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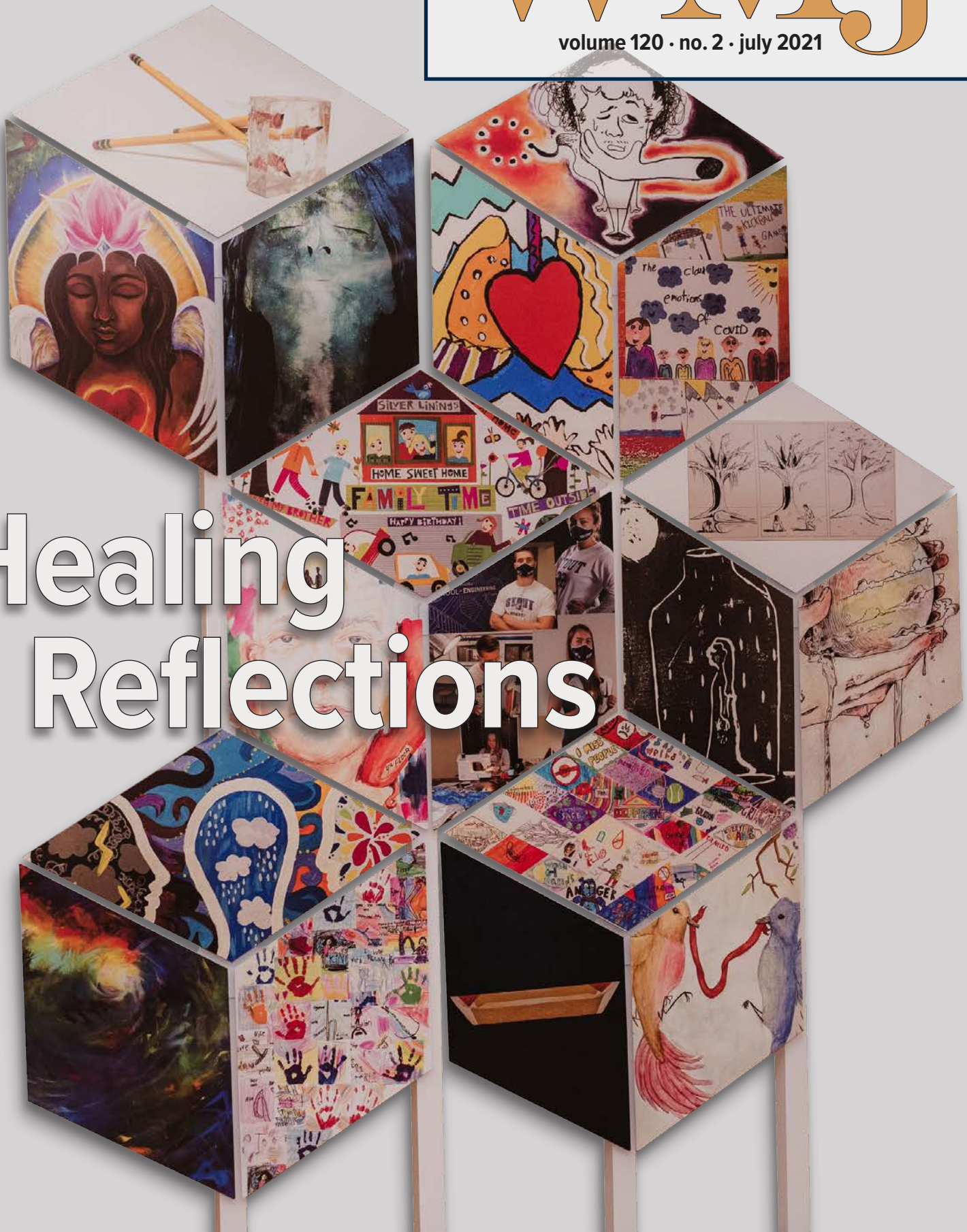
Healing Reflections



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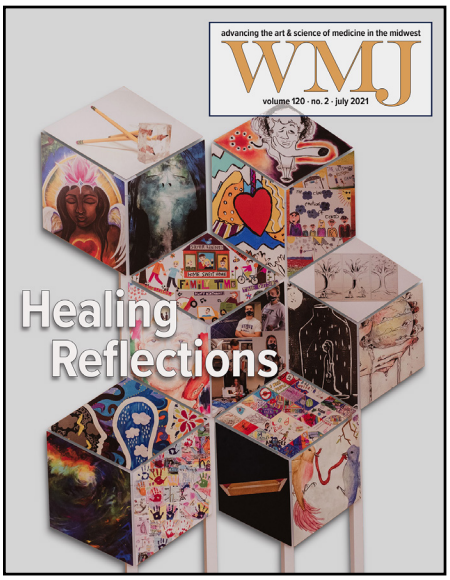

COVER THEME

Healing Reflections

Much has changed in our practices, profession, and communities since the first cases of COVID-19 were confirmed in 2020. And as the pandemic starts to quiet, the academic medical community is catching up--writing about lessons learned and reflecting on ways these experiences may shape the future. This issue of WMJ *includes a collection of these papers, as well as a narrative that describes a unique collaboration–the Healing Reflections mural—aimed at healing one Wisconsin community and documenting an historic year.*

Cover image: Panels from the "Healing Reflections" mural. Photo courtesy of Codi Leigh Photography. *Reproduced with permission.*

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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EDITORIAL

ORIGINAL RESEARCH

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CASE REPORTS

BRIEF REPORTS

FROM THE DEANS

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WMJ

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Mural Collaboration Aims to Heal Community

Nathan Hau; Julie Anderson, PhD; Donn Dexter, MD

The past year has left our communities deeply scarred and in need of healing. For many of us, it brought loss, grief, hope, and a newfound awareness of the fragility of life. In response to this, Mayo Clinic Health System recently unveiled Phase I of an important project, the Healing Reflections mural. This is a collaboration between the University of Wisconsin-Eau Claire (UW-Eau Claire), Mayo Clinic Health System, and the Eau Claire community in an effort to heal our community and document the historic year of 2020.

For almost a year, the Healing Arts committee at Mayo Clinic Health System in northwest Wisconsin has been collecting compelling stories from employees, patients, and community members. The stories are centered around themes of healing, resilience, inclusion, diversity, hope, and economic hardship. Sharing the stories has given people the opportunity to reflect on their personal experiences from the past year. The concept of the Healing Reflections mural was developed by Todd Wright, MD, an orthopedic surgeon at Mayo Clinic Health System, and Patricia Kleine, PhD, provost and vice chancellor for Academic Affairs at UW-Eau Claire. Stories are collected, and selected stories are sent to artists for inspiration. Artists receive two to four stories and then create a piece for the mural that represents one or more of the shared stories. The artists are local and range from art professionals to elementary school children. With the completion of the mural, a grand, diverse collection of artists' renderings of personal experiences from 2020 will be on display.

"Under the Same Sun," a mural panel created by Pa Kou Lee

> Together we can learn from each other's struggles and begin to mend the scars of 2020 that run deep in our lives, families, economy, culture, and entire way of life.

Currently, the mural is composed of 36 panels of artwork that illustrate 39 of the 95 stories shared thus far. One piece is by Pa Kou Lee, a certified ophthalmic assistant at Mayo Clinic Health System. Unique to the project, Pa Kou Lee both wrote her story and created the artwork titled "Under the Same Sun" to describe her struggles during the pandemic. She wrote, "The nights were getting longer, and I could feel myself sinking, struggling to keep my head above the waves of change and my own emotions, and struggling to carry what felt like boulders in my chest. I couldn't help but cry." She also shared the comfort she found talking with her mother about her experience as a child tending a garden as the warm sun shone down on her. "I was reminded that though I may feel weak and overwhelmed, I still have purpose. I am still protecting a garden, just a more human version of it under the same sun of my youth, which is the same sun that rises today, and in some way, I was comforted by that," she wrote. Her story is represented in the mural by a beautiful, abstract expressionist acrylic painting of a bright gold sun shining over rough blue water.

The Healing Reflections mural is far from

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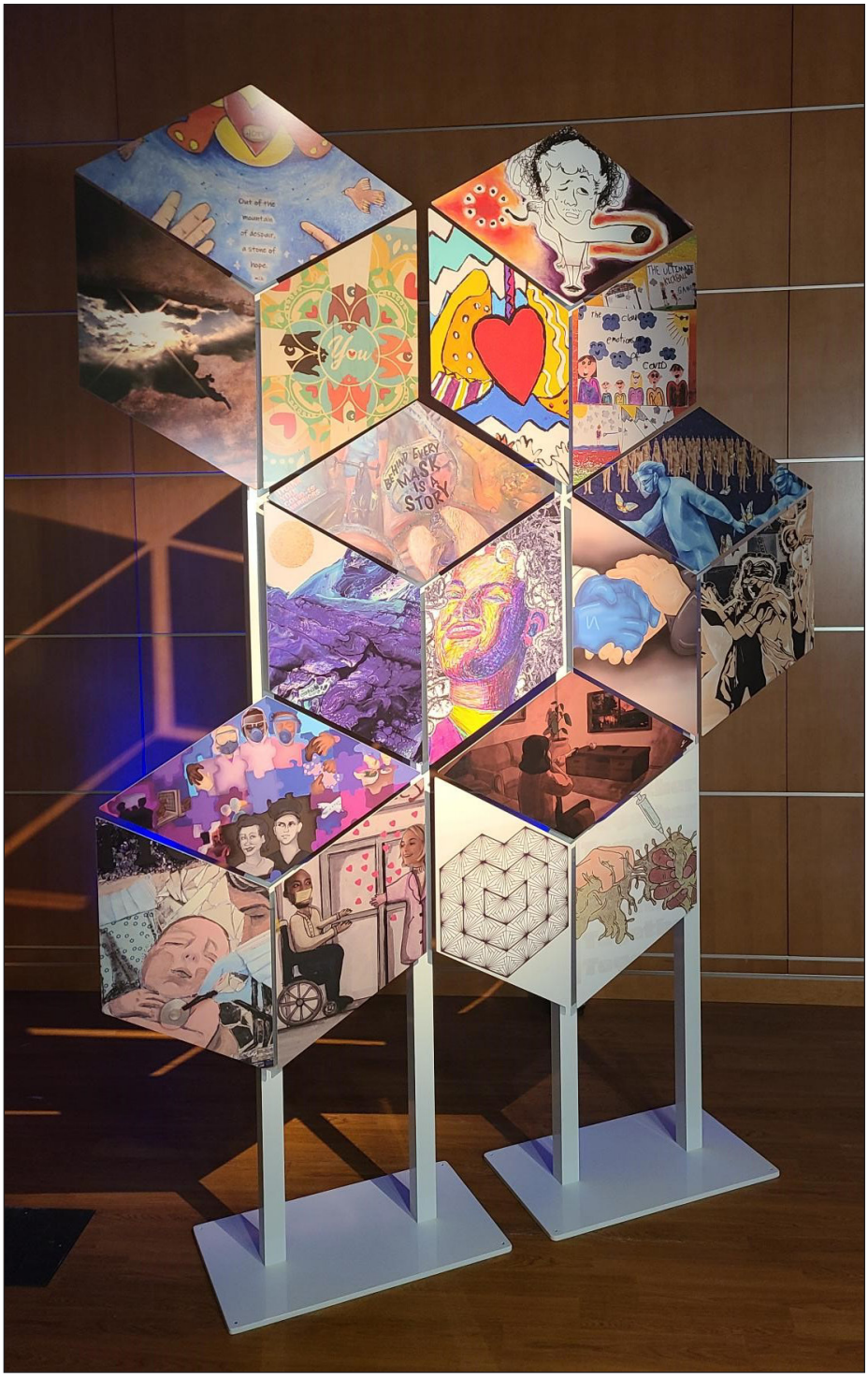

Panels from the Healing Reflections mural. Artwork was created by community members, ranging from professional artists to elementary school children, based on stories submitted by Mayo Clinic Health System employees, patients, and community members.

complete as stories are still being collected across the region. The completed mural will contain 135 panels. In addition, UW-Eau Claire has started a sister project, gathering stories and artwork from students, faculty, and staff to make 45 more artwork panels. Across the community, lessons of heartache, hope and healing are pouring into these collaborative art exhibits, and a grand display is planned for late summer or early fall on the UW-Eau Claire campus. The completed Healing Reflections mural will stretch 9 feet, 6 inches tall and close to 60 feet in length with the stories and reflections of people all across the community.

Funding for the project was supported through a donation by the Tri-County Medical Society of Eau Claire, Dunn, and Pepin counties, whose physician members are keen to help initiatives like this that recognize the work and sacrifice of our health care workers and others in our community.

This project began as a way to help the local community reflect and heal following the stress and loss from the difficult pandemic year. Through the sharing and telling of stories, the Healing Reflections mural provides an essential outlet for individuals to express their feelings and experiences. Sharing one's sorrows, hopes, and lessons learned allows an openness that invites healing.

The healing that was catalyzed by this project stretches beyond those who share their stories. "People heal by gaining insight and understanding to another's experience, and also by validating their own experiences," said Dr Wright. Through listening, reading, and viewing the stories of others, we can better heal ourselves. Understanding that we are not alone in a time when we are isolated from one another is crucial for our community to recover. Together we can learn from each other's struggles and begin to mend the scars of 2020 that run deep in our lives, families, economy, culture, and entire way of life.

Medicine can certainly address some of the challenges brought on by the pandemic, but through collaborating with others, we can work toward healing not only individuals but also entire communities. Through the Healing Reflections mural project, Mayo Clinic Health System, UW-Eau Claire, and our communities in northwest Wisconsin have come together to learn about each other, to give hope, and to heal. Fostering these connections and collaborations within and outside of medicine will help to ensure that our communities grow strong again.

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COVID, Hepatitis, and Cancer

Sarina Schrager, MD, MS, *WMJ* Editor-in-Chief

Eighteen months ago, no one had heard of SARS CoV-2, the novel coronavirus that causes COVID-19. The medical community was charged with learning everything there is to know about this deadly disease. It was a process of reading everything, looking at studies, talking to colleagues and friends, and watching the news. Caring for people with COVID was a challenge, with little data on what worked and what didn't. Clinicians in the hospital watched thousands of patients die, unable to effectively slow down the disease process. Public health leaders were pressured to make recommendations based on little to no epidemiologic data, and the management of this pandemic at times proceeded in fits and starts. It was a chaotic time to be a clinician.

This issue of the *WMJ* contains several articles about COVID-19 infections in Wisconsin. As the pandemic starts to quiet, the academic medical community is catching up and writing about experiences over the last 15 months. We publish a group of papers in this issue about a rural community that organized a COVID testing site outside of the clinic in the early stages of the pandemic,[1] a hospital system that activated a hospital incident command system (HICS) in order to reorganize and prioritize resources due to the pandemic,[2] and a variety of clinical case reports about patients with unusual presentations of COVID-19. One paper from clinicians at the Medical College of Wisconsin (MCW) describes two cases of adolescent males who presented with COVID-related delirium that required long-term treatment with antipsychotic medications.[3] Another paper from MCW authors describes comorbidities associated with mortality in hospitalized patients with COVID.[4] This study of patients at Froedert Hospital found that heart disease was associated with increased mortality but obesity was not, which is counter to several other studies around the country.

> "Knowledge comes from learning. Wisdom comes from living."
>
> —*Anthony Douglas Williams*

Authors from the University of Wisconsin School of Medicine and Public Health (UWSMPH) did a retrospective chart review looking at patients who were admitted to the hospital with COVID who had an atypical presentation (ie, no fever or cough).[5] They found that patients with atypical presentations were more likely to be older, reside in long-term care facilities, and had more comorbidities but lower levels of inflammatory markers. These patients with atypical presentations also had a higher mortality rate.

Finally, Hau and colleagues describe a collaborative initiative aimed at documenting 2020 and healing their community through art via the "Healing Reflections" mural, a portion of which is featured on the cover of this issue.[6] All of these papers provide data about the myriad presentations and complications from coronavirus infection.

We also include two papers and a commentary about hepatitis infection. In 2019, there were almost 2500 new cases of hepatitis C diagnosed in Wisconsin.[7] It is estimated that 70,000 people in Wisconsin are living with hepatitis C, but only about half know about the infection. One paper in this issue surveys primary care clinicians throughout Wisconsin and finds existing gaps in knowledge about treatment of hepatitis C.[8] The accompanying commentary by Tyska and Westergaard discusses hepatitis C as an epidemic that has a cure and advocates for increased screening for hepatitis C and expanded treatment in primary care. The other hepatitis paper looks at prevalence of hepatitis B and opportunity for education in a Hmong population in Milwaukee.[9] These papers were published online ahead of print in May to coincide viral hepatitis awareness month in the United States.

The third cluster of papers relates to cancer epidemiology and screening, as well as unique presentations. The paper by Pfau et al looks at colon cancer screening before

and after updated recommendations by the US Preventive Services Task Force.[10] Overall screening rates did not differ significantly, but the type of screenings did. It would be interesting to compare these rates to other national data. Decreased cancer screening has been a consequence of the COVID pandemic, with screening colonoscopies getting cancelled and patients being wary about interacting with the health care setting. In April 2020, numbers of colonoscopies decreased almost 80% compared to the previous year.[11] Procedures are increasing again, and it remains to be seen whether there will be excess deaths from cancer related to the pause in screening. Another paper looks at cancer incidence and epidemiology in North Dakota.[12] This group of researchers found different trends in cancer mortality based on county and sex. A third paper in this cluster describes a case of a 61-year-old man who presented with syncope and was diagnosed with renal cell carcinoma with metastases to the right ventricle and cervical lymph nodes.[13]

We hope that this issue contributes to the body of knowledge about COVID, cancer, and hepatitis. As we continue to weather the consequences of the pandemic, the medical community will work to transform new knowledge into wisdom that will allow all of us to recover and improve the quality of care we provide patients in the future.

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An Epidemic with a Cure

Steven Tyska, MD; Ryan P. Westergaard, MD, PhD, MPH

More than one year into the worst public health crisis of our lifetime, there is hope for an end to the deadly COVID-19 pandemic, even as significant challenges remain. While these challenges have demanded most of our recent attention, there is another epidemic that we must not neglect—an epidemic with a cure. Hepatitis C virus continues to spread in Wisconsin and in the United States, infecting a new generation, even as curative treatment has become simple to prescribe and barriers to treatment have been removed. We have the means to eliminate hepatitis C as a public health threat and need only the will to do so. We hope that May 2021, Hepatitis Awareness Month, will mark the beginning of a concerted effort to identify all who are infected and to cure them.

In another paper published in *WMJ*, Koepke and colleagues describe findings from a survey of Wisconsin family physicians to gauge their familiarity with hepatitis C treatment recommendations and awareness of recent changes in Medicaid policies designed to facilitate widespread access to hepatitis C cure.[1] The results were striking—the vast majority of family physicians were not aware, for example, that Wisconsin Medicaid now allows nonspecialists to prescribe hepatitis C treatment and does not restrict access to hepatitis C drugs for patients with no evidence of liver fibrosis or cirrhosis. Consequently, very few primary care providers have ever prescribed antiviral drugs to their patients with hepatitis C, missing valuable opportunities to prevent liver disease and stop the spread of the virus in our state.

These results are not surprising. Many physicians practicing today trained in medicine during an era when hepatitis C was described as a "silent epidemic" largely affecting older Americans from the Baby Boomer Generation. In the past, hepatitis C treatment consisted of injectable, interferon-based regimens that had high levels of toxicity and low cure rates. Treating hepatitis C required close monitoring by experienced subspecialist providers, and successful cure was achieved in only a minority of highly selected and motivated patients.

Two historic shifts occurred during the past decade that now demand we approach the hepatitis C epidemic differently. First, we have experienced a revolution in antiviral therapy, with the proliferation of direct-acting antiviral drugs (DAA) with high levels of effectiveness and tolerability. Hepatitis C can now be reliably cured with once daily, single-tablet regimens containing DAAs that are effective against all known genotypes of hepatitis C and require only an 8- or 12-week duration of treatment. Second, the epidemiology of new hepatitis C infections has shifted dramatically toward younger adults who inject drugs, fueled by the persistent epidemic of opioid and methamphetamine use disorder. Curing hepatitis C is now a public health imperative, not only because of the need to prevent severe liver disease in older adults but to prevent transmission of the virus among some of the most vulnerable members of our community.

We have the means to eliminate hepatitis C as a public health threat and need only the will to do so. We hope that May 2021, Hepatitis Awareness Month, will mark the beginning of a concerted effort to identify all who are infected and to cure them.

When the modern era of hepatitis C treatment began in 2011 with the approval of the first DAAs, they were at first not widely available. The high cost of the initial hepatitis C anti-

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virals necessitated prioritization of treatment to those most affected by the infection and those most likely to benefit from the treatment. Insurance companies and state Medicaid programs refused to cover hepatitis C treatment for most patients, except for those whose degree of liver fibrosis placed them at high risk for liver failure and the need for transplantation. Sobriety criteria were developed in an attempt to identify those who may fail to benefit from treatment due to continued drug and alcohol abuse. Furthermore, the daunting decision regarding who should receive this lifesaving treatment and who should not was appropriately relegated to gastroenterologists and infectious disease specialists who were better able to apply complex treatment guidelines and keep up with rapidly evolving science.

In the intervening decade, DAAs have become ever more affordable, simpler to prescribe, and can easily be prescribed in outpatient, primary care settings. Modeling studies have recently suggested that universal testing and treatment of all US residents, similar to the well-accepted paradigm for addressing the HIV epidemic, would, in fact, be a cost-effective national strategy.[2] Given these developments, we have a historic opportunity to eliminate hepatitis C as a public health threat. Rarely have opportunities like this arisen, where a simple change in clinical practice can have such a profound effect on morality and mortality. We just need to test and treat. As of March 2, 2020, the US Preventive Services Task Force recommends that all adults aged 18 to 79 should be screened for hepatitis C.[3] Primary care providers should be at the forefront of this screening effort and should primarily manage the care of their patients with hepatitis C who do not have complicated liver disease.

The Wisconsin Department of Health Services has taken a number of steps in the past few years to improve screening and access to hepatitis C treatment. In July 2019, the Division of Medicaid Services eliminated all sobriety and liver disease severity restrictions for prescribing hepatitis C antiviral medication and removed the requirement that these medications be prescribed by a specialist. In 2020, the requirement for prior authorization for these medications was removed for fee-for-service Medicaid patients as well. BadgerCare Plus patients in HMOs are equally entitled to these medications without more restrictive criteria.

Another state agency, the Wisconsin Department of Corrections, has shown important leadership in combatting the hepatitis C epidemic in the state. For the past several years, the department has universally screened all incarcerated adults for hepatitis C and has implemented treatment protocols to offer curative treatment to all who need it. Universal testing and treatment is the necessary approach to eliminating hepatitis C as a public health threat. People who are cured can no longer infect others, making our state healthier and safer. We wish to recognize with gratitude this valuable contribution to public health made by our colleagues in the Department of Corrections and encourage all health care organizations to follow this example.

Hepatitis C elimination is an attainable goal and, thanks to the paper by Koepke et al,[1] we now understand several challenges we face in its pursuit. Primary care providers can and should offer their patients screening and treatment for hepatitis C. With education and support from the Wisconsin Department of Health Services, we envision a future where hepatitis C screening and treatment is a routine part of primary care practice—that is, until it no longer needs to be.

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Risk Factors and Mortality for Atypical Presentation of COVID-19 Infection in Hospitalized Patients – Lessons From the Early Pandemic

Aurora Pop-Vicas, MD, MPH; Ambar Haleem, MD; Fauzia Osman, MPH; Ryan Fuglestad, BS; Daniel Shirley, MD; Robert Striker, MD; Nasia Safdar, MD, PhD

ABSTRACT

Objective: To assess the clinical epidemiology and outcomes of patients hospitalized with COVID-19 who did not experience fever and cough during the early pandemic.

Methods: Retrospective cohort of all patients admitted during March 13, 2020 through May 13, 2020 with laboratory-confirmed COVID-19 to 3 tertiary-care hospitals. Patient-level data (demographic, clinical manifestations, comorbid illnesses, inpatient treatment) were analyzed. The main outcome variable was atypical presentation, defined as any hospitalized patient with COVID-19 infection who did not experience both fever and cough. We identified risk factors for atypical presentation on univariate and multivariate analyses and assessed 30-day mortality differences via survival analysis.

Results: Of 163 patients in the study, 39 (24%) were atypical. On univariate analysis, atypical cases were significantly more likely to be older, reside in a long-term-care facility (LTCF), and have underlying diabetes mellitus, stroke, or cardiac disease; present without dyspnea or myalgia, have lower C-reactive proteins (CRP) and higher beta-natriuretic peptides. They were less likely to receive intensive care unit care or specific COVID-19 treatments ($P < .05$). The incidence of acute respiratory failure was not significantly different between the groups. On logistic regression, atypical cases were significantly more likely to be LTCF residents ($P = 0.003$) and have a lower average CRP ($P = 0.01$). Atypical cases had significantly higher 30-day mortality (hazard ratio 3.4 [95% CI, 1.6 – 7.2], $P = 0.002$).

Conclusion: During the first pandemic surge, COVID-19 patients without inflammatory signs and symptoms were more likely to be LTCF residents and had higher mortality. Timely recognition of these atypical presentations may have prevented spread and improved clinical outcomes.

