online sports medicine content. Our study focused on platelet-rich plasma (PRP) injections, a growing nonsurgical treatment option for osteoarthritis and sports-related injuries.[3]

Methods: We analyzed 68 relevant YouTube videos using 2 validated health information scoring systems: the DISCERN scale and the JAMA benchmark criteria. Human raters and ChatGPT independently graded the videos. Intraclass correlation coefficient (ICC) and Cohen's kappa were used to assess inter-rater agreement. Spearman's rank correlation analysis was performed to evaluate potential systematic bias in ChatGPT's scoring.

Results: Human raters observed a mean DISCERN score of 57.7 (SD, 14.0) and mean JAMA score of 2.54 (SD, 0.92). ChatGPT observed a mean DISCERN score of 56.6 (SD, 9.67) and mean JAMA score of 2.50 (SD, 0.93). Interrater reliability analysis revealed substantial agreement for the DISCERN scale (ICC, 0.76; 95% CI, 0.64-0.85) and strong agreement for the JAMA criteria (weighted kappa, 0.85; CI, 0.76-0.94). However, Spearman's analysis identified a negative correlation (ρ, -0.75, $P < .0001$) between human DISCERN scores and ChatGPT's rating discrepancies, indicating that ChatGPT systematically underrated higher-quality videos while overestimating lower-quality ones.

Conclusions: ChatGPT demonstrated strong agreement with human evaluators in assessing the quality and reliability of online sports medicine information. However, its tendency to moderate extreme DISCERN scores suggests a limitation in distinguishing between high- and low-quality content. Our results suggest that AI-driven tools may help patients identify more reliable online sports medicine educational content.

Significance: Patients frequently turn to unverified online sources for medical guidance. This study explores the potential of large language models as a tool for evaluating online health content.

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The *WMJ* would like to thank everyone who served as a manuscript reviewer in 2025. Manuscript review is essential to the integrity of *WMJ*. We are grateful for the assistance of these individuals in ensuring authors receive objective and insightful feedback on their work.

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