INTRODUCTION

The COVID-19 pandemic caused by the novel SARS-CoV-2 coronavirus has affected almost 144 million people globally, with more than 3 million deaths so far.[1] The virus continues to spread in multiple regions of the world, including the United States. Prompt diagnosis and management of all infected individuals with SARS-CoV-2 is crucial to contain further spread.

COVID-19 infection has a wide disease spectrum, ranging from asymptomatic infection to severe clinical conditions such as acute respiratory distress syndrome with multiorgan dysfunction. During the first pandemic surge, persistent fever and cough were the most common symptoms, present in 78% and 57% of patients, respectively, as confirmed by a large systematic review of more than 24,410 adults with COVID-19 infection.[2] While several cohort studies[3-5] have suggested that some hospitalized patients—particularly older adults—can present in an atypical fashion without fever and cough, this subgroup of patients is not otherwise well defined clinically and infection could be difficult to recognize promptly. Delays in diagnosis can prove fatal, given the much higher risk of death associated with older age.[6] Therefore, our main objectives for this study were to characterize the clinical manifestations, epidemiology, and outcomes of patients diagnosed and admitted to the hospital with COVID-19 infection during the first pandemic surge who did not experience fever and cough (atypical presentations). We aimed to (1) compare clinical

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manifestations and disease outcomes in patients admitted to the hospital with typical versus atypical COVID-19 presentations, (2) identify risk factors associated with atypical presentation in hospitalized patients, and (3) describe illustrative COVID-19 cases with atypical presentations in an effort to increase clinicians' awareness and ultimately improve care.

METHODS

Study Design and Setting

We performed a retrospective cohort study of all consecutive inpatients with COVID-19 infection admitted to 3 tertiary-care hospitals (1 university and 2 community hospitals, with 1,108 total beds) within our academic medical center in the Midwest over a 60-day period (March 13, 2020 - May 13, 2020). All patients with positive nasopharyngeal swab specimens for SARS-CoV-2 by reverse transcriptase–polymerase chain reaction were included. The Institutional Review Board deemed the study exempt.

Variables

We reviewed the electronic medical record (EMR) for each patient, including outpatient records within 2 weeks prior to admission and daily inpatient records, to assess factors relevant to COVID-19 infection and to verify accuracy of subjectively reported fever or lack of fever. We also reviewed outpatient records within 30 days post-discharge to assess clinical outcomes. Utilizing a standardized data collection tool, we collected data on the following characteristics:

- **Demographic variables:** age, sex, race, body mass index, smoking status (current, former, never), and place of residence (home vs long-term care facility [LTCF]). We defined LTCF as any skilled nursing home, assisted living facility, or group home for individuals with disabilities.
- **Comorbid illnesses:** diabetes mellitus, hypertension, cardiac disease, stroke, respiratory disease, chronic kidney disease, chronic liver disease, active malignancy, autoimmune disease, use of immune suppressive therapies, transplant recipient, or HIV infection.
- **Clinical manifestations:**
  1) ***Signs and symptoms:*** presence of fever, cough, dyspnea, myalgia, fatigue, sore throat, nasal congestion, headache, altered taste, altered smell, nausea, vomiting, diarrhea, chest pain as reported by the patient and/or recorded by a health care provider during hospitalization or during any outpatient health care encounter within 2 weeks prior to admission. We also recorded presence of hypoxia (oxygen saturation < 94% on pulse oximetry[7]) and acute lung infiltrates on chest x-rays or computed tomography on admission.
  2) ***Laboratory data:*** white blood cell count (WBC), platelets, creatinine, transaminases, creatinine kinase, troponin, beta-natriuretic peptide (BNP), ferritin, C-reactive protein (CRP), fibrinogen, lactic acid, D-dimers, lactate dehydrogenase (LDH) on admission; and highest creatinine, CRP, ferritin and D-dimers values during the hospital stay.
  3) ***Treatments:*** hydroxychloroquine or chloroquine, azithromycin, doxycycline, corticosteroids, remdesivir, tocilizumab, and/or convalescent plasma therapy for COVID-19 infection.
- **Clinical outcomes:** intensive care unit (ICU) admission, mechanical ventilation, pressor therapy, new hemodialysis requirement, length of hospital stay, and mortality (defined as death during hospital stay or within 30 days of admission to inpatient hospice).

Definitions

We defined atypical cases as patients who did not experience fever (temperature ≥ 100.4º F or 38º C) and cough and typical cases as patients who experienced both symptoms during hospitalization or within 2 weeks prior to admission.

Statistical Analysis

We conducted univariate analyses to compare clinical characteristics and outcomes of atypical vs typical cases and multivariate analyses to identify independent risk factors for atypical presentation. We analyzed categorical variables by chi-square tests or Fisher exact tests and continuous variables by *t* test of means for normally distributed data and Mann-Whitney U tests for nonparametric distributions. Risk factors identified on univariate analysis to be statistically significant and have at least 10 patients on each cell of the 2-by-2 tables were entered into logistic regression. The logistic regression model's discrimination ability was assessed by the area under the receiver operating characteristic (ROC) curve. Survival analysis was conducted using Cox-proportional hazard models and Kaplan-Meier curves. A 2-tailed *P* value of ≤ 0.05 was considered statistically significant, and all statistical analyses were performed in STATA SE 15.

RESULTS

Clinical Manifestations, Treatment, and Risk Factors for Atypical Presentation

There were 163 patients hospitalized with confirmed COVID-19 infection during the 60-day study period. Fever and cough were not reported in 39 (24%) of these patients, and these were considered atypical cases. Table 1 shows the risk factors associated with atypical cases, with demographic, comorbid illness, clinical manifestations, and treatment incidence data for atypical and typical cases shown in the Appendix. On univariate analysis, atypical cases were more likely to be older, reside in a LTCF, and have underlying diabetes mellitus, stroke, and/or cardiac disease. In addition to not manifesting both fever and cough, they were also less likely to experience myalgia or dyspnea. The presence of gastrointestinal symptoms did not differ significantly between the 2 groups. On laboratory analysis, atypical cases had a significantly lower CRP than typical cases, whereas other inflammatory markers and bio-

Table 1. Risk Factors for Atypical COVID-19 Presentations in Patients Requiring Hospitalization (Univariate and Multivariate Analysis)

Risk Factor [a]	Odds Ratio	95% CI	*P* value	Adjusted Odd Ratio	95% CI	*P* value
Demographics						
Age (mean, years)	1.05	1.03 – 1.08	< 0.001	1.01	0.98 – 1.05	0.50
Sex (female)	1.7	0.8 – 3.6	0.13			
Body mass index (mean)	1.0	0.9 – 1.0	0.12			
Current smoker	1.0	0.3 – 3.2	0.97			
Long-term care facility resident	6.7	3.0 – 14.9	< 0.001	5.1	1.72 – 15.0	0.003
Comorbid illnesses						
Hypertension	1.8	0.8 – 4.0	0.13			
Diabetes mellitus	2.2	1.05 – 4.7	0.04	2.25	0.86 – 5.9	0.10
Previous stroke	4.3	1.4 – 12.8	0.009			
Cardiac disease	3.4	1.6 – 7.3	0.002	1.34	0.48 – 3.7	0.57
Respiratory disease	1.0	0.46 – 2.2	0.99			
Renal disease	2.2	0.95 – 5.0	0.06			
Clinical manifestations						
No myalgia	5.8	2.1 – 15.8	< 0.001			
No dyspnea	9.9	4.4 – 22.3	< 0.001			
Hypoxia	0.6	0.3 – 1.3	0.23			
Abnormal chest x-ray	0.5	0.17 – 1.38	0.18			
Gastrointestinal symptoms	1.1	0.5 – 2.3	0.75			
Chest pain	0.3	0.08 – 1.0	0.05			
Abnormal troponin [b]	1.1	0.4 – 2.8	0.82			
Serum WBC count (mean)	0.98	0.92 – 1.0	0.56			
Platelet count (mean)	1.0	0.99 – 1.0	0.25			
Serum creatinine at admission (mean)	1.36	0.95 – 1.95	0.09			
ALT (mean)	0.99	1.0 – 1.0	0.19			
BNP (mean)	1.0	1.0 – 1.0	0.02			
CRP at admission (mean)	0.91	0.84 – 0.98	0.02			
Highest CRP (mean)	0.92	0.87 – 0.97	0.002	0.91	0.85 – 0.98	0.01
Highest ferritin (mean)	0.99	1.0 – 1.0	0.47			
Highest D-dimer (mean)	0.99	0.94 – 1.0	0.78			
Highest LDH (mean)	0.99	1.0 – 1.0	0.45			
Treatment						
Hydroxychloroquine	0.4	0.17 – 0.9	0.03			
Azithromycin	0.5	0.2 – 1.0	0.07			
Other systemic antibiotics	0.8	0.34 – 2.1	0.70			
Steroids	0.3	0.12 – 0.95	0.04			
Remdesivir	4.6	0.98 – 21.6	0.05			
Tocilizumab	[c]	[c]	0.13			
Convalescent plasma	1.1	0.36 – 3.1	0.90			

Abbreviations and normal ranges: WBC, white blood cell, 4.5 – 11 x 109/L, values in the table are multiples of 109/L; platelet count, 150 – 400 x 109/L; serum creatinine, 0.84 – 1.21 mg/dL; ALT, alanine transaminase, 7 – 56 units/L; BNP, beta-natriuretic peptide, ≤ 450 pg/mL for age ≥ 75 and ≤ 125 pg/mL for age < 75; CRP, C-reactive protein, ≤ 1.0 mg/dL (normal value); ferritin, 12 – 300 ng/mL for males, 12 – 150 ng/mL for females; D-dimer, < 0.4 mcg/mL; LDH, lactate dehydrogenase 140 – 280 U/L.

[a] Other variables (race/ethnicity, chronic liver disease, active malignancy, autoimmune disease, treatment with immune-suppressant agents, transplant recipient, presence of sore throat, fatigue, nasal congestion, headache, altered taste, altered smell, values for fibrinogen, lactic acid, and receipt of doxycycline) did not have significant differences between the 2 groups, and are not shown. There were no HIV-positive patients in our study sample.

[b] Percentages calculated out of total patients with troponin labs checked (26 cases and 87 controls).

[c] Could not be calculated due to zero observations for atypical cases.

chemical parameters (ferritin, D-dimers, lactate dehydrogenase [LDH]) did not differ significantly. WBC counts, platelets, serum creatinine, transaminases, and troponins were similar on average between the 2 groups. Prevalence of hypoxia, abnormal lung infiltrates on chest x-rays, and chest pain did not differ significantly between the 2 groups, although atypical cases were more likely to have a significantly higher average BNP level. On multivariate analysis, patients presenting atypically were significantly more likely to reside in a LTCF, and significantly less likely to have a very elevated CRP. The area under the ROC curve for this model was 0.82.

Clinical Outcomes for Atypical Cases

As seen in Table 2, atypical cases were significantly less likely to be admitted to the ICU, receive pressor or ventilatory support, and be treated with hydroxychloroquine and/or corticosteroids. The odds of 30-day mortality were 3 times higher for atypical cases. The Kaplan-Meier survival curve for hospitalized patients presenting atypically versus those with typical symptoms of COVID-19 infections is shown in the Figure. Of the 12 atypical patients who died, 11 (92%) declined aggressive therapy and transitioned to comfort care measures during inpatient stay versus 4 (25%) of the 16 typical cases ($P < .001$). Among the subset of hospitalized patients with hypoxia (Table 3), atypical patients were less likely to have received corticosteroids ($P = 0.059$) and more likely to have received remdesivir ($P = 0.07$), although this trend did not reach statistical significance. None of the hypoxic patients from this subset analysis who received remdesivir died. As seen with the atypical patients from the entire cohort, the subset of hypoxic atypical patients was also significantly less likely to be admitted to the ICU and receive aggressive medical therapies and remained 3 times more likely to die compared with typical patients.

Illustrative Atypical Cases

Case 1. An 82-year-old man with underlying hypertension, atrial fibrillation, and coronary artery disease presented to his primary care physician with several weeks of gradually worsening fatigue, a sensation of loss of balance without falls, and profound anorexia. He described that "nothing tastes good" and he had lost his desire to eat, especially after a close friend who used to cook for him had died 2 weeks earlier. The patient was thought to experience grief and bereavement and was prescribed an appetite stimulant. He was admitted to the hospital the next day when his wife reported that he was no longer able to get up from the floor after multiple episodes of diarrhea through-

out the night. On admission, his temperature was 99.3º F, with other vital signs, including oxygen saturation, normal. His labs were remarkable for a WBC count of 5.4 K/μL with lymphopenia, sodium 129 mmol/L, baseline creatinine 1.06 mg/dL, and alanine aminotransferase 86 U/L. His chest x-ray showed new patchy infiltrates in the left upper and lower lobes, and his SARS-CoV-2 polymerase chain reaction (PCR) nasopharyngeal swab was positive. His symptoms improved with intravenous fluids and supportive therapy, and he was discharged home after 3 days. He gradually regained his strength and appetite at home, and by 5 weeks post-discharge reported that he was able to ambulate without assistance, complete his usual daily exercise regimen on the stationary bike, and felt back to his normal self. His wife had remained asymptomatic throughout, and her SARS-CoV-2 PCR test was negative.

Case 2. An 86-year-old widow residing in an assisted-living facility with underlying diabetes mellitus, hypertension, obesity, and hypothyroidism was brought to the emergency department (ED) by her granddaughter due to worsening fatigue and decreased oral intake over a few days. She denied fevers, chills, nausea, vomiting, abdominal pain, cough, or chest pain. On admission, her temperature was 99.5º F and her oxygen saturation was 90% on room air. The chest x-ray showed diffuse bilateral airspace disease. Her SARS-CoV-2 PCR test was positive, and admission labs showed normal complete blood cell counts and electrolytes, with slightly elevated inflammatory markers (ferritin 276 ng/mL, CRP 2.6 mg/dL) and elevated LDH (324 U/L) and BNP (2,194 pg/mL). She became more hypoxic subsequently, requiring 3L of oxygen for most of her inpatient stay. She was treated for acute congestive heart failure and pneumonia and completed a 5-day course of hydroxychloroquine despite slight prolongation in QTc interval. She was discharged back to her assisted living facility with no further need for oxygen after 18 days of being in the hospital. At her 2-day telemedicine follow-up, she reported feeling back to baseline and expressed sadness at not being allowed to go on her usual nature walks with her relatives due to the facility's newly implemented social distancing restrictions.

Case 3. A 74-year-old woman current smoker with body mass index of 48, underlying diabetes mellitus, hypertension, atrial fibrillation, chronic obstructive pulmonary disease on 2L of oxygen at baseline, obstructive sleep apnea, and dementia was brought to the hospital after she was found hypoxic with an oxygen saturation of 85% at her nursing home. On arrival, she was afebrile, with a systolic blood pressure of 90 mmHg, heart rate of 130, and an oxygen saturation of 93% on 10L of oxygen. She had been seen in the ED on 2 previous occasions. During the first visit 4 days prior to admission, she presented with delirium, was diagnosed with a urinary tract infection caused by an extended-spectrum beta-lactamase producing *E coli,* and was discharged back to her nursing home on intramuscular ertapenem. Her second visit 2

Table 2. Clinical Outcomes Associated With COVID-19 Infection in Hospitalized Patients Presenting With Atypical vs Typical Disease (Univariate Analysis)

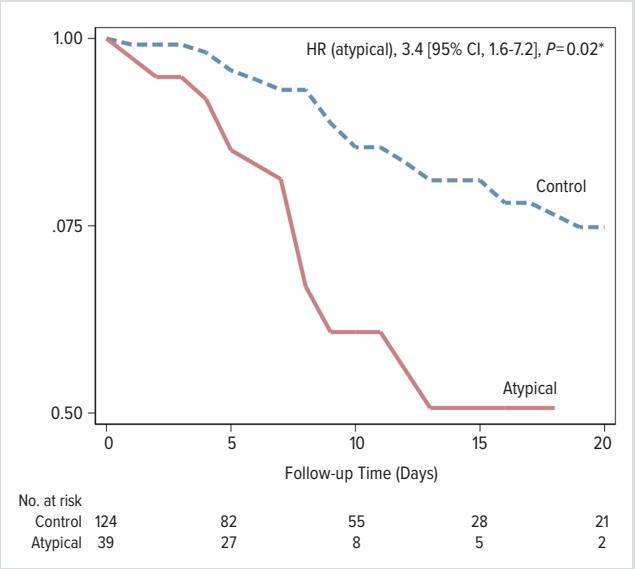
Outcome	Cases (N = 39) N (%)	Controls (N = 124) N (%)	Odds Ratio	95% CI	*P* value
Intensive care unit admission	3 (8)	44 (35)	0.15	0.04 – 0.5	0.003
Received pressor support	3 (8)	27 (22)	0.3	0.1 – 1.0	0.06
Received ventilator support	2 (5)	38 (31)	0.1	0.03 – 0.5	0.005
Length of hospital stay (mean, days)	7.8	10.4	0.95	0.90 – 1.0	0.09
30-day mortality [a]	12 (31)	16 (13)	3	1.3 – 7.1	0.01

[a] Includes patients who died in the hospital or within 30 days of admission to hospice.

Table 3. Treatments and Clinical Outcomes for Hospitalized Patients With Hypoxia and COVID-19 Infection, by Atypical vs Typical Presentation (Univariate Analysis)

Characteristic	Atypical N = 23 N (%)	Typical N = 86 N (%)	Odds Ratio	95% CI	*P* value
Treatments					
Remdesivir	3 (13)	3 (3)	4.2	0.5 – 32.7	0.07
Steroids	4 (17)	33 (38)	0.3	0.08 – 1.15	0.059
Convalescent plasma	5 (22)	12 (14)	1.7	0.4 – 6.1	0.36
Outcomes					
Intensive care unit admission	3 (13)	42 (49)	0.16	0.03 – 0.6	0.02
Need for pressors	3 (13)	25 (29)	0.36	0.06 – 1.41	0.12
Ventilator support	2 (9)	36 (42)	0.13	0.01 – 0.6	0.003
Length of hospital stay (mean, days)	9.7	12.0			0.22
30-day mortality	9 (39)	15 (17)	3.0	0.96 – 9.2	0.03

Figure. Kaplan-Meier Survival Curve for Hospitalized Patients Presenting With Atypical vs Typical COVID-19 Infections



*HR, hazards ratio of death; patients with typical COVID-19 presentation are labeled as "control."

days prior to admission was for dyspnea and hypoxia. Her chest x-ray showed bilateral interstitial opacities with small pleural effusions. A SARS-CoV-2 PCR test was obtained, but the probability of COVID-19 infection was considered "low" because she had been afebrile on both occasions and was not noted to be coughing. She was discharged back to her nursing home with a higher oxygen requirement (3 L) before the test results were available. On her third ED visit, which resulted in hospitalization, her chest x-ray showed bilateral interstitial infiltrates that had progressed from the prior study. She was admitted to the ICU and started on pressors and high-flow oxygen. Given her multiple underlying medical illnesses and poor overall prognosis, the patient and her guardian declined mechanical intubation and opted for comfort care. She died in the hospital the next day.

DISCUSSION

As the COVID-19 pandemic reached and expanded in the Midwestern US during March through May 2020 (first wave), approximately a quarter of our patients who were hospitalized with COVID-19 disease presented in an atypical fashion, without fever and cough. These patients were also less likely to experience myalgia and dyspnea, and their elevation in CRP was generally lower than that of patients with typical COVID-19 symptoms. Interestingly, hypoxia and radiological findings of multifocal airspace disease were as frequent in atypical patients as they were in patients hospitalized with typical clinical manifestations of COVID-19 pneumonia, suggesting that at least some of these patients experienced the "silent hypoxia" phenomenon previously described.[8] Patients presenting with atypical COVID-19 infection in our study were less likely to receive corticosteroids or aggressive medical treatment in the ICU—even when hypoxic—and were approximately 3 times more likely to die. Most of this mortality was among patients with progressive respiratory failure who declined mechanical ventilation and opted for comfort measures in the context of advanced age with multiple underlying illnesses that indicated a poor prognosis for recovery. In addition, the undertreatment of hypoxic, atypical patients with corticosteroids—which have been shown to reduce 28-day mortality among critically ill patients[9]— combined with delays in diagnosis until the disease was very advanced, likely also contributed to this finding.

Our findings underscore the importance of maintaining a high index of suspicion for COVID-19 disease in frail, older individuals. The blunted fever response and paucity of typical inflammatory symptoms and signs in older individuals presenting with severe infections, likely due to immune senescence-related changes in cytokine production and alteration in thermoregulatory responses, are well-documented in geriatric literature.[10] For example, older studies have shown that 20% to 50% of advanced age patients with pneumonia,[11] bacteremia,[12] influenza,[13] or other life-threatening infections[14] lack fever—a finding that has been associated with a poor prognosis on occasion.[15,16] This tendency for atypical infection presentation in older individuals is now increasingly apparent worldwide in the context of the COVID-19 pandemic.[17] In the study by Guo et al,[4] in an elderly COVID-19 cohort from Hunan Province, China, fever and cough were absent at admission in 33% and 35% of the patients older than 65, respectively. In the retrospective inpatient cohort study conducted in the United Kingdom by Brill et al,[5] COVID-19 patients older than 80 were significantly more likely to present without fever, cough, and dyspnea. Instead of these typical infectious disease symptoms, frail, elderly patients with COVID-19 disease may present with delirium, dehydration from gastrointestinal losses and decreased oral intake in the setting of ageusia or anosmia, falls, or exacerbation of underlying comorbid illnesses, as shown in our study and in several published case reports from Europe.[18,19]

In our study, LTCF residence was an independent risk factor associated with COVID-19 atypical presentation. This finding has important clinical and public health implications. The COVID-19 disease burden has disproportionately affected residents and health care workers in the LTCF setting, which was associated with 33% of all US coronavirus deaths as of April 22, 2021.[20] While reasons for this excess mortality are multifactorial, unrecognized COVID-19 infection in residents because of the lack of typical signs and symptoms may have contributed to this situation, as diagnostic and treatment delays can prove fatal to individuals of advanced age with multiple comorbid illnesses. In this regard, the multi-nursing home outbreak investigation conducted by Graham et al[21] showed that less than 40% of the infected LTCF residents reported either cough or fever, and many did not develop cough or fever even in the days leading up to death. In addition to the devastating clinical outcomes in this patient population, unrecognized disease undoubtedly increases the risk of viral transmission both within the facility and when these patients are cared for at other health care settings (ED, ambulatory care clinics, hospitals) if infection prevention protocols for COVID-19 are not appropriately activated. The study by Arons et al,[22]—which showed that after the first identified COVID-19 case in a Seattle nursing home, 64% of the residents contracted SARS-CoV-2 within 3 weeks and 26% died—highlighted the importance of early recognition and control of this disease in the LTCF setting. Isolation and visitor restriction policies, when stringently enforced, are effective at preventing community transmission. However, these efforts are not feasible indefinitely, considering their deleterious psychological effects on older adults.[23] As the pandemic eases and LTCFs reopen, prompt recognition of atypical COVID-19 through routine and widespread testing of all LTCFs is crucial in preventing further spread.

Our study has several limitations. Being retrospective in nature, it is subject to the biases associated with observational study designs. Our hospitalized patient population is drawn from 2 US states in the Midwest (Wisconsin, Illinois) and may not be gener-

alizable to other geographical areas. Our data collection relied on retrospective EMR review of outpatient and inpatient records; it is possible that some patients experienced certain COVID-19 symptoms before admission that were not documented in the records, which could have led to inadvertent misclassification of atypical cases. However, we believe this is unlikely, since our pandemic preparedness protocols required health care providers to electronically fill out COVID-19 screening questionnaires that prompted symptom documentation at each point-of-entry for both telemedicine and in-person clinical assessments, resulting in multiple symptom screenings for each patient prior to admission. Our study adds new findings to previous retrospective cohort studies and case reports by comparing atypical and typical cases, identifying independent risk factors for atypical presentations of COVID-19 infections, and describing their epidemiology and outcomes in more detail.

CONCLUSION

Long-term care facility residents are more likely to present with atypical COVID-19 clinical manifestations that lack classic symptoms of fever and cough. Their caregivers and health care providers should maintain a high index of suspicion for the diagnosis in this high-risk group to prevent treatment delays and limit intra- and interfacility spread.

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Appendix: Available online at www.wmjonline.org.

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Community-Based Testing for COVID-19 in a Low-Prevalence, Rural Area: Documentation of Logistics and Practical Aspects of Testing

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ABSTRACT

Introduction: Testing and mitigation strategies for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection often focus on high-prevalence, urban communities, leaving low-prevalence rural areas without specific strategies to maintain the health and safety of their populations. We evaluated a cost-effective strategy for SARS-CoV-2 testing to determine point prevalence in a rural community with a generally low prevalence of infection.

Methods: We voluntarily tested asymptomatic clinic employees and conducted 2 community SARS-CoV-2 testing events in Cashton, Wisconsin, that included testing for asymptomatic persons. We also partnered with local clinics and public health departments to conduct weekly drive-up clinics for asymptomatic, high-risk persons identified through enhanced contact tracing. This was possible as testing capacity in Wisconsin never reached its maximum, and we continued symptomatic testing through our clinic.

Results: We tested 61 employees, 268 individuals at 2 community events, 36 high-risk asymptomatic people at drive-up clinic events, and 128 symptomatic people within our clinic. We observed 1 positive result in asymptomatic people and 5 positive results in symptomatic patients, confirming the low prevalence in our area.

Conclusions: Our testing events confirmed a low prevalence of SARS-CoV-2 infection, providing prevalence information to local businesses and schools. We reinforced our partnership with local public health departments to facilitate enhanced contact tracing and test asymptomatic persons, and we provided a service to asymptomatic persons requiring testing for travel, school, or work. Local businesses and community members appreciated the services and expressed relief for point-in-time testing results during a period of stress and uncertainty.

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INTRODUCTION

Since the first case of coronavirus disease 2019 (COVID-19) in the United States, a wave of infection has left no state without disease burden.[1,2] The prevalence of disease, however, varies widely between states and between rural and urban communities within states. By August 2020, Wisconsin had more than 70,000 cases and 1,000 deaths due to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[3,4] Milwaukee County had the most cases (>23,000), whereas some rural counties had fewer than 50.[3,5]

Information from the Centers for Disease Control and Prevention and public health departments focused initially on high prevalence areas and includes recommendations such as masking, business closures, and occupancy restrictions. Information on managing disease in lower risk, lower prevalence rural areas is lacking. Ways to appropriately ensure safety for COVID-19 in rural populations already at risk for social isolation and related health issues, including increased rate of heart attacks, depression, and chronic disease, have not yet been fully elucidated.[6] Rural areas face particular challenges in the surveillance of SARS-CoV-2 because of greater travel distances for testing, risks of travel in and out the community, and diminishing capacities in rural hospitals.[6-10] In addition, rural physicians tend to be older and at greater risk themselves.[7]

Data on the transmission of SARS-CoV-2 indicate asymp-

tomatic people actively contribute to the reproductive number (R0), often without awareness they are infecting others.[11] Despite risk of transmission of SARS-CoV-2 by asymptomatic persons, appropriate testing strategies for asymptomatic persons, including health care workers, have not been fully determined. Limited testing resources and the focus on testing symptomatic patients have likely hindered the ability to accurately determine prevalence of the virus in both urban and rural communities.[7] However, within Wisconsin, testing capacity has not reached full capacity, allowing the opportunity to work with local health departments to offer testing to asymptomatic persons.[12]

Scenic Bluffs Community Health Center is a Federally Qualified Health Center (FQHC) with its primary site in Cashton, Wisconsin. Most patients are from Monroe County and the surrounding counties of Vernon and La Crosse. The first positive case of SARS-CoV-2 infection reported in Monroe County was on March 24, 2020.[13] In Vernon and La Crosse counties, the first cases confirmed were on April 22 and March 18, 2020, respectively.[14,15] Each of these counties had a low prevalence of disease when testing began in the area. A proactive testing protocol for symptomatic and asymptomatic patients was started to help determine the usefulness of enhanced contact tracing and community-wide testing. This report describes a collaborative approach to monitoring prevalence of disease burden of SARS-CoV-2 in a low incidence area of Wisconsin.

METHODS

Planning for Testing

Prior to large-scale community testing, we reviewed recommendations from health centers that had completed similar events.[16] We then created a map of our facility and contacted local authorities to determine logistics of traffic flow and set-up during an event. We advertised the first community event locally by word of mouth, flyers to local businesses for their essential workers, and flyers to local homes in English and Spanish. We encouraged preregistration by phone so that contact information for anyone who was not a patient at our clinic could be entered into our electronic health record. We requested insurance information to bill for staff time to administer the test; however, participants were not billed for any costs not covered by insurance.

To conduct testing while keeping costs at a minimum, we obtained test kits through Exact Sciences Laboratories, LLC (Madison, Wisconsin), which partnered with the state of Wisconsin to increase testing capacity and provide testing supplies, laboratory services, and results to any health care provider without cost.[17] Our health center also received grant funding from the federal government to continue to provide services throughout the pandemic, which allowed us to cover some staff expenses for testing events despite the ubiquitous decrease in revenue for primary care providers during this pandemic.

Testing Procedures

The procedures for the SARS-CoV-2 (N gene detection) test were followed as described by Exact Sciences and the Wisconsin Department of Health Services.[17] This test is a real-time reverse transcriptase polymerase chain reaction (RT-PCR) test for qualitative detection of nucleic acid from SARS-CoV-2 in respiratory specimens. Collection supplies were used for nasal (anterior nares) collection, including a synthetic-tipped swab on a plastic shaft and RNase-free normal saline transport media. Samples were stored in a biohazard bag and temperature controlled from the time of collection until shipment by courier for processing the evening of the sample collection. Laboratory processing included extraction of viral RNA from specimens followed by 1-step reverse transcription and PCR amplification with primer and probe sets specific to regions of the SARS-CoV-2 RNA genome.[18]

Employee Testing and Community Testing Events

Prior to the first community event, asymptomatic health center employees were screened to evaluate courier systems and testing protocols. The initial community-wide testing event was held May 20, 2020 in advance of a holiday weekend and included testing for both symptomatic and asymptomatic individuals. Advertising by flyers began approximately 10 days before the event. A second employee-only event was completed on June 1, 2020.

On July 10, 2020, a second community event was held just after a holiday weekend. Advertising included printed flyers and word of mouth through local public health organizations, including schools. Social media was used the day of the event but not before to ensure outreach was localized.

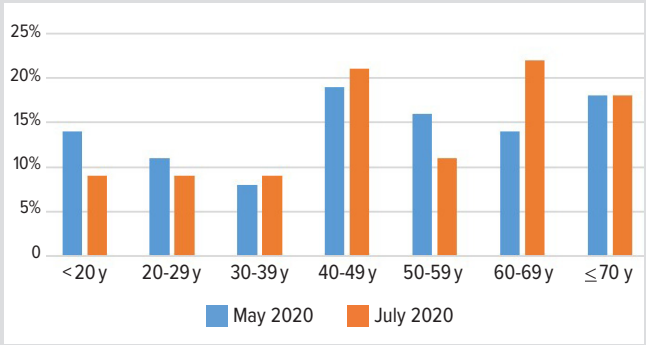
During the community testing events, 1 person directed traffic into 2 separate testing lanes. At the far end of the event site, registration staff assisted with test packets for preregistered people. Premade test packets included patient-specific lab labels, testing supplies, and a consent form. The consent form included a disclaimer and release explaining that deidentified test results may be used for education and research purposes, along with standard privacy and HIPAA policies. Participants were asked to sign the form prior to testing. The packet was then placed on people's windshields as they drove to the testing tent. For those who had not preregistered, the staff stationed at the registration tent helped them complete the information prior to advancing to the testing tent, and the packet was still placed on the windshield. Two staff members were assigned per testing lane: 1 person administered the test and the other verified correct labeling on the containers and information on the lab sheet. A clinician was available in the testing tent to answer patient questions or provide advice on maintaining quarantine if someone was experiencing symptoms or was thought to have a high-risk exposure. We defined high-risk asymptomatic persons as having a known exposure to another person who tested positive for SARS-CoV-2 infection or had exposure to another person under

Table 1. Testing of Employees and Persons at Community Testing Events or Weekly Clinics, May – July, 2020

	Date	N	Positive Tests (n)
Asymptomatic Employee Testing	May 14	37	1[a]
Asymptomatic Employee Testing	June 1	27	0
Community Testing Event #1	May 20	124	0
Community Testing Event #2	July 10	144	0
June (Thursdays) Drive-up Clinic Testing (High-Risk Asymptomatic Persons)	June 4	2	0
	June 11	2	0
	June 18	6	0
	June 25	15	0
July (Thursdays) Drive-up Clinic Testing (High-Risk Asymptomatic Persons)	July 2	4	0
	July 16	4	0
	July 23	3	0
	July 30	0	0
Symptomatic Persons Tested in the Clinic	May – July	128	4

[a]A second PCR swab was done 5 days after the first positive result (the day the positive test result was returned) and a third PCR swab was done on day 7. Both subsequent swabs were negative, and an antibody test done at 4 weeks also was negative. The patient was isolated until 2 negative results were obtained.

Figure 1. Age Distribution of People Tested at 2 Community Events



Abbreviation: y, years.

Figure shows results from community testing event held May 20, 2020 (N = 124) and July 10, 2020 (N = 144).

investigation. Staff in the testing tent only used full personal protective equipment (PPE), including a powered air purifying respirator (PAPR), gown, and gloves. Staff at registration wore masks, gloves, and gowns because they were reaching in and out of people's cars at various times, similar to other events across the country.[19] Participants were informed they would be called at the phone number they provided when results were available. Employees and community members were allowed to have a repeat test at a subsequent event.

Partnership With Local Health Departments for Drive-up Testing of High-Risk, Asymptomatic Persons

After the first event, the health center recognized there was a need/desire in the community for asymptomatic testing, based on public reactions and calls from patients and community members regarding testing capability. Callers primarily asked if the center was still willing to test people without symptoms for reasons such as travel, work clearance, and contact with a case. Active connections are maintained with the Monroe County Health Department—the local public health department (LPHD) and site of the main health center location. Health center staff is also in communication with LPHDs in Vernon and La Crosse counties, and the pandemic increased the frequency of these conversations and connections. Thus, it was natural to develop partnerships with LPHDs for SARS-CoV-2 testing.

After strategic conversations with representatives of LPHDs, we established a weekly 2-hour drive-up "clinic" by appointment and referral for asymptomatic testing only. We maintained that the patient had to have a recommendation from an outside provider (ie, either from a clinic or public health department) to ensure that patients had been counseled on the interpretation of test results. Specifically, patients were instructed that a negative result did not mean that quarantine was no longer necessary for a high-risk contact patients or that someone was no longer at risk for infection in the future. In the absence of a referral or contact with another provider, we offered the patient a visit with a clinic provider, but we did not schedule these patients for drive-up testing. The health department also started using our "high-risk clinic" for some enhanced contact tracing to obtain tests for high-risk contacts of known cases. Most drive-up testing clinics were held on Thursdays during June and July, with the exception of July 9 as people were scheduled for our large community-wide event the following day, if appropriate.

Testing of Symptomatic Patients at Our Clinic

Throughout these events, we maintained regular clinic hours and included symptomatic testing by appointment. People concerned about SARS-CoV-2 based on contact who did not have a referral to our high-risk clinic were offered an appointment with a provider, but with no guarantee of testing at that visit.

RESULTS

Asymptomatic Employee Testing

We tested 37 asymptomatic employees prior to the first community testing event and 27 asymptomatic employees at a second timepoint (Table 1). We observed 1 positive SARS-CoV-2 test in an asymptomatic employee who was not working in the building at the time.

Community Testing Events

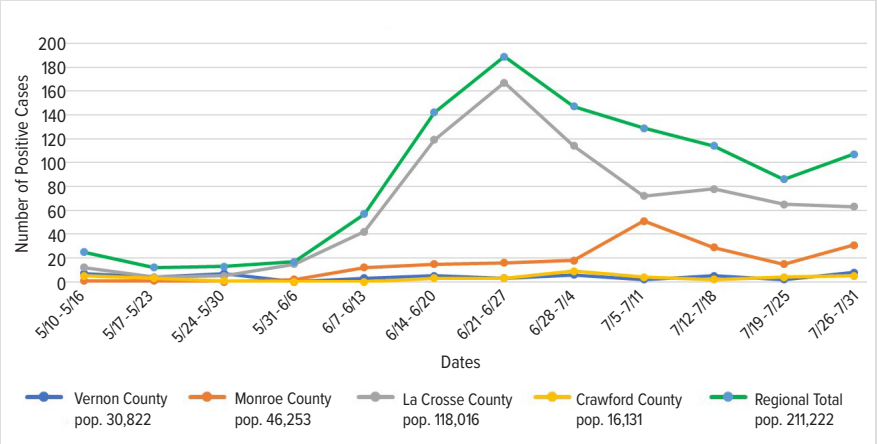
We tested 124 people—symptomatic and asymptomatic—at our first community event May 20 (Table 1). The majority were asymptomatic when tested. At a second community-wide event July 10, we screened 144 people. There were more symptomatic people at the second event, and many more had some type of contact to a positive case that was not considered high risk by the

health department. The majority of participants at community events were aged 40 years and older and nearly one-fifth (18%) were older than 70 years (Figure 1). In contrast, symptomatic persons tested within our clinic tended to be younger, and only 10% of those tested were older than 65 years (data not shown). Consistent with community demographics, most participants at community events were White/Caucasian (data not shown).

Testing of High-Risk Asymptomatic Persons at Weekly Drive-up Clinics

The 2-hour drive-up testing clinics were held weekly in June and July, 2020 (Table 1). No asymptomatic high-risk persons tested positive for SARS-CoV-2.

Figure 2. Weekly Positive Case Count by County[22]



Abbreviation: pop, population.
Data on weekly positive SARS-CoV-2 tests for 4 counties in Wisconsin from May 10 to July 31, 2020. Populations estimates are based on 2019 data.[23]

Testing at Our Clinics

From May through July, 2020, 128 symptomatic patients were teseted at our clinic during normal clinic hours (Table 1). Four patients (3.1%) tested positive for SARS-CoV-2 infection.

Availability of Test Results

Results were typically available within 3 to 7 days, depending on lab capacity. After our first community event, most results were received within 4 days; however, due to labeling errors, some results were delayed up to 7 days. After our second event, results were back within 4 days and all participants were contacted within 5 days of the event. For the weekly clinics, results were often received within 3 to 4 days.

Table 2. SARS-CoV-2 Test Positivity Rate by Date and County[22]

Dates (2020)	Vernon	Monroe	La Crosse	Crawford	Region Total
May 10 – May 16	4.1%	0.5%	2.7%	2.0%	2.3%
May 17 – May 23	1.9%	0.3%	0.5%	3.2%	0.8%
May 24 – May 30	3.2%	0.0%	0.4%	0.4%	0.5%
May 31 – June 6	0.0%	0.4%	1.0%	0.0%	0.6%
June 7 – June 13	1.4%	2.7%	4.5%	0.0%	3.3%
June 14 – June 20	2.6%	4.0%	9.2%	0.3%	5.1%
June 21 – June 27	1.3%	3.4%	9.1%	1.6%	6.9%
June 28 – July 4	2.6%	3.2%	6.0%	5.8%	5.2%
July 5 – July 11	0.4%	11.3%	6.1%	1.9%	5.6%
July 12 – July 18	2.7%	5.7%	13.3%	1.1%	7.7%
July 19 – July 25	0.9%	4.1%	6.2%	2.5%	4.8%
July 26 – July 31	2.4%	6.3%	5.7%	3.4%	5.1%

Estimated Costs of Events

Exhaustive cost analysis was not performed; however, we estimate each 6-hour event cost the health center approximately $7,100 for staff time the day of the event and for follow-up. Staff entered results into the Wisconsin Electronic Disease Surveillance System (WEDSS) and contacted each participant by phone with their results. Supply costs were approximately $4/person since lab supplies and costs were covered by Exact Sciences. We also implemented appropriate use of PPE, utilizing reusable equipment (PAPRs) if possible.

DISCUSSION

We aimed to determine the point prevalence of COVID-19 to help define cost-effective mitigation efforts for our community. Through increased access to COVID 19 testing, we sought to reassure community members and test travelers and other people at risk. Our results confirmed that point prevalence for the community remained low in an asymptomatic population when there was little prevalence in the symptomatic population, even as incidence began to increase in the region and throughout the state. We observed 1 positive result in asymptomatic persons and 5 positive results in symptomatic patients. We also had 1 positive test in a high-risk asymptomatic person tested on August 4, 2020, which was after our July 31, 2020 data cut-off date.

Other testing events occurred in the area around the time of our second community event on July 10: one in Monroe County on June 30, testing more than 200 people with 7 positives;[20] and one in Vernon County on July 7, testing over 400 people with no positives.[21] Both were run by the National Guard in partnership with local health organizations. Results were shared with us through the LPHDs. At the time of our events, the symptomatic positive rates in our surrounding area remained low but increased beginning at the end of May (Figure 2).[22,23] From May 10 through July 31, 2020, the positivity rate for the 4-county region ranged from 0.5% to 7.7% (Table 2).[22] The number of positive cases in Wisconsin increased in September 2020, with a peak number of cases in November 2020. Though our 2 community testing

events were open to everyone, all but 3 people tested were from ZIP codes starting with "546"—our primary service area—thus achieving our goal of testing local community residents.

Our informal, ongoing discussions with LPHD helped keep us informed of local trends and provided public health agencies a resource for their clients who had limited access to medical care or testing. As a smaller, independent organization, we were the only clinic in our region able to provide asymptomatic testing at the time of our events. We provided testing at no cost to patients, regardless of insurance status. Our community testing events appeared to provide reassurance to the people tested, as evidenced by many compliments received and requests for future events from local businesses and multiple local school districts. Our weekly "high-risk" clinic continues to receive referrals from LPHDs and physicians affiliated with other facilities whose patients have had exposures that warrant testing.

PCR testing of asymptomatic people with nasopharyngeal swabs is not ideal. Given the lower prevalence of SARS-CoV-2 in asymptomatic people, the positive and negative predictive values of PCR testing is predictably lower in asymptomatic people than in those who are symptomatic. Based on information provided by Exact Sciences, their PCR test for SARS-CoV-2 agreed with 100% of both positive and negative results versus another COVID-19 PCR test; however, a definitive way to measure sensitivity and specificity of the PCR test used was not available given the lack of a standard or other COVID-flu test for comparison.

We suggest that the benefits of testing asymptomatic people in our community outweigh the shortcomings, because asymptomatic participants were offered appropriate information on testing limitations. Through face-to-face education, people who were tested were instructed to continue their quarantines if exposed to a person who tested positive and that negative tests do not affect risk of future infections. All participants tested at community events received verbal information from a health care professional for any high-risk exposure and written materials reiterating recommendations on handwashing, wearing masks, and physical distancing.

Controlling the spread of SARS-CoV-2 infection involves enhancing awareness of testing, ensuring the availability of testing for symptomatic and asymptomatic persons, optimizing the ease of access to testing, and addressing community perceptions regarding testing.[24,25] Maintaining high capacity for testing and resources for contact tracing levels continues to be important in controlling the COVID-19 pandemic as mandates, such as limiting restaurant capacities, are lifted. Community testing events can develop and sustain effective links between testing and primary care. As a primary care provider, our health center understands community issues and can respond to both community and individual patient needs. We also understand privacy issues and the importance of follow-up for patients if they become symptomatic and/or require further intervention. Larger community-wide testing events may not allow for patient education and the relationship building we can offer. Through partnerships with local public health and community organizations, we continue to recommend mitigation and containment strategies for our patients and community. Prior to the availability of vaccine, we promoted strategies including mask-wearing in public, frequent hand hygiene, and limiting large group gatherings without masks.

In order to ensure reimbursement of costs, other area organizations limit community testing to patients covered by specific insurance plans. An insurance-based approach excludes those who are uninsured or have other financial, cultural, or linguistic barriers to care. FQHCs, such as Scenic Bluffs, operate on a sliding fee scale and accept patients regardless of insurance status or ability to pay. Thus, FQHCs are uniquely positioned to focus on low income or otherwise underserved communities. In our small, primary care clinic with modest federal grant funding, we were able to prioritize timely test results, patient notification, and effective systems to link participants with a primary care clinician. We are working to reduce costs by streamlining paperwork and assigning appropriate tasks to volunteers. Challenges with conducting an independent testing event include access to electrical supplies outdoors, reliable internet access, weather, and staff to ensure adequate testing, registration, and data management.

We will continue to hold asymptomatic community-wide testing events if requested by public health departments or other organizations. Through our partnership with LPHDs, we continue to provide "enhanced contact tracing" by testing asymptomatic contacts with significant exposure to confirmed cases. Ideally, this strategy will identify asymptomatic carriers before they spread the virus. Our results may help inform policies around business and school openings, and at the time of writing, we plan to test public school employees prior to their return to work as requested by 4 local school districts. Our continued testing program can provide reassurance to our community during this tumultuous and challenging era.

CONCLUSION

We were able to implement enhanced contact tracing that may not be possible in larger urban areas due to logistical and resource challenges. Our community testing and testing of high-risk asymptomatic persons served people without access to testing through other means and helped to reassure our community. We propose that additional partnerships and similar testing events be developed given anticipated reductions in testing through the National Guard or patient access to other means of testing. Along with mitigation strategies, testing events continue to be crucial to pandemic management,[24,25] even with the availability of safe and effective vaccines.

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Hepatitis C Treatment Knowledge and Practice Among Family Medicine Physicians in Wisconsin During the Current Hepatitis C Epidemic

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ABSTRACT

Background: Curative treatment for hepatitis C virus (HCV) exists, making elimination of HCV possible. However, most people with HCV have not received treatment. One barrier is limited access to treatment providers. HCV treatment can be effectively provided by primary care providers and, since 2017, Wisconsin Medicaid allows nonspecialists to prescribe treatment. We surveyed family medicine physicians in Wisconsin to evaluate capacity for the provision of HCV treatment.

Methods: We mailed a survey to family medicine physicians in Wisconsin from June 25, 2018 through September 7, 2018. Physicians were asked whether they prescribe HCV treatment and about their knowledge regarding HCV treatment and relevant statewide Medicaid policy. Using multivariable logistic regression, we evaluated physician characteristics associated with prescribing HCV treatment.

Results: Of 1,333 physicians surveyed, 600 (45%) responded. Few respondents reported prescribing HCV treatment independently (1%; n = 4) or in consultation with a specialist (6%; n = 35). Only 6% (n = 36) reported having a "great deal" of knowledge about HCV treatment. Most (86%; n = 515) were not aware that family medicine physicians can now prescribe HCV treatment covered by Medicaid. Physicians who practiced in offices affiliated with health systems were less likely to prescribe HCV treatment than physicians who practiced in an independent office or a Rural Health Clinic.

Conclusions: Among family medicine physicians in Wisconsin, experience with and knowledge of HCV treatment was limited. Developing knowledge and skills among primary care providers is needed to expand treatment access and make progress toward HCV elimination. Studies are needed to evaluate treatment access in primary care offices affiliated with health systems.

INTRODUCTION

Hepatitis C virus (HCV) infection is the most commonly reported bloodborne infection in the United States,[1] and more than half of infected people develop chronic infection.[2] Chronic HCV progresses slowly, often without symptoms, but is a leading cause of hepatocellular carcinoma, a leading reason for liver transplantation, and a leading infectious cause of death.[3,4] Before 1992, when universal screening of the blood supply began, transmission commonly occurred through receipt of contaminated blood products and organs. Today, the most common method of HCV transmission is injection drug use. Historically, the majority of people living with HCV were born during 1945-1965 (ie, the baby boomer generation).[5] In recent years, however, increasing numbers of younger adults, particularly in rural areas, have become infected with HCV as a result of increased injection drug use driven by the opioid crisis.[6-8]

Until 2013, treatment for chronic HCV was complex, had suboptimal cure rates, and caused many side effects, requiring management by a specialist. In contrast, the currently available HCV treatments, which consist of an 8 to 12 week course of all-oral direct-acting antiviral (DAA) medication, have >95% cure rates, far fewer side effects, and can be safely administered to individuals with most other chronic health conditions.[9] Furthermore, multiple studies have demonstrated that DAA medications can be safely and effectively administered by primary care providers.[10-12]

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Despite these advances in the treatment of HCV, a recent literature review found that only 39% of people who attended a follow-up visit after diagnosis with HCV received treatment.[13] There are multiple barriers to receiving HCV treatment, including medical insurance policies. For example, despite clear guidance that limitations to HCV treatment through state Medicaid programs violate federal law,[14] the high cost of DAAs has motivated many state Medicaid programs to limit access by requiring treatment to be prescribed by a specialist and by limiting treatment to patients who meet certain clinical and sobriety criteria.[15] However, the current specialist workforce is insufficient—particularly in rural areas—to treat the increasing numbers of people diagnosed with HCV.[16-18] To improve access to HCV treatment and make progress toward HCV elimination, the US Department of Health and Human Services and the Centers for Disease Control and Prevention have called for expanding the HCV treatment workforce to include nonspecialists, such as primary care providers.[16,19,20]

In Wisconsin, as many as 70,000 people are estimated to be living with chronic HCV, and new HCV infections have increased as a result of increased injection drug use.[6,8] Rates of new infections are highest in rural areas where there are few HCV treatment providers.[8,17,18] In recent years, Wisconsin Medicaid has removed all barriers to prescribing and receiving HCV treatment, including removing prior authorization (effective July 2020), sobriety restrictions (effective July 2019), and disease severity restrictions (effective July 2017). Also, in July 2017, Wisconsin Medicaid removed the requirement that HCV treatment be prescribed by a specialist, allowing all primary care providers to prescribe HCV treatment paid for by Medicaid. To evaluate the capacity of primary care providers in Wisconsin to provide HCV treatment, we surveyed family medicine physicians in Wisconsin 1 year after this change to assess their experience with and knowledge of HCV treatment. Because HCV has increased in rural areas of Wisconsin, we investigated differences in experience and knowledge by whether the provider practiced in a rural or urban area. In addition, we investigated the characteristics of family medicine physicians who reported already prescribing HCV treatment to gain insight into possible facilitators of or barriers to providing HCV treatment.

METHODS

We conducted a cross-sectional survey of family medicine physicians in Wisconsin to understand their knowledge and practices regarding prevention and treatment of opioid use disorder and HCV. This manuscript focuses only on the findings specific to HCV. The survey was administered and data were collected by the University of Wisconsin Survey Center from June 25, 2018, through September 7, 2018. Physicians were selected from a list of all family medicine physicians in Wisconsin procured from the data science company IQVIA (Plymouth Meeting, Pennsylvania). One thousand five hundred physicians were selected from 3,052 physicians on the list. The selected sample included all physicians

Table 1. Characteristics of Family Medicine Physicians Who Responded to the Survey, Wisconsin, 2018

Provider Characteristic	No.	(%)
Total	**600**	**(100)**
Age		
30-39	131	(22)
40-49	136	(23)
50-59	149	(25)
60+	163	(27)
Unknown	21	(4)
Sex		
Male	343	(57)
Female	239	(40)
Unknown	18	(3)
Race/ethnicity		
White or Caucasian	499	(83)
Asian or Pacific Islander	38	(6)
Latino or Hispanic	16	(3)
Black or African American	7	(1)
Native American	3	(1)
Other	13	(2)
Unknown	24	(4)
Number of years in practice after residency		
0-5 years	92	(15)
6-10 years	64	(11)
11-15 years	59	(10)
16-20 years	94	(16)
More than 20 years	274	(46)
Unknown	17	(3)
Practice type		
Hospital or health system-affiliated office-based practice	349	(58)
Independent office-based practice	96	(16)
Urgent care center	34	(6)
Rural Health Clinic	27	(5)
Federally Qualified Health Center/community health center	26	(4)
Emergency department	17	(3)
Hospital inpatient	11	(2)
Other	27	(5)
Unknown	13	(2)
Practice location, by ZIP code		
Rural	241	(40)
Urban	327	(55)
Unknown	32	(5)
Number of adolescent and adult patients cared for in past year		
<1000	133	(22)
1000-1999	172	(29)
2000-2999	122	(20)
≥3000	115	(19)
Unknown	58	(10)
Percent of patients covered through Medicaid		
<10%	58	(10)
10%-19%	134	(22)
20%-29%	117	(20)
30%-39%	99	(17)
40%-49%	47	(8)
≥50%	93	(16)
Unknown	52	(9)
Compared to all of Wisconsin, how serious is opioid misuse in the community where you practice?		
Not a problem at all in my community	1	(0)
Less of a problem	68	(11)
As much of a problem	432	(72)
More of a problem	95	(16)
Unknown	4	(1)

Unknown responses are those where the respondent did not provide a response to the question.
As a result of rounding, percentages may not sum to exactly 100%.

Table 2. Physician Knowledge and Experience Related to Hepatitis C Treatment

	Total No. (%)
Total	**600 (100)**
Hepatitis C Treatment: Experience and Knowledge	
Do you prescribe treatment for hepatitis C?	
Yes	4 (1)
Yes, but only in consultation with a specialist	35 (6)
No, but I would prescribe if I could	105 (17)
No	441 (74)
Unknown	15 (2)
How much do you feel you know about current treatment guidelines for hepatitis C?	
A great deal	36 (6)
A moderate amount	247 (41)
A little bit	254 (42)
Nothing	41 (7)
Not applicable	5 (1)
Unknown	17 (3)
Consideration of Hepatitis C Among Patients Who Inject Drugs	
If you have a patient who injects drugs with hepatitis C, would you ...? (select all that apply[a])[b]	
Encourage the patient to get treated	341 (59)
Treat the patient yourself	15 (3)
Make a referral to another provider for treatment	532 (92)
Tell the patient to return for treatment when he/she is no longer using/injecting drugs	19 (3)
Knowledge Gaps	
Which of the following training topics would help you improve your knowledge of hepatitis C? (select all that apply[a])	
Treatment of hepatitis C	436 (73)
Prevention of hepatitis C	204 (34)
Risk factors for contracting and transmitting hepatitis C	200 (33)
Liver disease, cirrhosis, and liver transplantation	189 (32)
I already know a lot about hepatitis C and do not need any more training	69 (12)
Knowing about hepatitis C is not very important to my job and I do not need training	18 (3)

[a]For questions where respondents were asked to "select all that apply," for each response, the percentage who chose this response was calculated using the total number of respondents as the denominator.

[b]Among 579 physicians who reported having patients who inject drugs. Unknown responses are those where the respondent did not provide a response to the question.

who were known to have a federal waiver to provide buprenorphine (a medication for opioid use disorder).[21] In addition, we oversampled physicians in rural areas to better understand their knowledge and practice. The survey design consisted of 3 mailings via the US Postal Service: a full mailing with cover letter to all 1,500 selected physicians (including a cover letter, questionnaire, a business reply envelope, and $5 bill), a postcard reminder, and 2 additional full mailings to those who had not responded to previous mailings. Physicians were excluded if they returned the survey and indicated they were no longer practicing medicine or if the survey was returned by the US Postal Service with no forwarding address.

The survey collected information on physician demographic and clinical practice characteristics in addition to 5 different domains related to the physician's (1) experience providing HCV treatment, (2) knowledge of HCV treatment, (3) knowledge of relevant statewide policy regarding HCV treatment, (4) treatment considerations for persons who inject drugs, and (5) self-identified knowledge gaps related to HCV. Physicians also were asked, "Compared to the epidemic of opioid misuse and opioid overdose across Wisconsin, how serious of a problem is opioid misuse in the community where you practice?". (See Appendix for survey.)

We categorized physician practice locations as rural or urban using the reported practice ZIP code and the designation by the Federal Office of Rural Health Policy.[22] Using chi-square and Fisher exact tests, physicians' knowledge and experience were compared by whether the physician was located in a rural or urban area.

To better understand the characteristics of family medicine physicians who have already started providing HCV treatment, we compared characteristics of 2 groups of physicians: (a) physicians who reported prescribing HCV treatment independently or in consultation with a specialist and (b) physicians who reported not prescribing HCV treatment, including physicians who reported that they do not prescribe HCV treatment but would if they could. We calculated percentages of physicians, by characteristic, who reported prescribing treatment. For each characteristic, we calculated bivariate odds ratios for prescribing HCV treatment. Characteristics significantly ($P < 0.05$) associated with prescribing HCV treatment were included in a multivariable logistic regression model to understand which characteristics were independently associated with prescribing HCV treatment.

All data were analyzed using SAS version 9.4. This study was approved by the University of Wisconsin-Madison Institutional Review Board.

RESULTS

Of the 1,500 family medicine physicians who were sent a survey, 11 reported being ineligible to participate (no longer practicing medicine), and 156 had surveys returned indicating the address was invalid. Of the remaining 1,333 physicians sent the survey, 600 (45%) responded. Respondents and nonrespondents were not significantly different in terms of sex, whether their practice site was primary care only or multispecialty, whether they practiced in a hospital, or rural location based on ZIP code. Among respondents, median physician age was 50 years, 57% were male, 83% were White or Caucasian, and 46% had practiced medicine for >20 years (Table 1). The majority (58%) reported practicing in an office-based practice affiliated with a hospital or health system, 16% reported practicing in an independent practice, and 5% reported practicing in a Rural Health Clinic. Respondents were from 69 of Wisconsin's 72 counties, and 40% were categorized as practicing in a rural area. The estimated percentage of patients with Medicaid reported by this group of providers ranged from 0

to 90% (median: 25%). Most respondents (88%) reported that opioid misuse in the community where they practice is as much or more of a problem than it is statewide.

Experience Providing HCV Treatment

Few physicians reported prescribing HCV treatment independently (1%; n = 4) or in consultation with a specialist (6%; n=35) (Table 2). In total, 546 (91%) physicians reported they did not prescribe HCV treatment. Among these 546 physicians, 105 reported that they did not prescribe HCV treatment, but they would if they could (Table 2). Fifteen (2%) physicians did not answer the question.

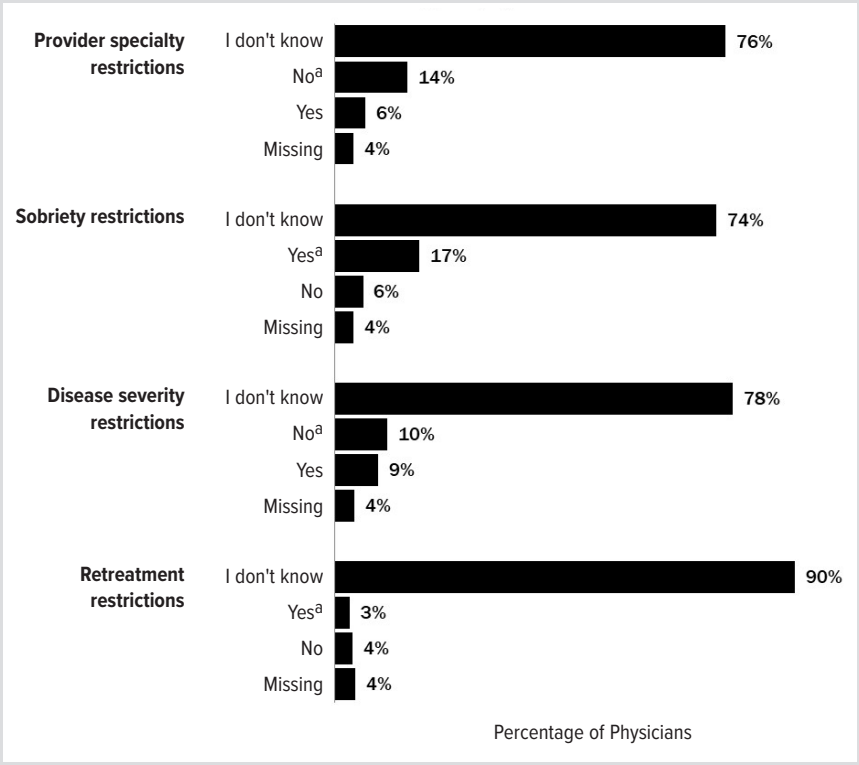
Knowledge of HCV treatment

When asked about knowledge of HCV treatment guidelines, 6% reported "a great deal," 41% reported "a moderate amount," 42% reported "a little bit," and 7% reported no knowledge of current HCV treatment guidelines (Table 2).

Knowledge of Relevant Statewide Policy Regarding HCV Ttreatment

Only 14% (n = 85) of physicians correctly responded that Wisconsin Medicaid does not require HCV treatment to be prescribed by a specialist. The majority of physicians reported they did not know whether Wisconsin Medicaid restricted HCV treatment based on patient sobriety, disease severity, or previous treatment (Figure).

Figure. Physician Knowledge of Whether Wisconsin Medicaid Has Restrictions to Prescribing and Receiving Hepatitis C Virus Treatment, by Type of Restriction



[a]Indicates the correct answer at the time of the survey (June 25, 2018–September 7, 2018). Starting in July 2019, Wisconsin Medicaid does not have sobriety restrictions or retreatment restrictions.

Percentages are of the 600 physicians surveyed.

The missing category includes respondents who did not respond to the question.

As a result of rounding, percentages may not sum to exactly 100%.

Physicians were asked if Wisconsin Medicaid had provider specialty restrictions (so that only gastroenterologists or infectious disease specialists can prescribe treatment), sobriety restrictions (so that patients must be abstinent from drugs or alcohol for at least 6 months), liver disease severity restrictions (so that only patients with documented fibrosis or cirrhosis are eligible), and retreatment restrictions (so Medicaid will only cover 1 treatment course per patient).

Consideration of Persons Who Inject Drugs

Among the 579 (97%) physicians who reported seeing patients who inject drugs in their practice, 59% (n = 341) reported they would encourage patients who inject drugs and have HCV to receive HCV treatment. However, only 3% (n=15) reported they would treat the patient themselves, and most (92%, n = 532) reported they would refer the patient for treatment. Few (3%; n=19) reported they would tell the patient to return for treatment when the patient is no longer using drugs (Table 2).

Knowledge Gaps

Physicians were asked which training topics would help improve their knowledge of HCV. Most (73%) reported that training regarding HCV treatment would help improve their knowledge (Table 2). Approximately one-third of physicians reported interest in each of the following training topics: HCV prevention, risk factors, and disease progression. Only 12% (n = 69) reported that they "already know a lot" about HCV and do not need additional training (Table 2).

Comparison of Rural and Urban Physicians

Experience with HCV treatment was minimal among physicians practicing in both rural and urban areas of Wisconsin, but physicians practicing in rural areas were more likely to report prescribing treatment (independently or in consultation with a specialist) than those practicing in urban areas (9% rural, 5% urban; $P < 0.05$) (Table 3). Only 7% of physicians practicing in rural areas and 6% of physicians practicing in urban areas reported having "a great deal" of knowledge about HCV treatment (Table 3). Similarly low percentages of physicians in rural (14%) and urban (16%) areas were aware that nonspecialists could now prescribe HCV treatment paid for by Medicaid. Physicians practicing in rural areas reported less often that they would tell a patient to return for HCV treatment when they are no longer using drugs (1% rural vs 5% urban; $P < 0.05$) (Table 3). Physicians practicing

Table 3. Comparison of Physician Knowledge and Experience by Whether the Physician Reported Practicing in a Rural or Urban Area

	Rural No. (%)	Urban No. (%)
Total	**241 (100)**	**327 (100)**
Hepatitis C Treatment: Experience and Knowledge		
Do you prescribe treatment for hepatitis C?		
Yes or Yes, but only in consultation with a specialist[a]	22 (9)	16 (5)
How much do you feel you know about current treatment guidelines for hepatitis C?		
A great deal	16 (7)	20 (6)
Consideration of Hepatitis C Among Patients Who Inject Drugs		
If you have a patient who injects drugs with hepatitis C, would you ...? (select all that apply[b])[c]		
Encourage the patient to get treated	147 (64)	186 (59)
Treat the patient yourself	8 (3)	6 (2)
Make a referral to another provider for treatment	218 (94)	295 (93)
Tell the patient to return for treatment when he/she is no longer using/injecting drugs[a]	3 (1)	15 (5)
Knowledge Gaps		
Which of the following training topics would help you improve your knowledge of hepatitis C? (select all that apply[b])		
Treatment of hepatitis C[a]	193 (80)	231 (71)
Prevention of hepatitis C[a]	96 (40)	102 (31)
Risk factors for contracting and transmitting hepatitis C	90 (37)	104 (32)
Liver disease, cirrhosis, and liver transplantation	81 (34)	104 (32)
I already know a lot about hepatitis C and do not need any more training	23 (10)	43 (13)
Knowing about hepatitis C is not very important to my job and I do not need training	6 (2)	12 (4)

[a]$P<0.05$.

[b]For questions where respondents were asked to "select all that apply," for each response, the percentage that chose this response was calculated using the total number of respondents as the denominator.

[c]Among 231 rural and 316 urban physicians who reported having patients who inject drugs.

in rural areas reported more often that training in HCV treatment (80% rural vs 71% urban; $P=0.01$) and prevention (40% rural vs 31%; $P<0.05$) would help improve their knowledge of HCV (Table 3).

Characteristics of Physicians Already Prescribing HCV Treatment

Overall, 39 physicians reported prescribing HCV treatment independently or in consultation with a specialist, and 546 physicians reported not prescribing HCV treatment. In bivariate analyses, physician characteristics significantly associated with providing HCV treatment included practicing in an independent practice or Rural Health Clinic (vs practicing in an office-based practice affiliated with a hospital or health system), practicing in a rural ZIP code (vs an urban ZIP code), and having a higher percentage of Medicaid-insured patients (Table 4). In addition, compared to physicians aged 60 years and older, younger physicians reported prescribing HCV treatment less often (Table 4).

In multivariable analysis, compared to practicing in a hospital or health system-affiliated practice, practicing in a Rural Health Clinic (odds ratio [OR] 5.37; 95% CI, 1.53-18.87) or an independent practice (OR 2.55; 95% CI, 1.01-6.42) was significantly associated with prescribing HCV treatment. Compared to the physicians age 60 years and older, physicians age 30-39 reported prescribing HCV treatment less often (OR 0.24; 95% CI, 0.07-0.83). Compared to physicians with <30% of patients insured by Medicaid, having ≥30% of patients covered by Medicaid was significantly associated with prescribing HCV treatment (OR 3.23; 95% CI, 1.38-7.56) (Table 4).

DISCUSSION

The results of this survey highlight the significant knowledge gap among family medicine physicians in Wisconsin regarding HCV treatment and Wisconsin Medicaid policy allowing for the delivery of HCV treatment in primary care settings. Only 7% of the respondents reported they had prescribed HCV treatment either independently or in consultation with a specialist, and most (86%) were not aware that family medicine physicians can now prescribe HCV treatment covered by Wisconsin Medicaid. This lack of experience with and knowledge of HCV treatment was similar among physicians in both rural and urban areas of Wisconsin. These findings suggest the need for additional training, clinical support, and incentivization of primary care providers to deliver HCV treatment. Engagement of family medicine physicians and other primary care providers—particularly in rural areas where there are few specialists[17-18]—will be critical to achieving HCV elimination throughout Wisconsin.

Coordinated efforts are needed to train primary care providers to treat HCV. In this survey, younger physicians reported prescribing HCV treatment less often. In addition, almost three-quarters of all physicians (and 80% of physicians practicing in rural areas) reported they would benefit from training about HCV treatment. Incorporating HCV treatment training into family medicine and other primary care training programs could equip new physicians with the knowledge and experience to treat HCV. For primary care providers already in practice, telementoring (eg, Project ECHO) is a demonstrated method for improving HCV treatment knowledge and practice among primary care providers and for increasing treatment access in rural areas.[10-12] Other specific knowledge gaps identified through this survey, including lack of knowledge about state Medicaid policy related to HCV treatment, also could be addressed through utilization of telementoring.

In addition to identifying important knowledge gaps among family medicine physicians in Wisconsin, the findings of this survey also suggest there may be institutional barriers limiting family medicine physicians from providing HCV treatment. For example, in this survey, physicians practicing in offices affiliated with a hospital or health system were less likely to report prescrib-

Table 4. Physician and Practice Characteristics Associated With Providing Hepatitis C Virus Treatment

	Physician Reported Prescribing HCV Treatment Independently or in Consultation With a Specialist				
	No (n=546)	Yes (n=39)	Percentage Yes	Odds Ratio and 95% CI of Prescribing HCV Treatment	
Characteristics	**No. (%)**	**No. (%)**	**% (n/N)**	**Unadjusted**	**Adjusted**
Age					
30-39	126 (23)	5 (14)	4% (5/131)	0.34 (0.12-0.94)	0.24 (0.07-0.83)
40-49	124 (23)	11 (30)	8% (11/135)	0.75 (0.34-1.67)	0.57 (0.21-1.56)
50-59	145 (27)	4 (11)	3% (4/149)	0.23 (0.08-0.71)	0.33 (0.10-1.08)
60+	144 (27)	17 (46)	11% (17/161)	ref	ref
Sex					
Male	318 (59)	23 (59)	7% (23/341)	ref	
Female	222 (41)	16 (41)	7% (16/238)	1.00 (0.52-1.93)	
Race/ethnicity					
White or Caucasian	464 (87)	32 (84)	6% (32/496)	ref	
Asian or Pacific Islander	36 (7)	2 (5)	5% (2/38)	0.81 (0.19-3.50)	
Latino or Hispanic	15 (3)	1 (3)	6% (1/16)	0.97 (0.12-7.55)	
Black or African American	6 (1)	1 (3)	14% (1/7)	2.42 (0.28-20.69)	
Native American	2 (0)	1 (3)	33% (1/3)	7.25 (0.64-82.11)	
Other	12 (2)	1 (3)	8% (1/13)	1.21 (0.15-9.59)	
No. of years in practice after residency					
0-5 years	86 (16)	6 (16)	7% (6/92)	0.86 (0.34-2.22)	
6-10 years	62 (12)	1 (3)	2% (1/63)	0.20 (0.03-1.51)	
11-15 years	53 (10)	5 (14)	9% (5/58)	1.17 (0.42-3.24)	
16-20 years	87 (16)	5 (14)	5% (5/92)	0.71 (0.26-1.95)	
More than 20 years	247 (46)	20 (54)	7% (20/267)	ref	
Practice type					
Hospital/health system affiliated office-based practice	328 (63)	16 (50)	5% (16/344)	ref	ref
Independent office-based practice	83 (16)	10 (31)	11% (10/93)	2.47 (1.08-5.64)	2.55 (1.01-6.42)
Rural health clinic	22 (4)	5 (16)	19% (5/27)	4.66 (1.56-13.9)	5.37 (1.53-18.87)
Urgent care center	32 (6)	1 (3)	3% (1/33)	0.64 (0.08-4.99)	0.6 (0.07-4.98)
Federally Qualified Health Center/community health center	25 (5)	0 (0)	0% (0/25)		
Emergency department	17 (3)	0 (0)	0% (0/17)		
Hospital inpatient	11 (2)	0 (0)	0% (0/11)		
Practice location, by ZIP code					
Rural	218 (41)	22 (58)	9% (22/240)	1.95 (1.00-3.80)	1.23 (0.51-2.98)
Urban	309 (59)	16 (42)	5% (16/325)	ref	ref
No. of adolescent/adult patients cared for in past year					
<1000	123 (25)	8 (24)	6% (8/131)	0.61 (0.24-1.57)	
1000-1999	158 (32)	9 (26)	5% (9/167)	0.53 (0.21-1.33)	
2000-2999	113 (23)	6 (18)	5% (6/119)	0.50 (0.18-1.39)	
≥3000	103 (21)	11 (32)	10% (11/114)	ref	
% Patients covered through Medicaid					
<30%	292 (58)	11 (34)	4% (11/303)	ref	ref
≥30%	213 (42)	21 (66)	9% (21/234)	2.62 (1.24-5.54)	3.23 (1.38-7.56)
Compared to the epidemic of opioid misuse and opioid overdose across Wisconsin, how serious of a problem is opioid misuse in the community where you practice?					
As much or more of a problem	480 (88)	37 (95)	7% (37/517)	2.43 (0.57-10.32)	
Not a problem at all in my community/less of a problem	63 (12)	2 (5)	3% (2/65)	ref	

Abbreviations: HCV, hepatitis C virus; ref, reference.

Data for physicians with unknown or missing responses are not included in Table 4. In the first 2 columns, percentages were calculated excluding physicians with unknown or missing responses and, as a result of rounding, percentages may not sum to exactly 100%.

ing HCV treatment than physicians practicing in an independent practice or Rural Health Clinic. Little has been documented in the peer-reviewed literature about the barriers to accessing HCV treatment within health systems. It is possible some health systems have restrictions, including that treatment be provided by a specialist. Alternatively, it is possible that physicians working in health systems have easier access to specialists or are more familiar with the specialists in their system and, therefore, are more likely to refer than to prescribe treatment themselves. Additional research is needed to understand what barriers—institutional or otherwise—might be contributing to family medicine physicians in health systems not prescribing HCV treatment.

Barriers to prescribing and receiving HCV treatment covered by state Medicaid programs are well-documented, and many states, including Wisconsin, have removed restrictions in recent years.[15] At the time of this survey, Wisconsin Medicaid allowed nonspe-

cialists to prescribe HCV treatment but still restricted access based on patient sobriety. In this survey, physicians who reported higher percentages of patients covered by Medicaid were more likely to report prescribing HCV treatment. This could be because physicians in these settings have more patients with HCV (national results indicate Medicaid-insured patients have a higher prevalence of HCV than commercially insured patients[23]) and have recognized a need among their patient population. Alternatively, having higher percentages of patients with commercial insurance might be a barrier to prescribing treatment. Little is documented in the peer-reviewed literature about barriers to accessing HCV treatment through commercial insurance. However, one study of HCV treatment prescriptions submitted to a national pharmacy found that more than half of persons insured by commercial plans had their HCV treatment medication claims denied.[24] In addition to removing all barriers to receiving HCV treatment within Medicaid programs—as Wisconsin Medicaid has now done—efforts must be undertaken to identify and remove barriers to HCV treatment among commercial insurance plans.

This study has several limitations. Because the survey focused on HCV and opioid use disorder, physicians who chose to respond might have more interest, knowledge, or experience with HCV treatment than nonrespondents. Nevertheless, few respondents reported HCV treatment knowledge or experience. This study included only family medicine physicians. Future studies should explore whether similar trends are found among primary care providers of different specialties (eg, internal medicine) and disciplines (advance practice nurses and physician assistants). We did not assess barriers to providing HCV treatment that may be specific to employer type (health system vs independent practice) or commercial insurance plans. We also did not explore facilitators or incentives that may support or encourage physicians who already prescribe HCV treatment. Future studies should evaluate the extent to which employers and insurers can encourage primary care providers to prescribe HCV treatment, including but not limited to educational opportunities, clinical staff support in treatment delivery, mentorship programs, alleviation of insurance administrative barriers such as prior authorizations, and financial incentive programs.

CONCLUSION

Our study highlights the need to engage more Wisconsin family medicine physicians in efforts to eliminate HCV. Primary care providers should be encouraged and supported in providing HCV treatment, and coordinated efforts are needed to train and mentor these providers to prescribe HCV treatment. Further research is needed to better understand both the barriers and facilitators to delivering HCV treatment in primary care settings. Health insurers and health systems have important roles to play in examining existing policies that may promote or limit access to HCV treatment. Given the increasing rates of HCV infection and the highly effective, simplified HCV treatment regimens, now is an opportune time to expand access to HCV treatment through primary care.

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Hepatitis B Screening and Awareness in the Milwaukee Hmong Community

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ABSTRACT

Introduction: Hepatitis B virus (HBV) infection disproportionately affects the Hmong ethnic group, with reported US prevalence rates up to 20%, but data for Wisconsin's large Hmong community are lacking. We assessed the prevalence of HBV at Hmong screening events and whether small-group counseling affects HBV knowledge.

Methods: Free HBV screening events were held in Milwaukee, Wisconsin at a Hmong market, a local church, and annual Hmong New Year festival. Eligible Hmong subjects age 18 years and older also were invited to complete a 15-point survey on HBV knowledge at baseline and after education sessions. Hmong interpreters were available, and free HBV screening was offered.

Results: A total of 187 participants were tested for HBV, and 161 completed surveys. After education sessions, the mean knowledge score rose to 10.6 (71%) vs the pre-education score of 6.7 (45%) ($P<0.0001$). Active HBV [HBsAg(+) HBsAb(-)] was diagnosed in 18 participants (9.6%), 53 (28.3%) were susceptible [HBsAg(-) and HBsAb(-)], 5 (3.4%) were in the gray zone [HBsAg(-) with low/inadequate HBsAb(+) titer], and the remaining 110 (58.8%) were immune [HBsAg(-)/HBsAb(+)]. Of the 18 individuals with active HBV, 13 were male and 5 were female [age range 24-66].

Conclusion: Despite evidence that small-group education with visual aids is effective in enhancing HBV knowledge in the Hmong population, a significant knowledge gap remained on post-education scores, suggesting that better tools or repeated interventions may be warranted. While we acknowledge that this convenience sampling may have introduced biases, the rate of active HBV infection in Wisconsin is much higher than general US population reports, and a quarter of those tested were found to be susceptible to HBV.

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INTRODUCTION

Although the overall prevalence of hepatitis B virus (HBV) infection in the United States has decreased since the implementation of vaccination programs in the 1980s, Asian Americans still have disproportionately high infection rates. Not only are up to 1 in 10 Asian Americans infected with hepatitis B, they are also 5.5 times more likely to develop chronic hepatitis B infection compared to non-Hispanic Whites[1] and have the highest rate of liver cancer deaths.[2,3] Furthermore, foreign-born Americans from endemic countries, including most Asian countries, account for approximately 95% of new US cases.[4]

Among Asian ethnic groups, the Hmong have the highest prevalence of HBV, with rates as high as 1 in 5 individuals in California and Minnesota— almost double the rate of other Asian groups.[5-7] Additionally, the Hmong experience the lowest survival rates due to liver cancer and tend to present at later stages of disease.[8] Most Hmong acquire the infection through vertical transmission or household transmission in the perinatal period, which confers a higher likelihood of chronic, often asymptomatic, disease.[9-12]

Hepatitis B may be identified through serologic testing, permitting early management, which may prevent liver damage and improve survival.[13] Testing can also identify susceptible individuals (eg, unvaccinated) at risk of contracting the virus, providing an opportunity for intervention to protect those individuals and potentially reduce the risk of future transmission.

Wisconsin has the third-largest Hmong population in the

nation, with almost 14,000 Hmong residents in Milwaukee County alone. However, the prevalence of HBV infection in the Hmong population, measured through community screenings in Milwaukee or Wisconsin, has not been documented previously.[14,15] Additionally, efforts in HBV education have been lacking. We set out to provide free HBV education and screening events in the Hmong community. In the process, we also aimed to assess the prevalence of HBV infection in this convenience sample of the Milwaukee-area Hmong community and determine whether small-group education sessions during these events would increase awareness and knowledge of HBV.

Table 1. Serological Interpretations of Hepatitis B Lab Tests

Hepatitis B Surface Antigen (HBsAg)	Hepatitis B Surface Antibody (HBsAb)	Hepatitis B Status
Negative	Positive	Immune
Negative	Weakly positive[a]	Gray zone
Negative	Negative	Susceptible
Positive	Negative	Positive

[a] Per LabCorp testing guidelines, any antibody value that was positive on the qualitative assay but had a titer of < 10 mIU/mL likely indicating susceptibility to infection.

METHODS

Subject Eligibility

All adults 18 years and older who identified as Hmong were eligible for the study. Subjects were recruited during the education and screening events. All subjects provided informed consent prior to enrollment. The Medical College of Wisconsin (MCW) and Froedtert Hospital Institutional Review Board (Milwaukee, Wis) approved the study protocol.

Study Design and Site

A 1-group pre- and posttest research design was used to evaluate participants' knowledge, attitude, and behavior. Participants were given a 15-point questionnaire to complete before and after intervention with HBV education sessions (see Appendix). For those who opted for screening, a cross-sectional sample was used to determine the prevalence of HBV.

Through collaboration with and feedback from local Hmong community centers and organizations, we established culturally appropriate methods of material development and education. Subjects attended 1 of 5 free education and screening events between March 2013 and December 2015. Events were held at a highly frequented Hmong market, a Hmong community church, and the annual Hmong New Year festival. Events were all scheduled on a weekend date during the late morning to afternoon based on the high level of community traffic at these locations during these times. A $10 market gift certificate was given during the first community event to all who completed the screening. The purpose of this incentive was to increase interest and participation in the event, as this was the first screening event of its kind. Blood testing and education sessions were available at all events, but not all of those who had their blood tested participated in the education sessions or completed the pre- and post-education knowledge surveys. Similarly, not all of those who completed the surveys had their blood tested for hepatitis B.

Education Session

The HBV education session consisted of a 10- to 20-minute standardized small-group (2-4 subjects) or one-on-one discussion with a physician or trained medical student. All such sessions were included in the analysis of education results. Sessions covered hepatitis B and its prevalence, transmission routes, natural history, prevention strategies, and treatment options. Sessions were offered in both English and Hmong, with the assistance of a trained Hmong interpreter. Flow charts, illustrations, and diagrams available in both Hmong and English supplemented discussions, and participants could ask questions throughout. Educational pamphlets from the Asian Liver Center (Stanford, CA) were available for participants to take home. All forms and documents were provided in both English and Hmong. After the education session, interested participants gave consent and underwent serological testing for HBV.

Data Collection and Reporting

During the event, participants filled out registration forms that included information on demographics and medical history, followed by a survey on HBV knowledge (Appendix) both before (pre-education) and immediately after (post-education) the education session. The survey was developed by study investigators and reviewed by MCW hepatologists and Hmong community members. Hmong interpreters assisted subjects in completing the surveys, which were available in both languages. Both surveys consisted of 15 questions in "yes/no/I don't know" or multiple-choice formats. For each survey, the total number of correct answers was scored to evaluate overall knowledge about HBV, as well as knowledge of its prevalence, transmission, prevention, and natural history. One point was given for each correct answer; no points were given if individuals marked "unsure," more than 2 answers, or no answers.

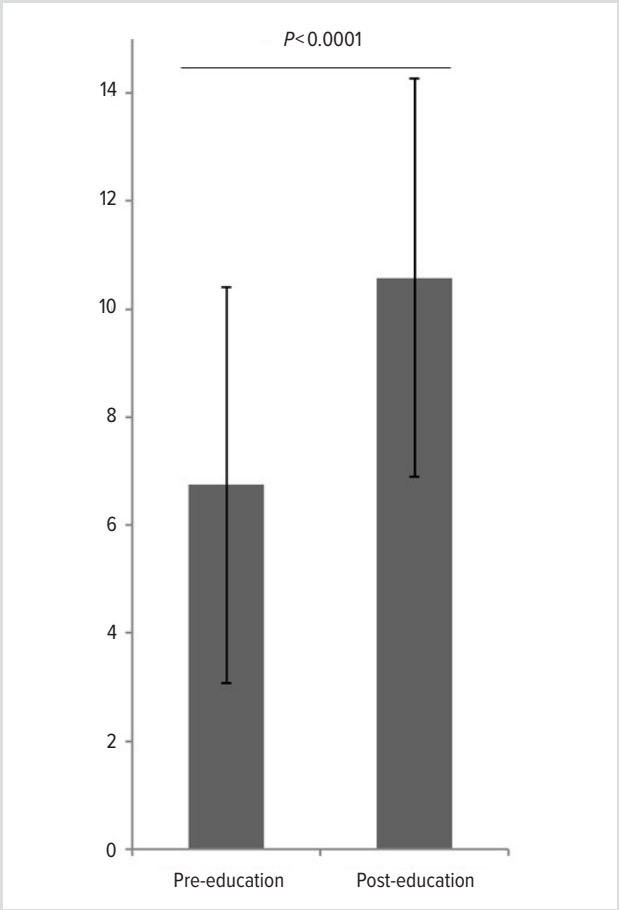
If participants opted for a screening test, blood samples were collected after the education session. Samples were coded and centrifuged on-site. Serum was tested for both hepatitis B surface antigen screen and qualitative hepatitis B surface antibody through LabCorp (Chicago, Illinois), which uses an immunochemiluminometric assay (ICMA) for both tests. Due to funding limitations, more detailed serologic testing (eg, Hepatitis B core antibody, hepatitis B e antigen, or hepatitis B e antibody) was not performed. Serological test results were divided into 4 categories as outlined in Table 1. Screening subjects were contacted with

Table 2. Demographic Characteristics of Screening Participants

Variable	Positive % (n = 18)	Susceptible % (n = 53)	Immune % (n = 110)
Sex: male	72	44.2	35.5
Age [a]	54.2 ± 10.7	42.2 ± 16.3	47.5 ± 15
18-24	5.6	17.3	7.3
25-34	0	21.2	15.6
35-44	16.7	19.2	14.7
45-54	27.8	13.5	25.7
55-64	50	21.2	24.8
65+	0	7.7	11.9
Birth country			
Laos	83.3	55.8	76.4
Thailand	5.5	17.3	9.1
United States	0	21.2	10
Unanswered	11.1	5.8	4.5
No. of years in US [a,b]	26.8 ± 7.8	25 ± 11.4	27 ± 8.5
No. of persons in household [a]	6.9 ± 4.1	5.6 ± 2.8	5.5 ± 2.5
Have health insurance	64.7	59.6	68.2
Have primary care provider	47.1	55.8	70.9
Family member with hepatitis B	17.6	11.6	10

[a] Mean ± standard deviation used for age, number of years in US, and number of persons in household.
[b] If born outside of the US.

Figure. Pre- and Post-Education Survey Scores; Number Correct



results by telephone, or confidential result letters were sent out 2 to 3 weeks following the event. Study investigators contacted all individuals with test results in the positive, susceptible, or "gray zone" categories and provided information regarding the need for physician follow-up, additional testing, and/or vaccinations; they also asked if additional assistance with insurance or ascertaining a physician was needed. Those who required vaccinations or follow-up care were sent a list of Hmong providers and free clinics in the area, along with a vaccination card to keep track of their immunizations. Investigators continued to call patients at 1-month intervals for up to 6 months after the event to assess progress on follow-up care or if contact could not be established.

Statistical Analysis

Baseline characteristics of subjects were summarized using mean ± standard deviation, median (range), and frequencies. To assess the change in overall knowledge of HBV before and after intervention, the exact Wilcoxon sign-rank test was performed on the total 15-point pre- and post-education survey scores. The same test also was performed to assess knowledge within 4 specific categories: prevalence, transmission, prevention, and natural history. Since the same subjects completed the survey before and after the education, pre- and post-education data were paired, and the McNemar test was performed to assess the intervention's effect by each question.

Univariate analysis using *t* test and analysis of variance was performed to evaluate factors associated with pre-education knowledge scores and change in knowledge score following education. Multivariate regression modeling was used to evaluate factors independently associated with pre-education score and change in knowledge score following education. A P value < 0.05 was considered statistically significant. All analysis was performed using STATA version 8.0 (STATA Corp, College Station, Texas).

Descriptive statistics were calculated and reported for demographic variables; 95% confidence intervals were calculated for each variable.

RESULTS

Demographic information is displayed in Table 2. The majority of participants were not born in the United States but had been living in the US for over 2 decades. A total of 187 individuals were tested for HBV and 161 completed knowledge surveys. As noted previously, those having their blood tested were not required to participate in the education sessions or to complete the surveys. Similarly, those who participated in the education sessions and/or completed the surveys were offered to have their blood tested but were not required to do so. Thus, while there was likely overlap between the groups, we did not track which individuals specifically had blood tested and which completed the surveys.

Survey Results

One hundred sixty-one participants completed both the pre- and post-education surveys. As shown in the Figure, there was a statistically significant rise in the knowledge score after the education session ($P < 0.0001$). Out of a maximum of 15 points, the mean pre-education score was 6.74 (45% correct; SD 3.67) and the mean post-education score was 10.6 (71% correct; SD 3.69). Nevertheless, despite the educational session intervention immediately prior to administration of the posttest, there remained a substantial knowledge gap since, on average, subjects answered 4 to 5 questions incorrectly on the posttest. No significant trends were identified when analyzing prevalence, transmission, prevention, and natural history.

Serologies and Prevalence

Of the 187 participants, active HBV infection [HBsAg(+) and HBsAb(-)] was identified in 18 (9.6%); 53 (28.3%) were susceptible to infection [HBsAg(-) and HBsAb(-)]; 6 (3.2%) were designated as gray zone—defined as HBsAg(-) in conjunction with low HBsAb(+) titer—which was inadequate to confirm protection. The gray zone group may indicate individuals who are (1) susceptible without prior immunization, (2) previously vaccinated, now with waned HBsAb titers, or (3) previously infected and cleared of the virus but also with waned HBsAb titers. In the absence HBcore Ab (HBcAb) testing, we could not distinguish whether any fit in to this third category.

The remaining 110 patients (58.8%) were found to be immune to HBV infection and likely vaccinated [HBsAg(-) and HBsAb (+)], although without HBcAb testing we could not distinguish whether any in this group represented those with prior infection who had cleared the virus and achieved immunity.

Of those who tested positive (N=18), the majority were men (13 vs 5 women), and less than half (47%) had a primary care provider (See Table 2). Those with HBV infection appeared to be more likely to be born outside the United States (none reported the US as their country of birth, but not all reported country of birth). Those who tested positive also seemed more likely to have a family member with HBV (17.6% [$P < .05$] vs 11.6% of those susceptible, and 10% who were immune [$P < .05$]) but did not appear to have a lesser rate of health insurance or a statistically significantly higher number of members in their household.

Follow-Up

Only 44.4% of patients with active HBV infection completed or scheduled an appointment with a physician at the 1.5-month follow-up point. Others indicated they planned to make an appointment in the immediate future, had health insurance but indicated a lack of a primary care provider as their reason not to follow up, or were lost to follow-up due to our inability to contact them. At the 1.5-month follow-up point, 12.2% of the susceptible population had started their hepatitis B vaccination series.

DISCUSSION

As part of free community HBV screening events, we set out to determine the prevalence of HBV infection in the Milwaukee Hmong community and assess whether small-group education would increase awareness and knowledge of HBV infection. Our project was the first to offer free education and screening for hepatitis B in the Milwaukee Hmong community. Over the course of 4 years, we conducted 5 screening events and screened a total of 187 participants. In total, 18 (9.6%) tested positive for HBV infection. These results suggest that the Hmong HBV infection rate is similar to Asian Americans as a whole (10%), though not quite at a prevalence of 1 in 5 as reported in previous studies done with Hmong Americans.[5,7] It is possible that some of the difference may be due to prior studies being conducted through chart review of clinic records, which targets a different population than that which may attend a free screening event.

Moreover, 53 participants (28.3%) tested as "susceptible," meaning they likely never received the vaccination series and are still at risk for acquiring the infection. It is true that hepatitis B surface antibody titers may wane over time after immunization, so this group may include some of those cases but would likely benefit from a booster immunization in any case. We feel strongly that identification of this large group of susceptible individuals in a community with a high rate of HBV infection presents a great opportunity for intervention by encouraging these at-risk individuals to receive vaccination.

We were not able to ascertain Wisconsin HBV susceptibility or prevalence data for the general population or subgroups. The 2013 Wisconsin Hepatitis B Surveillance Summary provided by the Wisconsin Department of Health Services does provide the cases reported to the state.[16] These numbers are not true "incident" or "prevalent" cases. Of the 354 total cases reported in 2013, only 7 were acute ("incident") and 347 were nonacute; this latter group likely reflects chronic cases that were not identified previously.

While there is no specific ethnicity breakdown of the 2013 reported cases for the Hmong, those of Asian/Pacific Islander background comprised 46 % (n = 162) of the cases, whereas those categorized as White (19%, n = 68) and Black/African American (15%, n = 54) are proportionately less represented. According to the 2010 US Census, there were 49,240 Hmong persons living in Wisconsin, making up ~0.9% of the state's population.[17] Since it is estimated that 38% of Asians in Wisconsin are Hmong, it is likely that a large number of the reported 2013 HBV cases are Hmong.[18] In conjunction with our findings, these data reinforce the concept of focusing screening and vaccination efforts on this population. These measures would identify those infected who may require active treatment to prevent complications and would also identify those who are susceptible for vaccination, since they are potentially at higher risk of household transmission. Such efforts also would protect the community at large from wider spread of HBV.

Screening participants also filled out 15-question surveys before and after they received a small-group education session. The Figure illustrates the significant improvement in average survey scores—from 6.7 to 10.6—among participants after the education. The data suggest that small-group education was an effective means of increasing HBV knowledge within our sample population. The survey results did suggest an initial knowledge gap that needs to be addressed. Whether this type of intervention resulted in a sustained improvement in knowledge is not evident in this study. We contemplated administering a longer term follow-up survey to assess sustainability of the increase in knowledge, but due to limited resources, concerns about biases introduced by self-selection of those more willing to participate in longer term follow-up, and concern that some would be deterred from participating due to the longer-term commitment, we did not do a longer-term follow-up survey.

Follow-up for test results was, in fact, one of the more challenging aspects of our project. Difficulties included subjects lost to follow-up, patient noncompliance with recommendations, and barriers to access health care, including lack of insurance, lack of a physician, and cultural/language barriers. The initial goal of the project was to ensure that for those who test positive or susceptible for HBV, at least 60% successfully complete an appointment with a physician or complete a vaccination series. Unfortunately, less than half (44.4%) of the patients with active HBV infection completed or scheduled an appointment with a physician at the 1.5-month follow-up point. Lack of a primary care provider seemed to be a major reason for lack of follow-up for the entire cohort, including those susceptible individuals who had not yet started their vaccination series.

As of 2014, the largest Hmong populations in Wisconsin were in Green Bay, La Crosse, Milwaukee, Sheboygan, and Wausau.[19] It is unclear how many of the people who came to the screening events were from the Milwaukee area or commuted from other cities with large Hmong populations. As the project continues to this day with involvement by new groups of MCW medical students, we hope to better identify barriers and perhaps extend our project to other Wisconsin cities with large Hmong populations.

Our study was limited by the fact that it was comprised of a convenience sample of those coming to these events, thus we cannot be certain that the group undergoing screening is reflective of the Milwaukee or Wisconsin Hmong community in general. It is certainly possible that this group was either more educated than others or more connected to services within the community and, therefore, more apt to participate in these events. In addition, the funding limitations of this study precluded us from completing full serologic evaluation, including HBcAb testing or hepatitis B viral DNA assessment. This deficiency prevented us from fully characterizing the status of the "gray zone" subjects. In addition, it also may have underestimated those with evidence of prior infection, since some HBsAg (-) /HBsAb (+) may not have been vaccinated but rather developed natural immunity after a resolved infection. Identifying those with resolved infection may be helpful in targeting family members who should definitely be tested for HBV. As discussed previously, we may also have overestimated the subjects who were unvaccinated, since hepatitis B surface antibody titers are known to wane—particularly in those who may not be fully immunocompetent. If able to procure more funding in the future, we intend to perform more detailed serologic evaluation with reflex HBV testing when HBsAg positive status is detected. We also intend to develop better measures to ascertain follow-up of screened subjects and, if feasible, administer longer interval follow-up surveys.

The absence of any reported US-born subjects with active HBV infection may provide an opportunity to better focus limited screening resources. In addition, the low overall rate of health insurance and a lower likelihood of affiliation with a primary care provider for those with HBV infection also provide potential opportunities for impactful interventions.

CONCLUSION

Overall, our results show that hepatitis B infection remains a prominent health issue in the Milwaukee and likely Wisconsin Hmong community, and additional outreach and screening events are needed to help identify at-risk members of this population. Particularly because many HBV patients—especially immigrants and minorities—often do not receive the recommended levels of care, there is a critical need for developing culturally appropriate and effective strategies that can be incorporated into existing clinical practice.

Public health services are needed to enhance HBV surveillance in the Milwaukee Hmong community, formulate strategies for effective vaccination and post-exposure prophylaxis, and to provide better access and linkage to care. We believe implementation of such measures will diminish the disease burden and the expected sequelae of untreated HBV, including cirrhosis and its myriad complications such as decompensated liver disease (ascites, portosystemic encephalopathy and variceal bleeding) and hepatocellular carcinoma—all of which are associated with a higher mortality rate.

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Cancer Mortality and Research Outcomes in a Rural State

Mark R. Williamson, PhD; Rashid M. Ahmed, PhD

ABSTRACT

Background: North Dakota is a rural state with high rates of cancer. Determining how various demographic, geographic, and funding factors contributed to cancer incidence on a state and county level helps improve cancer prevention and control.

Objectives: We examined cancer incidence rate trends by demographic (sex and ethnicity) and geographic (county, population, rural/frontier status) factors. We also examined cancer funding and research output by year.

Methods: Cancer incidence rates were obtained from the North Dakota Cancer Statewide Registry and stratified by sex, ethnicity, and county. US cancer rates also were obtained for comparison. Generalized linear models were used to compare overall incidence rates and yearly trends.

Results: Male melanoma incidence rates increased faster than the US average across year ($P = 0.020$). Incidence rates for prostate, lung, and colorectal cancer among American Indians/Alaska Natives (AI/AN) decreased faster than Whites across year ($P < 0.001$, $P = 0.001$, $P < 0.001$, respectively). Four counties—2 for breast cancer and 2 for prostate cancer—had differential trends compared to the North Dakota average across year ($P = 0.011$, $P = 0.029$; $P = 0.046$, $P = 0.042$). County-level lung cancer incidence rates were positively correlated with county population size, while rates for cervix/uteri were negatively correlated ($P = 0.001$, $P = 0.023$). Funding from the National Institutes of Health for North Dakota increased across year along with cancer papers published increased ($P < 0.001$, $P < 0.001$).

Conclusions: Examining state and county data revealed several surprising trends and the need for a more fine-scale approach to cancer cause, control, and prevention.

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INTRODUCTION

Cancer remains a difficult disease to treat and a major source of mortality despite a decades-long nationwide decrease in incidence.[1] Using a rural state as a natural laboratory, we examined incidence rates for top cancers by sex, ethnicity, county, and population size. We also examined funding level by year to understand resource impact.

North Dakota and Cancer

North Dakota is a rural state with a small population (760,777) and has been called a natural laboratory due to high cancer incidence rates and high county-level variation.[2] Demographically, Whites are the ethnic majority (85%), with American Indian/Alaskan Natives (5.4%) as the only other ethnic group with a population size big enough for analysis. Lung cancer incidence is declining,[3] although rates are higher for American Indian/Alaskan Natives (AI/AN) versus non-Hispanic Whites.[4] Both the incidence and mortality of liver cancer in North Dakota are the lowest in the nation.[5,6]

Unfortunately, some North Dakota cancer rates are elevated. Despite dropping for 3 decades, oral cancer in the state has risen in recent years.[7] Prostate cancer mortality is high compared to the national average,[8] as is thyroid cancer;[2] and colorectal cancer incidence in North Dakota is one of the highest in the nation.[9]

Sex and Ethnicity

Incidence and mortality across specific cancer types differ by sex

and ethnicity, often significantly.[10] AI/ANs are an underserved population with higher rates of illness and mortality and lower access to health resources.[11] They are less likely than the general public to have preventive measures like screening for colorectal, prostate, and breast cancer.[12]

While total cancer incidence rates are lower in the AI/AN population than those for non-Hispanic Whites nationally, AI/ANs in the Northern Plains region (North Dakota, South Dakota, Nebraska, and Iowa) have higher cancer incidence rates[13] and the highest mortality rates of AI/ANs in any US region.[14] For specific cancer types, both male and female AI/ANs have notably higher colorectal cancer mortality rates.[15]

County and Rural Status

North Dakota has 53 counties and is the 19th-largest state with the 47th-highest population. The North Dakota Center for Rural Health classifies 6 counties as urban, 10 as semi-rural, and the majority—37—as rural. Rural populations are more vulnerable to health issues because of comorbidities such as cancer, heart disease, diabetes, hypertension, and obesity.[16,17] Rural areas also have older age structures.[18] These vulnerabilities, combined with reduced health care access, make rural areas potentially high areas of cancer incidence and mortality.[19]

Cancer Funding

Despite its high burden of cancer, North Dakota has low access to cancer research funding. Indeed, while the American Cancer Society currently supports 739 cancer research grants, North Dakota—along with Montana and South Dakota in the Great Plains Region—holds no current grants. Meanwhile, the North Dakota cancer care expenditure estimate for 2010 was $274.2 million, distributed among 8 cancer categories.[20] To address this issue, North Dakota became part of the Institutional Development Award (IDeA) Program, a National Institutes of Health (NIH) initiative to support states with low historical funding. In the last 4 reported years of NIH grants (2015-2018), North Dakota had 41 awards for general cancer. There were 5 grants towards 2 prostate projects, 4 grants for 2 colorectal projects, and 2 grants for 1 lung project. Since 1976, there have been 151 cancer-related journal articles reported by the 2 research universities—the University of North Dakota (UND) and North Dakota State University (NDSU).

Hypothesis

We hypothesized that incidence rates by sex and ethnicity would be significantly higher for prostate, colorectal, and thyroid cancers than the national average, but that all trends would be comparable. We also hypothesized that there would be county-level differences in cancer trends, rural counties would have higher cancer rates, and that cancer funding would be increasing by year to meet the demands of high cancer incidence rates.

METHODS

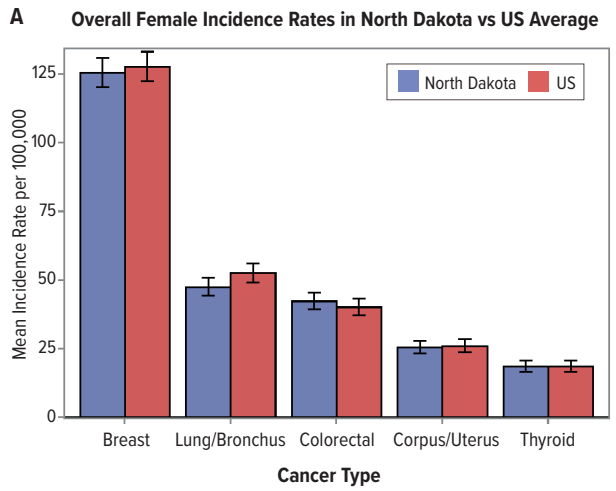
Data Collection

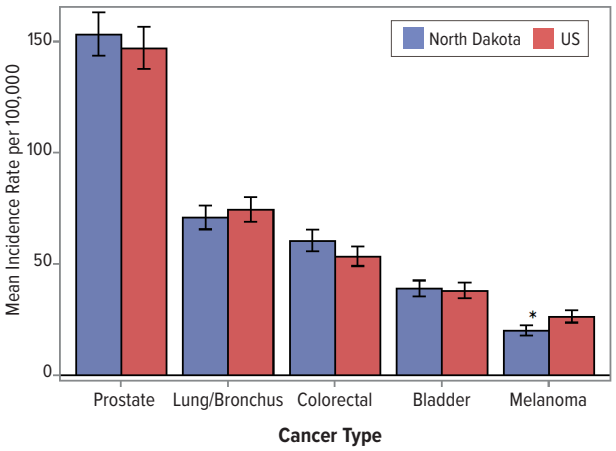
Cancer Rates: North Dakota cancer incidence rates, age-adjusted per 100,000, were obtained from the North Dakota Statewide Cancer Registry (ndcancer.org) by submitting a Type I data request. Institutional Review Board approval was not required because the data were deidentified and aggregated. Data were obtained for all available years (1997-2016) and included prostate, breast, lung, colorectal, bladder, melanoma of the skin, thyroid, and corpus/uterus cancers; non-Hodgkin's lymphoma; and leukemia. The top 5 cancers for males (prostate, lung, colorectal, bladder, melanoma) and females (breast, lung, colorectal, thyroid, corpus/uterus) were stratified by sex. Only incidence rates for colorectal, lung, prostate, and breast cancer had enough data to stratify by ethnicity (White, AI/AN). Overall county-level rates were available for most counties, but yearly rates were limited to all but a few counties, because counts lower than 10 in any category were unavailable as they were suppressed due to confidentiality policies. Similarly, county rates could not be separated by ethnic group or sex due to suppressed rates. To compare to the national average, US cancer incidence rates were obtained from 21 areas of the Surveillance, Epidemiology, and End Results (SEER) Program database.[21]

Geography: Each county was classified with a rural (rural, semi-urban, and urban) and frontier status (yes/no) using maps from the North Dakota Center for Rural Health (ruralhealth.und.edu). Urban counties were designated as having at least 1 city with a population of 50,000 or having close ties with an adjacent county with such a city. Semi-rural counties were designated as having at least 1 town or city with a population of 2,500 to 49,999, and rural counties as having no towns with a population greater than 2,500. Frontier counties were designated as having population densities of less than 7 persons per square mile. Population size by county was obtained from the US Census Bureau, based on 2010 estimates. They were natural log-transformed so that population size would approximate a Gaussian distribution clearer analysis and visualization.

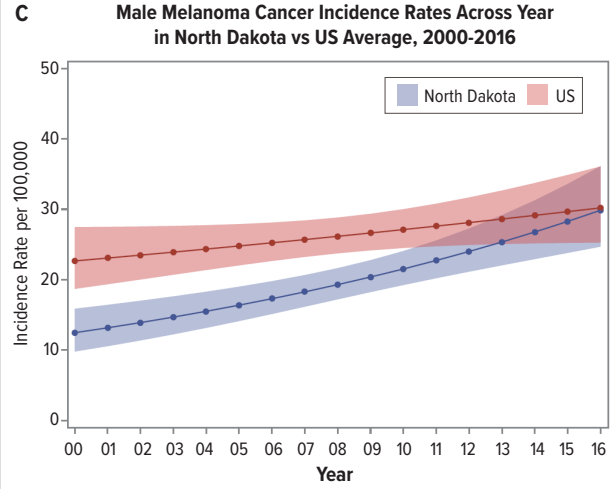
Cancer Funding: Funding information was obtained from 3 sources: NIH Portfolio Online Reporting Tool (RePORT), the UND Grants Office, and the North Dakota Office of Management and Budget. All 3 were searched for cancer-based projects for the available year ranges of 1985-2020, 1994-2020, and 2010-2019; and the resulting numbers of projects and funding amounts were aggregated by year for the same range as the cancer incidence rates (1997-2016). Finally, Scopus was searched by institution for each of North Dakota's 2 research universities (UND and NDSU) for 1997-2016 using the keyword "cancer." The number of cancer-related journal articles was aggregated by year.

Figure 1. Cancer Incidence Rates by Sex





*Asterisk indicates a significant difference. Values are model-adjusted mean incidence rates per 100,000 during 2000-2016.



Lines were generated from prediction mean values from a generalized linear model with a negative binomial distribution and bands are 95% confidence limits of the mean.

Statistical Analysis

Cancer incidence rates can be modeled as a count variable with a Poisson distribution.[22] However, because the Poisson distribution is a special case of the negative binomial distribution and tends to have a better fit statistic (chi-square/degrees of freedom [df]), all models used in this analysis utilized a negative binomial distribution unless optimization could not be completed. *F*- and *t* statistics were calculated using SAS Studio Software, V.3.8 (2018; Cary, North Carolina).

Sex: Cancer incidence rates by year and sex from both North Dakota and the US average were considered together. Region was designated as either North Dakota or US. Male and female cancer incidence rates were modeled as a function of cancer type, region, and their interaction with a generalized linear model. Then, the incidence rates for each sex's top 5 cancers were modeled as a function of the interaction between year and region. Male bladder cancer incidence rates were modeled using the Poisson distribution, as optimization could not be completed with a negative binomial distribution.

Ethnicity: Cancer incidence rates by year were compared across the 2 major ethnic groups in North Dakota—Whites and AI/ANs. Cancer incidence rates were modeled as a function of ethnicity, cancer type, and their interaction. Then, for each cancer type that had enough data points (prostate, breast, lung, colorectal), incidence rates were modeled as a function of the interaction between year and ethnicity.

Geography: To compare county-level cancer incidence rates by year to overall North Dakota incidence rates, counties were first checked to determine if they had enough data points. Only counties that were missing 3 or fewer years (out of 20) were included. Counties that met the criteria were used in subsequent modeling. For each county and cancer type, the incidence rate was modeled as a function of the interaction between year and region, with the region as either the specific county or the state average.

Next, all cancers that had enough data points per year (lung, colorectal, kidney, prostate, breast, bladder, melanoma, thyroid, corpus/uterus, non-Hodgkin's lymphoma, and leukemia) were modeled by county as a function of the natural log of county population size. Then, cancer rates were modeled as a function of rural status (urban, semi-urban, rural) and a function of frontier status (yes/no). Because there were no urban counties that were also frontier counties, rurality and frontier status were modeled separately.

Funding: The number of cancer-related journal articles published by North Dakota institutions was modeled as a function of year. So was the number of NIH cancer grants, funding from NIH cancer grants, number of UND grants, funding from UND grants, and funding from the North Dakota state government.

RESULTS

Sex

Female incidence rates were not significantly different by region and cancer type (Figure 1A). In contrast, males had a significant difference ($F=4.47$, $P=0.002$). Model-adjusted melanoma incidence rates were significantly lower in North Dakota (20.0) compared to the US average (26.3) (Figure 1B). The yearly incidence trends for the top 5 female cancers in North Dakota were not significantly different than the US average. The same was true for yearly trends in all male cancers except melanoma ($F=6.1$, $P=0.020$). North Dakota melanoma rates rose faster than the US average in the last 2 decades (Figure 1C).

Ethnicity

There was no difference between overall cancer rates between Whites and AI/ANs when considering ethnicity alone. In the interaction model, both ethnicity ($F=17.9$, $P<0.001$) and the interaction between ethnicity and cancer type ($F=5.8$, $P<0.001$) were significant. AI/ANs had higher overall mean incidence rates (108.5 vs 86.8). AI/ANs had higher rates than Whites for colorectal (66.9 vs 51.2) and lung (114.8 vs 55.8) cancer, though only lung cancer incidence was significant (Figure 2).

The yearly incidence trends between Whites and AI/ANs were significantly different for prostate ($F=22.1$, $P<0.001$), lung ($F=12.5$, $P=0.001$), and colorectal ($F=41.2$, $P<0.001$), but not breast cancer. AI/AN prostate cancer incidence rates decreased faster by year than Whites. White lung and colorectal cancer incidence rates were stable, while AI/AN rates decreased by year. By 2016, all 3 AI/AN cancer rates were comparable to Whites.

Geography

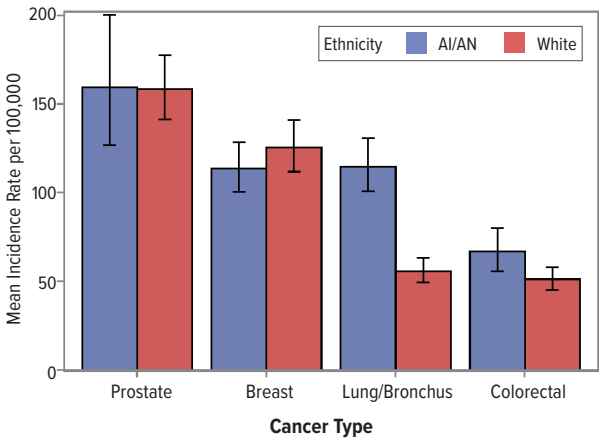
A limited number of counties had enough data points to analyze (prostate, n = 9 counties; breast, n = 8 counties; lung, n = 7 counties; colorectal, n = 6 counties; bladder, n = 3 counties; uteri, n = 1 county). Of those, 4 counties had significantly different cancer incidence trends across year compared to North Dakota overall. Two counties had breast cancer incidence rates that significantly fell while the overall state rate remained stable ($F=7.2$, $P=0.011$; $F=5.2$, $P=0.029$). Two other counties had prostate cancer incidence rates that did not decrease as fast as the state rate ($F=4.3$, $P=0.046$; $F=4.4$, $P=0.042$).

Only lung and corpus/uteri cancer rates were significant across population size. Lung cancer incidence rates significantly increased ($t=11.7$, $P=0.001$) with log population size, while corpus/uteri cancer rates decreased significantly ($t=5.6$, $P=0.023$) (Figure 3). Across rurality status and frontier status, only lung cancer by frontier status was significant ($t=16.8$, $P<0.001$). Model-adjusted lung cancer incidence rates were higher in nonfrontier counties (60.7) than frontier (49.7).

Funding

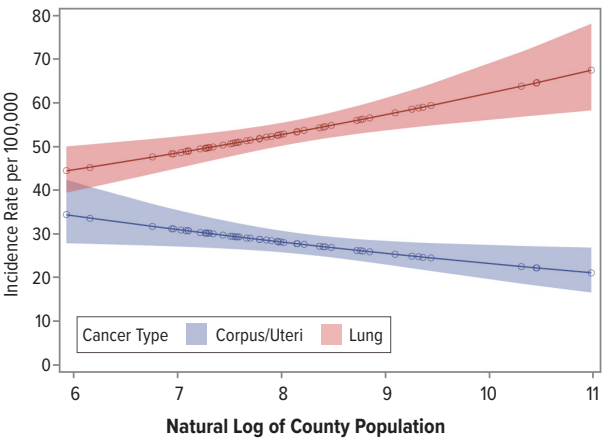
The number of cancer-related journal articles, NIH grants, and NIH funding increased significantly by year ($t=363.4$, $P<0.001$; $t=16.3$, $P<0.001$; $t=35.6$, $P<0.001$, respectively) (Table). Neither UND grants nor UND funding were significant by year, and data were insufficient to model government funding.

Figure 2. Cancer Incidence Rates by Ethnicity, 2000-2016



Overall incidence rates for American Indians/Alaska Natives (AI/AN) compared to Whites. Values are model-adjusted mean incidence rates per 100,000.

Figure 3. Cancer Incidence Rates by Population



Overall county lung and corpus/uteri cancer incidence rates by log county population. Lines were generated from prediction mean values from a generalized linear model with a negative binomial distribution; bands are 95% confidence limits of the mean.

DISCUSSION

Sex

Male melanoma was lower in North Dakota compared to the US average when averaged across all years. A recent study on ultraviolet-attributed melanoma rates backs this assertion; North Dakota was ranked the 41st highest.[23] The point of interest is

Table. Number of Cancer Paper Publications and NIH Grants and Information on NIH Funding for the University of North Dakota and North Dakota State University, by Year

Year	Published Cancer Papers	No. of NIH Grants	Funding From NIH Grants (Millions)
1997	25	2	0.34
1998	31	2	0.39
1999	29	4	0.74
2000	22	2	0.49
2001	21	2	0.66
2002	39	2	0.84
2003	49	2	0.64
2004	42	4	0.53
2005	54	3	0.84
2006	59	5	1.49
2007	59	14	3.41
2008	61	19	4.52
2009	69	18	4.88
2010	93	15	4.16
2011	103	11	2.59
2012	120	6	2.48
2013	143	5	4.15
2014	129	8	7.77
2015	146	10	8.36
2016	143	18	12.57

Abbreviation: NIH, National Institutes of Health.

that looking at the yearly trend, rates in the state are increasing faster. This was unexpected because the major risk factor for melanoma is ultraviolet (UV) light exposure. North Dakota has a low UV light climate and outdoor recreation does not appear to be a significant risk factor. The latest report from the Bureau of Economic Analysis showed that North Dakota had 2.2% of its gross domestic product from outdoor recreation compared to the 2.1% national average.[24] Regarding artificial UV sources, because North Dakota has not pursued data collection on tanning prevalence from national surveys, artificial UV exposure is unlikely to be a major risk factor.

However, it may be that North Dakotans have more acute sun exposures. In the 2012 Behavioral Risk Factors Surveillance System, compared to the nation overall, North Dakotans had a higher rate of sunburns (32.3% with at least 1 sunburn in the last year) compared to the overall US (21.28% unweighted, 26.36% weighted). North Dakota males had higher rates (33.9%) than females (30.8%).[25]

Ethnicity

As shown in other studies, AI/ANs have higher cancer incidence rates for overall cancers and lung/colorectal cancers separately. Our results agree with the most recent data from the North American Association of Central Cancer Registries,[26] as well as from research in the broader Northern Plains region.[4,27] The good news is that AI/AN cancer rates are falling significantly faster for prostate, lung, and colorectal cancers in North Dakota, and currently are on par with Whites' rates. This may be due to an increased focus on AI/AN communities. The most recent North Dakota Cancer Control Plan includes objectives to decrease smoking in American Indian adults as well as utilizing and evaluating cancer health disparity data.[28] Similarly, the North Dakota Colorectal Cancer Roundtable has a goal for an 80% colorectal cancer screening rate in every community and specifically recognizes the need to address disparities for American Indians. Furthermore, data from the Behavioral Risk Factors Surveillance System indicates that smoking rates in AI/ANs, while still elevated, are falling faster than non-AI/ANs. The percentage of AI/ANs who reported smoking every day was 48.5% in 2003 and dropped to 26.3% in 2019 (compared to 15% and 11.6%, respectively, in non-AI/ANs).

Geography

Most counties had the same yearly incidence trends for major cancers as North Dakota overall. However, 2 counties had falling breast cancer incidence rates compared to the level rate of North Dakota overall, and 2 counties had prostate cancer incidence rates that were not falling as fast as the state overall. This shows that cancer incidence rates are not uniform across even states, so county-level information can reveal more nuanced patterns.

It was interesting that lung cancer incidence increased by log population size while cervix/uteri decreased. Higher smoking rates—a risk factor for lung cancer—is typically higher in the US for rural areas (28.5%) than urban areas (25.1%).[29] Another risk factor, radon levels, does not vary by population size because all counties in North Dakota have zone 1 levels (>4.0 pCi/L). Therefore, it remains unclear why the state's lung cancer rates by population size are the inverse of what risk factors would predict. The dominant cause of cervical cancer is human papillomavirus (HPV), so women living in more urban areas conceivably have more access and education on HPV vaccination. This is supported by Centers for Disease Control and Prevention reports that found a 15-percentage point deficit of HPV vaccinations in rural versus urban areas[30] and lower rates of at least 1 HPV dose in nonmetropolitan areas (64.2%; 95% CI, 61.2-67.2) versus metropolitan areas (71.2%; 95% CI, 69.2-73.1).[31]

Another possible county-level difference in cancer incidence rates is the area deprivation index, which ranks socioeconomic status disadvantage. Counties with higher average indices could plausibly have higher incidence because of lack of access to health care services or lower rates of healthy behaviors. Using averaged state index values from the Neighborhood Index for North Dakota,[32] we explored the relationship between the indices and the incidence rates for lung, prostate, breast, and colorectal cancer. Only breast cancer had a significant relationship, and it was negative (t=-2.02, P=0.486), meaning that counties with higher indices (more disadvantaged) had lower incidence rates of breast cancer. It seems that disadvantage status does not predict a higher cancer incidence, at least with univariate analysis.

Funding

Both extramural cancer funding (from NIH) and cancer output in the form of journal articles in North Dakota have increased over the past 2 decades. These trends are not just a reflection of the overall increase in NIH budget, which almost tripled from 1997 ($12.11 billion) to 2016 ($32.26 billion). North Dakota's funding increased during that timeframe an order of magnitude more–$342,596 to $12.57 million. Intramural funding does not appear to be increasing. However, UND's funding in 2018-2019 was double the next highest year, so could be increasing in the short term. Also, the shift from individual funding (research, prevention/control) to infrastructure-based funding (cancer registry, translational cancer collaborations) seems to provide a more permanent investment in cancer. Finally, there was only a decade's worth of data from the North Dakota government checkbook, so it is too soon to determine a trend. There may be changes in the fiscal year that are not appropriately reflecting the true trends.

Limitations

There were some limitations to this study. First, not all years (1997-2016) had reportable cancer incidence rates for AI/ANs. Out of the 20 years covered for breast, lung, colorectal, and prostate cancer, there were 18, 16, 9, and 5 years, respectively, reportable for each. This suggests, for colorectal and prostate cancer rates especially, that the true cancer trend may be significantly different from what could be calculated here. Second, most counties did not have enough cases (10 or more) to analyze. The ones that did have enough cases had higher populations, biasing the presentable analyses towards more populated counties.

CONCLUSIONS

North Dakota has surprising cancer incidence nuances. Despite being a state with low UV exposure, male melanoma rates are increasing faster than the national average. Cancer incidence rates for highly prevalent cancers are dropping among AI/ANs faster than Whites. Some counties have yearly incidence trends for breast or prostate cancer that deviate from the state average. Lung cancer incidence rates, despite possible risk factors that point towards an opposite trend, were more elevated in urban areas.

Future work on male melanoma trends in North Dakota would benefit from an individual-level analysis, possibly with a follow-up questionnaire with survivors on sun exposure and tanning usage. Similarly, an individual-level approach would provide a complete dataset by year for AI/AN cancer rates to confirm the decrease in the state-level lung, prostate, and colorectal cancer incidence and tease out possible underlying factors behind the decrease. Once the factors behind the declining incidence rates are understood, they could be applied to AI/AN communities in other regions. Finally, work remains to link cancer incidence with outcomes. One way would be to compare state-level cancer control plans and determine how objectives are met over time.

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Colorectal Cancer Screening After Changes in US Preventive Services Task Force Guidelines With Increased Screening Options

Mark Benson, MD; Andrew Johannes, MD; Jennifer M. Weiss, MD, MS; Michael Lucey, MD; Jeff Pier, BS; Patrick Pfau, MD

ABSTRACT

Introduction: In 2016, the US Preventive Services Task Force (USPSTF) added multitarget stool DNA and computed tomography colonography (CTC) as accepted colorectal cancer screening modalities to the already recommended tests: fecal immunochemical test (FIT), sigmoidoscopy, and colonoscopy. The aim of our study was to determine trends in screening after the USPSTF update, with the effect of additional tests on the use of existing colorectal cancer screening modalities and overall screening rates.

Methods: We prospectively compared monthly colorectal cancer overall screening rates and the mean total numbers of patients screened by multitarget stool DNA, colonoscopy, sigmoidoscopy, CTC, and FIT 6 months prior to the new USPSTF guidelines until 30 months after.

Results: At completion of the study, 72,202 patients were eligible for screening. The overall rate of eligible patients screened for colorectal cancer did not change (80.9% vs 81.3%; $P = 0.287$). There was a significant increase in the percent of patients screened with multitarget stool DNA (1.6% to 15.6%; $P = .001$) and a significant decrease in the percent of patients screened using CTC (3.8 % to 1.5%; $P = .004$), FIT (9.3% to 4.9%; $P = .003$), and sigmoidoscopy (2.4% to 1.5%, $P = .024$). There was a nonsignificant decrease in the percent use of screening colonoscopy, from 82.9 % to 76.5% ($P = .313$).

Conclusion: While the overall colorectal cancer screening rate did not increase after the USPSTF update with additional recommended screening tests, practice patterns did change with a shift in the type of screening test used.

INTRODUCTION

Colorectal cancer (CRC) is the second-leading cause of cancer-related deaths in the United States. Although the incidence is declining, it is estimated that there were approximately 135,000 new cases of CRC diagnosed in 2017.[1] Several CRC screening modalities have been shown to decrease disease mortality.[2-8] Despite this, many Americans are not up-to-date with recommended CRC screening guidelines. In 2016, 67% of US patients between the ages of 50 and 74 years were up-to-date with colon cancer screening.[9] In an effort to increase patient compliance, there has been growing interest to develop alternative screening tests.

In June 2016, the US Preventive Services Task Force (USPSTF) included multitarget stool DNA and computed tomography colonography (CTC) as accepted CRC screening modalities for average risk patients to the already recommended tests: colonoscopy, fecal occult blood test (FOBT), fecal immunochemical test (FIT), or flexible sigmoidoscopy.[10,11] The updated guidelines recognize the different sensitivities, specificities, strengths, and weaknesses of each screening test but report that no single modality is more effective than the others.[10] Given the current lack of screening for approximately 30% of eligible US adults, the goal of the update was to increase the use of CRC screening by offering several screening options.[12,13] The theory is that more screening options will result in more patients being screened, and offering less invasive options will result in patients screened who otherwise might not agree to testing. The USPSTF added a multitarget stool DNA test, which consists of a FIT test in combination with an assessment for DNA biomarkers shed into stool, and CTC to the recent guideline update. The multitarget stool DNA is more sensitive but less specific than FIT alone.[14] CTC using software technology creates a 2-dimensional and 3-dimensional image of the colon to detect polyps with the aid of a bowel prep but without the need for sedation.[15]

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The goal of this study was to determine the effect of the USPSTF expansion of acceptable CRC screening tests on overall CRC screening rates and on existing CRC screening modalities within a unified academic primary care network. We wished to examine primarily if CRC screening rates would increase with more screening tests recommended as equal options. Additionally, though stool DNA and CTC have been available to some degree, we wanted to examine whether moving these tests to first tier tests recommended equally to existing modalities would result in an increase in stool DNA and CTC use and whether it would it affect already existing screening modalities.

METHODS

Data from the Wisconsin Collaborative for Healthcare Quality (WCHQ) on overall colorectal cancer screening rates and type of screening modality used were prospectively collected on a monthly basis on individuals 50 to 75 years old. WCHQ is a voluntary, statewide partnership of health care organizations that has tracked CRC screening rates across multiple health systems in Wisconsin since 2005.[16,17] The University of Wisconsin health system (UW Health) has been a member of WCHQ since 2005. We prospectively collect data on overall screening rates and the type of method used at our institution each month. We present overall screening rates to WHCQ on a quarterly basis, and they are published annually to the public.

Adults aged 50 to 75 years are included as eligible for screening if they are "currently managed" by the University of Wisconsin physician group. Patients are considered "currently managed" if they had at least 2 primary care office visits in an outpatient, nonurgent care setting within the previous 36 months, with at least 1 of those visits in the prior 24 months. This group is the ongoing cohort of patients who can and should be screened for CRC.

Completion of CRC screening is defined as having completed 1 of the 5 recommended tests by the USPSTF within the correct screening interval. A patient is considered screened if FOBT/FIT has been completed in the prior 12 months, if multitarget stool DNA has been performed within the previous 3 years, flexible sigmoidoscopy or CTC in the past 5 years, or colonoscopy in the prior 10 years. Both screening and diagnostic colonoscopy, if complete, satisfied screening requirements. If a patient underwent a positive test (FIT, stool DNA, sigmoidoscopy, or CTC) and then subsequent colonoscopy, the initial screening modality was the test recorded for that patient. Tests were identified using current procedural terminology (CPT); logical observation identifiers, names, and codes (LOINC); and healthcare common procedure coding system (HCPCS) codes for the above-mentioned CRC screening tests based on codes designated by the Healthcare Effectiveness Data Information Set (HEDIS) to calculate CRC screening metrics. Within the primary care network, all primary care providers have open access to order the various screening modalities, which are all covered by local third-party payers.[18] The decision on the type of screening modality used was made by the primary care providers.

We evaluated the screening practices for eligible average risk patients within UW Health. We compared the monthly overall CRC screening rate and overall number of patients screened from 6 months prior to the updated USPSTF to 30 months after. We calculated mean monthly total numbers and relative percentage of multitarget stool DNA, colonoscopy, flexible sigmoidoscopy, CTC, and FOBT/FIT for eligible 50- to 75-year-old patients from January 2016—6 months prior to the USPSTF update—through December 2018.

Statistical Analysis

The analysis was focused on comparisons between the colorectal cancer screening rates and numbers 6 months prior to the June 2016 USPSTF update compared to the subsequent 30 months. Comparisons were made using the Student *t* test for continuous outcomes and a chi-square analysis for categorical outcomes. Statistical significance was considered at a 2-tailed P value < 0.05.

The Institutional Review Board at the University of Wisconsin granted the study an exemption as a project of quality control and program evaluation.

RESULTS

In our primary care network, 65,327 patients were eligible for colorectal cancer screening at the initiation of this study, and 72,202 patients were eligible for CRC screening during the last month of the study, providing the study cohort.

There was a significant increase in the number of eligible screening patients within our primary care network during the study period, from 65,327 to 72,202 ($P < .001$). There was also a significant increase in the absolute number of patients screened for CRC (52,906 to 60,100; $P < .001$) during the course of the study, before and after the 2016 USPSTF screening guidelines. However, the overall percent of eligible patients screened within the primary care network did not change significantly during the study period (80.9% vs 81.3%; $P = 0.287$).

There was a significant increase in the percent of eligible patients screened with multitarget stool DNA, from 1.6% (mean 3.9%, SD ± 1.37) to 15.6% (mean 7.9%, SD ± 2.65) ($P = .001$), as well as a significant increase in the absolute number of stool DNA tests completed per month, from 48/month (SD ± 18) to 117/month (SD ± 48) ($P = .002$). There was also a significant increase in the absolute number of colonoscopies completed, from 970/month (SD ± 116) to 1152/month (SD ± 140) ($P = .005$), but a nonsignificant decrease in the percent use of screening colonoscopy as a percentage of all screening tests employed—from 82.9% (mean 80.5%, SD ± 1.54) to 76.5% (mean 79.7%, SD ± 1.95) ($P = .313$).

There was a significant decrease in the percent of patients screened using CTC, from 3.8% (mean 3.3%, SD ± .31) to 1.5% (mean 2.5%, SD ± .58) ($P = .004$) and a decrease in the absolute number of screening CTC exams completed, from 40/month (SD ± 3) to 37/month (SD ± 7) ($P = .35$). There was a significant decrease in the percent of patients screened using FIT, from 9.3%

(mean 9.6%, SD ± .98) to 4.9% (mean 7.6%, SD ± 1.49) (P = .003) and a decrease in the absolute number of tests completed, from 114/month (SD ± 16) to 109/month (SD ± 14) (P = 0.52). The smallest percent of eligible patients were screened using flexible sigmoidoscopy; however, there was also a significant decrease in the percent screened using flexible sigmoidoscopy—from 2.4% (mean 2.5%, SD ± .50) to 1.5% (mean 2.0%, SD ± .38) (P = .024)—but no significant change in the absolute number of tests completed (n = 29/month, SD ± 6) and (n = 29/month, SD ± 5) (P = 0.96).

DISCUSSION

In June 2016, the USPSTF reported that multiple screening modalities could be used for patients 50 to 75 years old to detect early-stage colorectal cancer and adenomatous polyps. The previous USPSTF guidelines, from 2008, recommended screening with colonoscopy, annual FOBT/FIT, or flexible sigmoidoscopy plus FOBT/FIT.[19] Thus, the aim of our study was to determine the effect of the updated USPSTF guidelines expansion of acceptable CRC screening tests on overall CRC screening rates and existing screening modalities.

In our cohort, since the 2016 USPSTF update, there was an increase in the overall number of patients screened for CRC within our network but no increase in the overall rate of CRC screening. The screening rate within our health care system is one of the highest in the nation,[20] approaching or above 80% for the past 5 years. This may explain why the overall screening rate did not increase with the additional CRC tests recommended. To have shown a statistical improvement in overall screening rate at our institution, we would have had to see an increase of 2.0% rather than the 0.4 % we witnessed. This means we would have needed to have screened approximately 1,300 more patients than the already added 8,000 patients who received CRC screening during the study period. Further, as screening rates for colorectal cancer or any cancer get closer to 100%, there may be a subset of patients who will never get screened or will be more challenging to get screened. However, for health care systems with lower than average screening rates, it is possible that the increased number of CRC screening modalities would lead to a significant percentage increase in eligible patients screened. In addition, our health care system has a long history of a colonoscopy-dominated screening practice, with >80% of patients screened by colonoscopy. It is also possible that at health care systems with lower screening rates and less resources to provide colonoscopy, the addition of more screening tests may further increase screening rates.

Of the CRC screening modalities studied, the utilization of stool DNA increased the most within our health care network. The reason for the increase in adoption is likely multifactorial, with contributions from its lack of invasiveness compared to an endoscopic exam, increased perceived patient privacy, increased sensitivity compared to alternate stool based tests, local and national media attention, lack of pretest preparation, ease of use, and the fact it is a new or novel screening modality. The multitarget stool DNA test Cologuard also uses direct-to-consumer advertising and sales representatives, which may affect patient choice and primary care ordering practices. Exact Science, producer of the multitarget DNA stool test (Cologuard) is also based in the same city as our institution, likely further influencing local provider practices and ordering patterns. Primary care providers are the ultimate decision-makers as to which type of screening modality is used and, thus, were likely influenced by all of these factors, resulting in an increase in screening with stool DNA.

Previous studies have shown a gradual increase and stability in the use of CTC once a program has been established.[21,22] CTC has a sensitivity and specificity to detect adenomas ≥ 10 mm that ranges from 67% to 94% and 86% to 98%, respectively.[23-25] Of all CRC screening tests, CTC's detection of polyps and cancer is closest to endoscopic colonoscopy. Interestingly, since the USPSTF update, there was a gradual decrease in the use of CTC within our health care system. Reasons for this are not completely clear, as we assumed that just as fecal DNA testing increased after the USPSTF 2016 recommendations, that the use and ordering of CTC would have increased with CTC being considered a relatively equivalent screening test compared to other modalities. It is possible that this decrease is secondary to the impact and increased adoption of multitarget stool DNA as a less invasive means to screen for colon cancer at our institution. To patients and ordering providers, while stool DNA is an at-home study, CTC still requires a full bowel prep and requires a visit to a clinic or hospital to be performed. In addition, CTC is not a new screening test at our institution and has been covered by third-party payors for greater than 10 years. This may explain why CTC did not receive the same "bump" in its relative ordering for CRC screening by our primary care providers as compared to multitarget stool DNA.

Colonoscopy continues to be the most commonly used test to screen for CRC nationally and at our institution. During the study period, the absolute number of colonoscopies increased significantly. However, although nonsignificant, there was a decrease in the percent of screening colonoscopy within our health care system, from 82.9% to 76.5%. Further screening colonoscopy was the only screening test that had a wait time during the study, which may further explain the ascent of stool DNA as a screening test compared to colonoscopy. Still, colonoscopy remains the dominant screening modality at our institution, as it does nationally. It is unknown but possible this decrease in colonoscopy use as a screening test will continue as the use of multitarget stool DNA increases.

Some limitations of our study include possible lack of generalizability to different health care systems. The Midwest and the state of Wisconsin have one of the highest colon cancer screening rates in the nation.[20] Within Wisconsin, our institution has one of the higher screening rates—over 80% at the initiation of our study. This actually may have blunted the effects of the additional screening tests being recommended, while at other institutions with lower rates of CRC screening the changes in the 2016

in USPSTF guidelines may lead to an even greater increase in screening rates. Further, our CRC screening program was one of the first to adopt and implement a CTC screening program. Such results and patterns might not be applicable to health care systems with different insurer coverage and CTC availability for CRC screening. Lastly, as stated, the geographic location of Exact Sciences—the maker of Cologuard—may contribute to both patient and provider preferences in our study. However, with the national advertising and distribution of Cologuard, it is unlikely that the significant increase in multitarget stool DNA as a screening test will remain a local phenomenon.

Our study does not mean to imply that the changes in the 2016 USPSTF update were the actual cause or the only factor that affected CRC screening rates at our institution. There are other screening guidelines present for CRC screening, and we do not have data or information on which guidelines our primary care providers use and how they use them. However, what is unique about the 2016 USPSTF update is that it recommends an increased number of screening modalities, and while not indicating that all are equal per se, it states that no modality is more effective than the other and all satisfy screening requirements.

CONCLUSION

Colorectal cancer continues to lead to significant patient morbidity and mortality, and screening can decrease this burden. Focusing on the health care benefits of screening, the most recent USPSTF update recommended providing multiple screening options for patients and providers rather than prioritizing one modality over another. This change did not influence overall screening rates but did influence screening patterns within our large unified academic primary care network. The use of multitarget stool DNA testing increased significantly and will likely continue to increase based on this early data. Colonoscopy continues to be the most frequently used screening modality, but it did show a decline in the rate of use compared to other modalities. Further time out since the 2016 USPSTF guideline changes and data from other institutions with varying patient populations will help to further determine if offering more CRC screening modalities will truly help increase national CRC screening rates.

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Pediatric COVID-19 Delirium: Case Report of 2 Adolescents

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ABSTRACT

Introduction: Neurological complications of COVID-19, including delirium, are emerging in the adult population but have not been well described in pediatrics.

Case Presentation: We report the cases of 2 adolescent males, ages 16 and 17, who presented with delirium secondary to an acute COVID-19 infection in the fall of 2020 at Children's Wisconsin in Milwaukee, Wisconsin. The foundation of our treatment strategy was the triad of alpha-2 agonists (clonidine, dexmedetomidine, guanfacine), antipsychotic agents (quetiapine, haloperidol, olanzapine), and melatonin. Discharge planning required involvement from inpatient psychiatry, case management, social work, and the family. Both patients showed improvement after several weeks.

Discussion: We believe these are the first reported cases of COVID-19-associated delirium in children outside of multisystem inflammatory syndrome in children (MIS-C).

Conclusion: Pediatric COVID-19 delirium is a new manifestation of the COVID-19 disease. Treatment guidelines are emerging and lessons regarding therapies and discharge considerations are described in these 2 unique cases.

INTRODUCTION

A growing body of literature describes COVID-19 neurological complications in adults, ranging from headache and dizziness to encephalopathy and delirium.[1-7] SARS-CoV-2, the virus that causes COVID-19, may infect neural cells via angiotensin-converting enzyme 2 (ACE2) receptors given its similarities with SARS-CoV-1.[8-14] ACE2 appears to have a lower expression in children compared to adults,[15] which may explain why disease and neurological complications are less likely in pediatric patients. Neurological involvement may be prompted by a secondary inflammatory response, vascular injury or insult, or immune-related post-infectious disorders.[11] Here we describe 2 adolescent COVID-19 delirium cases that presented to Children's Wisconsin, Milwaukee, Wisconsin in October 2020.

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CASE 1

A 16-year-old African American male with a history of obesity (body mass index [BMI] 38kg/m^2) presented with a 3-day history of altered mental status. Two days prior to his altered mentation, he had rhinitis and congestion for which he took over-the-counter cough medicine and acetaminophen. He also lost his sense of taste and smell but had no fever or cough. He was found talking to himself and staring into the distance for long periods of time. He had not slept for 2 days prior to arrival and had limited oral intake. He then mentioned demons and passive thoughts of suicide, prompting his mother to bring him to the emergency department (ED). He had no prior history of mental illness. He did have a history of intermittent marijuana use (last use 4 days prior to admission) but no other known drug use. He earned mostly As in school, including in advanced placement courses, was active in athletics, and had a healthy social life. Family history includes schizophrenia and bipolar disorder in the maternal grandmother and a cousin suffering from hallucinations of unknown etiology.

On presentation, the patient's vital signs were within normal

limits. He was awake, alert, and looking around the room as if something was there. Initially, he would not speak or follow any commands. There were no gross neurological abnormalities noted other than his mentation. He tested positive for COVID-19 by nucleic acid amplification test (NAAT) via nasopharyngeal swab. Initial laboratory workup was notable for mild transaminitis, an elevated creatine kinase, and elevated creatinine (Table). Remainder of laboratory workup, including inflammatory markers, infectious workup, thyroid workup, and encephalitis evaluation were normal, including a normal cerebrospinal fluid (CSF) profile and neuroimaging (Table). CSF COVID-19 polymerase chain reaction (PCR) was negative, although this test was not yet validated. A urine drug investigation showed marijuana, cotinine, and cough medications (including dextromethorphan), but our toxicologists felt these results did not explain the waxing and waning nature nor duration of altered mentation. Urine tests for synthetic opioids and cannabinoids were negative.

On hospital day (HD) 3, the patient occasionally responded appropriately to questions. He knew his name and the year but not the month. He began to follow simple commands intermittently (open eyes, open mouth, squeeze hand), and exam was frequently interrupted by volitional movements. A 48-hour electroencephalogram (EEG) showed diffuse background slowing suggestive of mild to moderate encephalopathy without epileptiform activity. He continued to have fluctuating episodes of agitation, confusion, delirium, hallucinations, and intermittent unresponsiveness. He frequently required 5-point restraints for acts of self-harm or aggression towards staff and/or family members. He responded well to intramuscular (IM) haloperidol 1-2 mg given as needed for severe agitation but then had decreased alertness and several episodes of dystonia requiring transfer to the pediatric intensive care unit (PICU) on HD 4. His dystonic reaction resolved after several doses of benztropine, but he continued to vacillate between minimal responsiveness and severe agitation punctuated by physical outbursts requiring high levels of sedation and 5-point restraints. His severe agitation led to an increase in his creatinine kinase, which peaked at 3757[iU]/L and decreased appropriately with intravenous (IV) fluids. He required intermittent nasogastric feeds to ensure proper nutrition.

At the peak of his delirium, the patient required frequent doses of benzodiazepines, ketamine, dexmedetomidine, clonidine, olanzapine, and quetiapine, in addition to a continuous infusion of dexmedetomidine. His regimens were adjusted daily in a multidisciplinary effort between psychiatry, neurology, and the PICU. The regimen that proved most efficacious included high doses of quetiapine, clonidine, and melatonin, with haloperidol as a rescue medication. Haloperidol was favored given the deliriogenic nature of ketamine and benzodiazepines and the inefficacy of dexmedetomidine. He began to have periods of lucidity where he was directable, could respond to basic prompts, and feed himself. However, he remained confused about his environment with continued agitation and outbursts. Given his continued encephalopathic presentation, a repeat lumbar puncture was done on HD 8 and CSF was again unremarkable (Table). CSF COVID-19 PCR was again negative as well.

Due to continued concern that his presentation could be due to a COVID-19-related inflammatory process, IV immunoglobulin (IVIG) was administered at 0.4mg/kg of ideal body weight for 5 days on HD 8-12. He showed gradual improvement during this time, although whether his improvement was due to IVIG or optimization of his medication regimen is unclear. He was retested for COVID on HD 11 and was persistently positive.

By HD 13, he was verbalizing more frequently and clearly with extended periods of lucidity but still experiencing confusion, difficulty focusing, and difficulty interpreting stimuli. After transfer back to the acute floor, his agitation decreased, but he became more emotionally labile in which he was often tearful or afraid. Greater periods where he was alert and fully oriented continued to alternate with episodes of paranoid thoughts, delusions, and acts of attempted self-harm. On HD 21, he had a self-resolved period of echopraxia, mutism, staring spell, and posturing suspicious for catatonia. His quetiapine continued to be titrated throughout the admission, ultimately to 700 mg/day in divided doses. He was also on a clonidine transdermal patch 0.3 mg changed weekly, oral clonidine 50 mcg q6 hours and melatonin 20 mg nightly for delirium. Through his admission, he never had significant respiratory involvement, thus was never started on remdesivir or steroids. On HD 25, he was discharged to a psychiatric facility for ongoing medication management. He had a negative COVID-19 test prior to transfer per facility policy.

That evening, he had a temperature of 39.2° C and continued altered mental status and, therefore, was transported back to our pediatric ED where he exhibited evidence of delusions and paranoid psychosis. He was again found to be COVID-19 positive by PCR. The fever resolved after 4 days without any other symptoms or focal signs. During this admission, he continued to have periods of lucidity punctuated by physical outbursts and expressed suicidal ideation, paranoia, ideas of reference, and internal preoccupation. Lorazepam was added to haloperidol and diphenhydramine as part of his rescue regimen to reduce psychotic agitation, with good effect. He was again discharged to a psychiatric facility after a 12-day hospitalization, 36 days after first admission. Delays in discharge were due to the psychiatric facility's hesitancy with his persistent positive COVID-19 tests; however, he did not have respiratory symptoms. On discharge, he was awake, alert, and more interactive. He continued to have paranoia but intermittently answered questions.

The patient spent 12 days in a psychiatric facility with significant improvement and was discharged home 47 days after his initial presentation. Home medications included quetiapine and clonidine, though he self-weaned these medications as his mood improved. During follow-up with primary care 77 days after ini-

Table. Labs and Imaging Results

	Case 1	Case 2
COVID-19 NAAT NP	**HD 2:** + S gene Ct = 31.2, ORF gene Ct = 31.3; **HD 12:** + E gene Ct = 34.6; **HD 23**: -; Readmission: +, S gene Ct = 33.8	Positive
Complete blood cell count	Normal	Normal
Coagulation studies	Normal INR/PT/PTT	NA
Comprehensive metabolic panel: creatinine (ref range 0.5-1.06 mg/dL), AST (ref range 5-35 [iU]/L), ALT (ref range 10-35 [iU]/L)	Glucose 103, creatinine 1.14, AST 89, ALT 90, otherwise normal	AST 37, ALT 38, otherwise normal
Creatinine kinase (ref range 33-145 [iU]/L)	**HD 1:** 1076, peaked on **HD 5** 3757; **HD 16:** 473	NA
C-reactive protein (CRP) (ref range 0-1 mg/dL)	< 0.5 mg/dL	< 0.5 mg/dL
Procalcitonin (ref range < 0.11 ng/mL)	0.20 ng/mL	NA
Erythrocyte sedimentation rate (ref range 0-15 mm)	10 mm	8 mm
Troponin 1 (ref range 0.012-0.034 ng/mL)	< 0.012	NA
Cerebrospinal fluid (CSF)		
Counts	**HD 3:** TNC 2, RBC 0, neutrophils 1%, lymphocytes 85%, glucose 58, protein 16; **HD 9:** TNC 0, RBC 0, glucose 76, protein 17	**HD 2:** TNC 0, RBC 81, protein 25
Culture	Negative x2	Negative
Meningoencephalitis NAAT[a]	NA	Negative
Varicella-zoster virus IgM antibody	NA	Negative
Autoimmune encephalitis panel (CSF)	**HD 3 and 7:** negative	Negative
Neurotransmitter metabolites	**HD 9:** normal	NA
Neopterin (ref range 8-28)	**HD 9:** 17	NA
COVID NAAT	**HD 3 and 7:** negative	Negative
Additional Infectious		
Respiratory polymerase chain reaction panel[b]	NA	Positive for COVID-19, otherwise negative
Epstein-Barr virus IgG	+ IgG, - IgM consistent with past infection	+ IgG, - IgM consistent with past infection
HIV	Negative	Negative
Lyme Ab blood	NA	Negative
Tickborne panel NAAT[c]	NA	Negative
Immune/Thyroid		
Antinuclear antibody titer (ref range < 40)	NA	< 40
Autoimmune encephalitis panel (blood)	**HD 3:** negative	NA
Thyroid studies	Normal TSH, negative thyroid peroxidase Ab	Normal TSH, negative thyroid peroxidase Ab, thyroglobulin Ab
Toxicology		
Serum drug screen	**HD 2:** acetaminophen, doxylamine	NA
Urine drug screen	**HD 2:** positive for marijuana (THC 30 ng/mL), cotinine, acetaminophen, dextrorphan, doxylamine, dextromethorphan, diphenhydramine, negative for ethanol, methamphetamine	H**D 2:** positive for acetaminophen, lidocaine, quetiapine, citalopram, ibuprofen; negative for THC, ethanol, methamphetamine
Urine synthetic opioids	**HD 9:** negative	NA
Urine cannabinoids	**HD 9:** negative	NA
Imaging/Procedures		
Electrocardiogram	**HD 1:** normal	**HD 14:** Sinus tachycardia, otherwise normal
Brain MRI with and without contrast	**HD 2:** normal	**HD 2:** No acute intracranial abnormality. Unchanged subcortical linear T2 FLAIR hyperintensity the mid-left temporal lobe likely represents gliosis surrounding a developmental venous anomaly. Globes normal. Intraorbital optic nerves mildly tortuous, representing a nonspecific finding
Echo, transthoracic, obtained to evaluate for MIS-C	**HD 16:** normal	NA
Electroencephalogram (EEG)	**HD 3:** mild-moderate slowing of the background suggestive of a mild-moderate encephalopathy; HD 7: EEG indicative of mild diffuse cerebral dysfunction (encephalopathy), improved from prior	**HD 2:** normal; **HD 10:** excess beta activity that could be secondary to sedative/hypnotic medications

Abbreviations: NAAT, nucleic acid amplification test; NP, nasopharyngeal; HD, hospital day; Ct, cycle threshold; INR, international normalized ratio; PT, prothrombin time; PTT, partial prothrombin time; NA, not applicable; AST, aspartate aminotransferase; ALT, alanine transaminase; TNC, total nucleated count; RBC, red blood cell; Ig, immunoglobulin; TSH, thyroid stimulating hormone; THC, tetrahydrocannabinol; MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery; Echo, echocardiogram; MIS-C, multisystem inflammatory syndrome in children.

[a]Tests NAAT for: *Escherichia coli* K1, *Haemophilus influenzae*, Listeria monocytogenes, *Neisseria meningitidis*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, cytomegalovirus, enterovirus, HSV 1 and 2, HHV-6, parechovirus, varicella, and *Cryptococcus neoformans/gatti*.

[b]Tests NAAT for adenovirus; coronavirus-229E, -HKU1, -NL63, and -OC43; novel coronavirus; human metapneumovirus; rhinovirus/enterovirus; influenza A and B; parainfluenza 1, 2, 3, and 4; RSV, *Bordetella pertussis*; *Bordetella parapertussis*; *Chlamydophila pneumoniae*; and *Mycoplasma pneumoniae*.

[c]Tests NAAT for *Anaplasma phagocytophilum*, *Babesia microti*, *Borrelia miyamotoi*, *Babesia duncani*, *Ehrlichia chaffeensis*, *Ehrlichia ewingii*, *Ehrlichia canis*, *Babesia divergens*, *Babesia* MO-1, *Ehrlichia muris eauclairensis*.

tial presentation, the patient and his mother reported his mood was significantly better, with no hallucinations or suicidal or homicidal thoughts. He was eating and drinking normally and having no issues with sleep. He reported generally being happy and stress-free. He was attending group therapy weekly and doing well in school.

CASE 2

A 17-year-old White male with high-functioning autism spectrum disorder and anxiety presented with 2 days of worsening altered mental status. At baseline, he had significant anxiety but was able to perform the majority of his activities of daily living independently and clearly communicate his needs. He was taking escitalopram and buspirone, with recent adjustments in both medications per his outpatient psychiatrist. Per his parents, he had become mentally altered over the course of 48 hours. He initially was less interactive with his parents and ruminated on bizarre ideas, such as building a piano. He progressed to having visual and auditory hallucinations, bursts of inappropriate laughter, poor eye contact, abnormal but nonrepetitive hand movements, limited oral intake, and inappropriate urination. He lost his sense of taste and smell. After >24 hours without sleep, his parents sought medical evaluation.

On admission, the patient had normal vital signs and physical exam, except for an elevated blood pressure and his neurologic and mental status exam. He had nonpurposeful, nonrhythmic upper extremity movements and was able to follow some simple commands but not consistently. He interacted minimally, predominantly using echolalia—vocalizing to "parrot" words he was hearing. He was able to ambulate without falling, although he appeared somewhat unsteady on his feet and needed assistance. On HD 1-3 he was described as "euphoric," with pressured speech and grandiosity, bouts of agitation, talking in nonsensical phrases, laughing inappropriately, yelling random words, and using loud profanity-laden language, which was not his baseline.

Serotonin syndrome was considered given recent adjustments to psychiatric medications, but his exam was inconsistent with this and symptoms did not improve with cessation of home medications. Drug screen was consistent with prescribed medications. A COVID-19 NAAT was positive. Laboratory workup, including complete blood count, comprehensive metabolic panel, inflammatory markers, thyroid studies, and encephalitis evaluation, were unremarkable, including a normal CSF profile (Table). Magnetic resonance imaging (MRI) demonstrated known unchanged subcortical linear T2 fluid-attenuated inversion recovery (FLAIR) hyperintensity in mid-left temporal lobe attributed to gliosis surrounding a developmental venous anomaly but no other intracranial abnormalities. CSF COVID-19 PCR was negative. Short-term EEG on HD 2 was normal.

Given concerns for COVID-19 delirium, melatonin and quetiapine were started in addition to behavioral interventions for delirium. His symptoms waxed and waned but showed gradual improvement. Melatonin was started at 5mg and increased to 10 mg several days later. The quetiapine dose was increased gradually in the first week of hospitalization. He showed improvements in his interaction with parents and voiding behaviors, but he continued to speak in nonsensical sentences and exhibited hallucinations. He required several as-needed doses of quetiapine and IM haloperidol due to behavioral outbursts (agitation, shouting, spitting, throwing, and hitting his mother once), but he never required physical restraints. He also required IV hydration for poor fluid intake for the first few days of admission.

By HD 8, he was still delirious, pacing around his room, babbling, and had intermittent tic-like movements and facial grimacing with headshaking. He put nonfood items in his mouth, like string and pieces of plastic. When called by his name, he would often refer to himself by another name, such as his friend's name. Repeat EEG was done on HD 9 and showed excess beta activity, likely secondary to quetiapine sedative effects, but was otherwise normal without change in semiology. On HD 10, he was started on guanfacine extended release (ER) 1 mg each morning. By HD 11, the quetiapine dosage was 350 mg/day divided 3 times per day. He started having more coherent sentences, knowing his name, recognizing some staff members, properly used utensils and dishes, and had improved fluid intake. By HD 13, he was answering questions more appropriately and was much more redirectable by his mother. He still had moments of yelling and nonsensical speech but was interacting more appropriately with people in his room.

He was discharged home on HD 14 after continued small improvements in his mental status and parental comfort in safely caring for him at home. He was oriented to self, parents, and birth date, though not to his age or location. He continued to have generally nonsensical speech but would answer direct questions with complete and more coherent sentences. He was discharged on melatonin 10 mg nightly, guanfacine ER 1mg daily, quetiapine 100 mg in the morning and noon and 150 mg at bedtime, and quetiapine 50 mg daily as needed, with plans to follow closely with his outpatient psychiatrist. His symptoms continued to improve slowly with near resolution of hallucinations and more consistent self-orientation. However, 43 days after his admission, he continued with disordered thoughts and paranoia but improving nutritional intake.

DISCUSSION

We highlight 2 adolescent males with persistent delirium symptoms after COVID-19 infection. Both suffered from anosmia and ageusia but lacked significant respiratory symptoms. Other organ systems showed no sign of dysfunction, and steroids were not used. We believe these are the first reported cases of COVID-19-associated delirium in children outside of multisystem inflammatory syndrome in children (MIS-C).

Delirium has emerged as a prevalent but likely underdetected

manifestation of COVID-19. Among 71 adults with COVID-19, mostly admitted to the intensive care unit, 42% met DSM-IV criteria for delirium.[16] Another study reported on 10 adult patients with confirmed or probable COVID-19 who developed encephalopathy with features of delirium and psychosis; workup including MRIs and CSF analysis were largely unrevealing and most recovered at discharge.[4] In 1 case report, a 55-year-old woman developed delirium with slow improvement and recovery by day 52 of illness,[17] which follows a similar timeline in our patients.

Delirium has significant morbidity in pediatric patients, and it is critical to diagnose rapidly in order to discern its etiology and determine management.[18] Children with developmental delay and family history of delirium appear to be at higher risk for delirium. Emotional lability, hallucinations, depression, and anxiety have been reported in children with SARS-CoV-1.[19] Encephalitis and seizures in children with COVID-19 have been reported; however, delirium has only been reported in MIS-C.[10,11,20,21] A 14-year-old boy with MIS-C developed hyperactive delirium requiring physical restraints, haloperidol, lorazepam, and dexmedetomidine,[22] similar to Case 1. His evaluation of delirium was complicated by ionotropic support, anakinra, and steroids for MIS-C; he made a full recovery. Four children with MIS-C in a United Kingdom hospital developed encephalopathy; all cases resolved.[23]

The management of delirium associated with COVID-19 poses additional challenges given the lack of evidence-based guidelines and difficulty performing nonpharmacologic interventions under heightened isolation requirements.[24,25] The foundation of our treatment strategy for addressing symptoms of delirium, agitation, and psychosis was the triad of alpha-2 agonists (clonidine, dexmedetomidine, guanfacine), neuroleptic agents (quetiapine, haloperidol, olanzapine), and melatonin.[2,26] Dexmedetomidine and clonidine have a significant history of being effective agents in the treatment of hyperactive delirium. A dopamine agonist can be used if there is concern for akinetic mutism or catatonia but should be used with caution in delirium.[26-28] If patients display violence toward self or health care providers, faster titration of antipsychotics may be indicated.[29] IVIG also has been trialed with success[30] and may have helped in Case 1.

Recent literature suggests a positive role for guanfacine, especially with its lower cardiovascular effects compared to clonidine.[31] The extended-release formulation of guanfacine eliminates the potential for rebound hypertension/tachycardia that could be seen with oral clonidine or guanfacine. We preferred second generation/atypical neuroleptic agents because of their lower potential for both dystonias/extrapyramidal side effects and QTc prolongation. We chose the low-potency D2 blockade agent quetiapine (which probably has the broadest range of experience of atypical antipsychotics in treating pediatric delirium) rather than a high-potency D2 blockade agent (such as olanzapine or haloperidol) out of concern for catatonic-like symptoms and abnormal movements that could have represented dopamine-depletion symptoms. Olanzapine and haloperidol were used only when a rapid-response IM agent was necessary.

Melatonin has long been a therapeutic staple for restoring and maintaining the sleep-wake cycle that is often disrupted in delirium. It has antioxidant properties, eliminating free radicals to a much greater degree than vitamin C and E, anti-inflammatory and immunoregulatory effects, cytoprotection and neuroprotection benefits, and some indirect evidence of possible antiviral effects.[32-34] Several recent studies have suggested that melatonin may have antiviral action towards COVID-19. While there is no clear guidance in the literature regarding dosage, dosing above chronobiotic benefit has been proposed—up to 36-100 mg per day.[32,35,36]

Multiple psychiatric medication classes have been used to treat delirium in the setting of COVID-19, and close follow-up care is warranted for patients. However, the COVID-19 pandemic has disrupted the normal process of obtaining psychiatric care, with many routine services limited or closed.[37] Many psychiatric programs also have adjusted enrollment criteria during the pandemic, which may delay or deny acceptance until the patient recovers.[38] Meanwhile, virtual modalities for providing follow-up care have increased.[38] Because of these limitations on follow-up, discharge planning required involvement from inpatient psychiatry, case management, social work, and the family.

As our understanding of COVID-19 rapidly evolves, we should be aware of the possible pediatric neuropsychiatric complications, including delirium, and the potential management strategies and discharge challenges that may emerge in these patients.

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Activating the Hospital Incident Command System Response in a Community Specialty Practice: The Mayo Clinic Experience

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ABSTRACT

Introduction: The COVID-19 pandemic presented health care organizations with a unique challenge in determining effective management of a large-scale incident across an extended time period.

Case Presentation: This report describes the response of a multisite integrated system to the COVID-19 pandemic through activation of the Hospital Incident Command System.

Discussion: A robust emergency response plan with multidisciplinary involvement can help to ensure clear lines of accountability and expedite decision-making. Consistent physician input across affected specialties allows for a robust understanding of impacted areas, peer-to-peer communication, and a sense of ownership across the medical staff. The necessity of effective communication with staff and patients during times of crisis cannot be understated. The potential for information overload in a pandemic is significant but can be overcome through consistent and transparent communication from leadership.

Conclusion: Health systems should have a well-organized emergency response system prepared to launch in small-scale or large-scale situations. The threshold to implement the response system and accountability to make that decision must be a clearly defined organizational policy.

INTRODUCTION

The Mayo Clinic Health System is a series of 16 hospitals and 35 clinics across 3 states within a 120-mile radius of Mayo Clinic in Rochester, Minnesota (See Appendix). The Northwest Wisconsin region of the Mayo Clinic Health System is comprised of a clinic and 200-bed hospital campus in Eau Claire, Wisconsin; 25-bed critical access hospitals in Barron, Bloomer, Menomonie, and Osseo, Wisconsin; and clinics in Chetek, Chippewa Falls, Elmwood, Glenwood City, Mondovi, and Rice Lake, Wisconsin. The practice across these sites is primarily community-based primary and secondary care, with tertiary care provided in Eau Claire. The hospitals and clinics operate as an integrated system, with shared leadership, expertise, and resources. The critical access hospitals strive to provide state-of-the art care that is equivalent to the Eau Claire hub, minimizing the need to transfer patients outside of rural communities. The region employs over 300 physicians and 4,000 staff.

Operating under a highly matrixed leadership structure, the region is led by an executive triad comprised of physician, nursing, and administrative leaders. Service line and site leadership teams are structured similarly. Service line leaders support their practice at all sites within the region; site leaders oversee a regional service line in addition to their local responsibility. Historically, this structure has allowed for broad knowledge development across leaders and ensures decisions are made with consensus from all affected sites and services.

The Hospital Incident Command System (HICS) was created in 1991 by the Orange County Emergency Medical Services Agency.[1] HICS is used to coordinate the response to an internal or external event that impacts normal operations. The structure enables common terminology and consistent procedures for emergency response across health systems. Examples of situations requiring HICS activation include hazardous materials incidents, mass casualty incidents, severe weather events, and infectious disease outbreaks.[2] The HICS structure is typically used to respond to a short-term incident that is isolated to a single location.

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Table. Challenges Faced During Hospital Incident Command System (HICS) Activation for COVID-19

Challenge	Solution
Ongoing preparedness to implement an emergency response plan	Clear policies and procedures for activation of HICS are combined with regular training for leadership team
Lack of an existing multisite, long-term emergency management system	Adjusted the HICS structure to increase physician involvement, create leadership redundancy, and clearly define accountability for decision-making
Need to prioritize patient care and effectively manage capacity in case of a surge in positive cases	Providers triaged outpatient visits and surgical procedures based on urgency of care need. Visits and procedures deferred or converted to telemedicine when appropriate
Safe and timely care for urgent, semi-urgent, and elective patient care	Created COVID-mitigated surgical and hospital spaces with enhanced screening and sterilization processes
Allocation of limited resources, including medical staff	Implemented physician and allied health labor pools to reallocate staff to surge areas based on skills and prior training. Provided inpatient education to outpatient staff to prepare for potential reassignments
Communication of rapid changes to patients	Leveraged multiple communication pathways to provide patients with reassurance and up-to-date information
Communication of rapid changes to staff	Provided staff with consistent daily messaging and frequent opportunities to ask questions of leadership

In early March 2020, the Northwest Wisconsin region of the Mayo Clinic Health System activated HICS in response to the potential for COVID-19 impacts to its communities based on rising international cases and concerns about personal protective equipment (PPE) supply levels. The first confirmed case in the region was identified in Eau Claire on March 19, 2020, with gradual community transmission.[3] As cases began to rise in the United States and positive cases were identified in the region, the focus of incident command shifted to management of COVID-19 within the organization. Response tactics included titration of the outpatient and surgical practices, creation of labor pools, and surge capacity planning. As cases reached a plateau, the need for integration of pandemic response activities into daily operations was recognized in coordination with continued monitoring of positive case volumes. Throughout the pandemic, a multidisciplinary and robust incident command structure was required to manage the systematic response.

PROBLEM

The HICS structure exists as a single-site solution to a short-term incident; utilizing this system to respond to a multi-month pandemic across a network of hospitals and clinics presented a number of challenges (Table). The use of HICS to manage a pandemic response required a detailed consideration of leadership role assignments, physician involvement and time allocation, and reporting structure of the emergency response system within the overall organization. Due to the matrix organizational structure, we needed to clearly define accountability for decision-making between incident-related problems and operational challenges. Throughout the response, effective collaboration across departments, sites, and shared services was critical.

In addition to the systematic challenges faced, we realized the need to prepare for the unknown of the pandemic. Specifically, we needed to be prepared for a rising surge in hospitalized patients with COVID-19 across our region, while safely providing necessary patient care. This meant identifying ways to prioritize care needs, ascertain and appropriately allocate needed resources, and source both provider and care staff labor.

Finally, robust and real-time communication of rapid policy changes to staff and patients was critical throughout the pandemic. It was clear we needed to address staff uncertainty and patient concerns quickly and effectively. We questioned what the most effective communication channel would be for these stakeholders and how to quickly convey the state of the virus and its impact on our operations.

SOLUTION

Hospital Incident Command System

Activation of HICS should be defined by a clear policy within the organization, specifically citing who has the accountability for activating HICS and the cadence of required action steps to stand up the system. At Mayo Clinic, the first person who identifies a hazard is to notify the house supervisor or administrator on call (AOC), who then has the authority to activate incident command for any event the leader determines is a disruption to normal operations. This leader now serves as the incident commander in the HICS structure and is responsible for the overall direction of the incident response.[4] The incident commander assigns the roles of section chiefs, officers, and technical specialists

The incident commander makes the determination of when the event has stabilized and incident command can be demobilized. For a successful HICS activation, it is critical that detailed training and tabletop exercises are held regularly to ensure any leader in the AOC rotation is prepared to serve as incident commander and any potential section chiefs understand the roles and structure of HICS.[5] Supplemental documentation detailing how the organization uses HICS, the procedure for activating and deactivating, the location of resources, and a roster of appropriate leaders for each role within the system assists in an efficient emergency response.

Recognizing the potential for an extended timeline of HICS activation for the system COVID response, 2 people were identified for each of the section chief roles to create redundancy and rotations among leaders. The role of incident commander was rotated across a team of senior level administrators in 2-week

increments. Importantly, the regional chief executive officer and chief administrative officer did not serve as incident commander to allow for objective decision-making and consistent leadership outside of the HICS structure. This early establishment of HICS allowed for a well-organized structure and quick reactivity to missteps or unanticipated issues.

Multidisciplinary HICS Involvement

In establishing the HICS structure for the COVID-19 pandemic response, the incident commander identified the need for multidisciplinary involvement from physicians, nursing, and administration. Consistent physician input across affected specialties, including critical care, primary care, and surgical specialties—provided a robust understanding of impacted areas and a sense of ownership across the medical staff. Critical areas of input and involvement in HICS from support departments included infection prevention and control, emergency preparedness, employee health, and public affairs. Additional support sections that are not typically included in HICS were added as critical areas to the pandemic, such as a senior services branch to coordinate with local skilled nursing facilities.

Physician participants in HICS were selected from the specialties considered to be critical to the emergency response. Physician administrative time was allocated based on the level of involvement as identified by the incident commander; for example, the infectious diseases chair was allocated a 1.0 full-time equivalent (FTE) to HICS, while the pulmonary and critical care chair was allotted 0.5 FTE. This physician administrative time was charged to the HICS accounting unit. A cardiovascular surgeon was selected as medical branch director based on the need for a physician with knowledge of clinic, surgical, and hospital operations. The medical branch director was assigned 1.0 FTE based on the scope of changes to be implemented and coordination of the physician labor pool. This level of physician FTE allotment was specific to the COVID-19 response and level of complexity required in the medical response. A typical emergency response activation may not require significant physician administrative time and would utilize services appropriate to the response, such as trauma providers for a mass casualty incident.

Multidisciplinary involvement in HICS also created the need for a clear definition of accountability between incident-related and operational decisions. AOC responsibilities were maintained separate from incident command to respond to non-COVID-19-related emergencies. Collaboration between regional incident command, enterprise incident command in Rochester, operations leadership at each hospital and clinic site, and shared support services was necessary to identify an effective pandemic response across a system while still maintaining normal operations. Clearly defined accountability and effective collaboration allowed for rapid decision-making in a historically consensus-driven organization.

Planning for a Surge

In anticipation of a rapid surge in positive cases as experienced in other areas of the United States and Europe, additional bed capacity availability at each hospital site in the region was identified—particularly focused on intensive care-level capacity in Eau Claire. Emergency credentialing and privileging policies were implemented to allow any Mayo Clinic credentialed and privileged provider to practice at any Mayo Clinic site, in any department, for the duration of the national emergency. In order to limit the number of individuals onsite, elective surgical procedures and outpatient visits were rapidly deferred, with the clinical practice declining to approximately 20% of normal volume. Physicians triaged all existing and requested outpatient appointments and surgical procedures based on urgency of care needs into emergent, urgent, semi-urgent, and elective categories. This was completed to determine which patients had the most acute needs and which patients could safely be deferred for 4 to 6 weeks. All suitable visits were shifted to video visits to ensure continuity of care while limiting the volume of patients on campus. If a patient was unable to complete a video visit, a phone visit was offered. Those patients whose acuity or care needs indicated they would benefit most from an in-person visit continued to see their provider on-site. Overall, this strategy allowed our practices to continue safely providing care in a way that best fit patient needs while minimizing negative effects to chronic disease management.

At a system critical access hospital, "COVID-mitigated" surgical and hospital spaces were formed with the goal of providing necessary care in a safe manner. The focus was to treat surgical patients whose health status, chance of cure, or long-term function would be diminished if procedures were delayed until after the pandemic. The virus-free space was created through robust presurgical patient testing and isolation, employee screening, and enhanced sterilization measures. The COVID-mitigated zones had designated traffic flows, separate entry and exit points with limited access, and facilities adjustments for sufficient air exchange.

A robust process was implemented to ensure the safety of surgical patients and staff. The department surgical team was expected to evaluate all cases on their need for surgery and submit those determined to be urgent and semi-urgent to a review committee. If the case was approved, the patient was contacted by a preoperative evaluation team 7 days prior to surgery to complete an enhanced COVID-19 screening. If the patient screened negative at this initial evaluation, a COVID-19 nasopharyngeal test was scheduled for 3 days prior to surgery. At 1 day prior to surgery, the preoperative evaluation team completed a final screening visit with the patient, and the surgeon completed a virtual visit to review the surgery and obtain informed consent. Upon arrival to the facility on the day of surgery, the patient was screened for symptoms and fever a final time. If at any point the patient reported symptoms or tested positive, the surgical procedure was cancelled and the patient was referred to their primary care provider for follow-up.

At a patient level, this robust process allowed us to ensure that patients were receiving necessary care to prevent long-lasting effects and were doing so in a safe manner with as minimal risk of exposure to the virus as possible. It also taught our care teams how to provide safe patient care in a pandemic, lessons that were shared with the specialty practices and facilities across the system. The learnings gained from implementation at the nearby critical access hospital allowed for the addition of a COVID-mitigated surgical area in the Eau Claire center. This enabled the separation of appropriate surgical cases by specialty across the 2 sites and the resumption of complex cases that could not be completed in the critical access hospital surgical space. Patients were able to receive urgent, semi-urgent, and elective care in the manner and facility most appropriate for them.

Physician and Allied Health Staff Labor Pools

Physician and allied health staff labor pools were created to prepare for a surge in cases and fill incremental roles created by the pandemic response. The physician labor pool, led by the medical branch director, was created to rapidly shift care providers from lower volume services into areas experiencing a surge based on the provider's specialty. A COVID medical officer of the day (CMOD) role was added as part of the medical branch of HICS and was rotated weekly across the medical branch director, chief medical officer, and outpatient practice chair. The CMOD was responsible for identifying and matching areas of the practice needing additional physician support with those departments with available labor, utilizing daily reports from the department managers.

To organize the physician labor pool, an inventory was first compiled of the physicians and advanced practice providers employed in the region, along with their prior training, experience, and current practice volume. Alternative assignments were then identified for each specialty practice based on the provider skillsets and training background, as well as the decline in clinic volume. In the case of a surge in intensive care-level inpatients, hospitalists, cardiovascular surgeons, and general surgeons would be moved to support the critical care unit. If additional hospitalist support was needed, internal medicine, cardiology, endocrinology, rheumatology, and nephrology providers would be shifted to support the hospital general medical floors. Behavioral health, cardiology, dermatology, family medicine, orthopedics, and pediatrics were all designated as emergency department backup in case of a surge. All other specialties were put into an available resource pool to be assigned to surge areas as needed by the CMOD. Once these assignments had been created, the above departments were trained on the electronic medical record functionality for their surge assignment.

An allied health staff labor pool was implemented to fill critical assignments that resulted from changes in operations. Employees shifted assignments to serve in testing site roles, as patient and employee symptom screeners, and as patient transport. Clinic-based nursing staff attended supplemental training on inpatient care and electronic medical record documentation in preparation for an increased need in hospital staff. Software typically used to manage volunteer assignments was leveraged to create and organize labor pool roles, gather available staff information from department managers, and notify staff of schedules and role assignments.

Communication with Patients and Staff

Early in the pandemic response, the need for frequent and transparent communication between regional senior leadership, incident command, front-line staff, and patients was identified. The pandemic led to rapid changes in policies and procedures that needed to be quickly communicated to patients, staff, and leaders across multiple venues. To reach patients, the following tactics were utilized: news releases, website banners, signage at physical locations, and patient portal notifications. As scheduled appointments and procedures were deferred or converted to virtual care, patients were contacted by scheduling staff to notify them of the change and offer an opportunity to respond to any questions or concerns. The leadership team also participated in virtual community events and newscasts to provide patients with the most up-to-date information. From the first quarter of 2020 to the second quarter of 2020, patient experience scores for likelihood to recommend care at our organization remained relatively consistent, which we view as a reflection of the effectiveness of our patient safety tactics and varied communication methods.

In the same week that the HICS structure was stood up in March, the regional chief executive officer, chief administrative officer, and chief nursing officer recognized the need to communicate the regional response tactics to staff. Initially, the team planned to share a prerecorded video with employees. The internal public affairs department advised that a regularly scheduled, interactive forum would be more effective, as it would allow for employee concerns to be addressed rapidly. The regional leaders began holding twice-weekly employee town halls on consistent days and times each week. Each forum was livestreamed to all employees and recorded for those who could not view in the moment. The platform Slido was used to solicit anonymous questions from staff, providing an opportunity to address concerns that otherwise may not have been escalated. In March and April, the employee forums averaged a total view count of approximately 1,400 views per forum and peak views of 2,200. The positive feedback received from staff indicates that the interactive forums were the most effective communication tool used during COVID-19. This has led to continued weekly forums throughout the pandemic response.

In addition to the twice-weekly forums, daily all-staff emails were utilized to reach employees. The emails were used to address pressing concerns, share regional planning updates, and inform

staff of urgent policy changes. In March and April, the daily emails had an average open rate of 64%.

LESSONS FOR THE FIELD

While our response to COVID-19 was generally effective, there were a number of lessons learned that will impact our future HICS activations for pandemic-level events. We recognize that we were late to comprehend the severity of the virus in the US and, as a result, were reactive rather than proactive in our response. Early activation of incident command as a monitoring function allowed us to quickly evolve into a phase of active response. The overall implementation of incident command, including leadership assignments and flexibility in structure, provided for a well-organized decision-making mechanism in a constantly changing environment.

When establishing the HICS assignments, we failed to adequately include leadership from our critical access hospitals into the structure and relied primarily on leaders based in the tertiary center. This resulted in communication errors and a lack of understanding of how policy changes affected other sites in the system. The extended HICS activation meant that the leaders serving as section chiefs were doing so in an incremental manner to their normal leadership roles for a prolonged period. This additional responsibility combined with the need to frequently and rapidly pivot directions, created the potential for burnout across staff.

Early in the pandemic response, we had substantial concerns about PPE levels and made the decision to scale back both inpatient and outpatient services. Focusing instead on aggressively acquiring additional PPE and proactive supply chain management would have allowed us to prevent deferrals of semi-urgent and elective patient care. In addition, our delay in implementing universal masking across all staff and patients led to avoidable employee exposures to the virus.

A high level of physician leadership promoted peer-to-peer communication of changes to provider workflows and ensured a robust plan for surge capacity staffing. Multidisciplinary involvement and clear lines of accountability helped facilitate rapid decision-making, but effectively managing across multiple sites with a single emergency response structure presented unanticipated challenges.

The necessity of effective communication with staff and patients during times of crisis cannot be understated. There is no such thing as over communicating. While we felt we were continuously communicating with employees at all levels through a wide range of tactics and a clear cadence, gaps in staff knowledge and understanding still existed. The potential for information overload in a pandemic is significant but can be overcome through consistent and transparent communication from leadership.

Overall, we recognize that a tremendous amount of leadership and physician time, along with numerous resources and expense, went into creating and maintaining this robust incident command system. We feel that the investment was worthwhile and has allowed our organization to respond to the pandemic with the least amount of waste possible.

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Appendix: Available at www.wmjonline.org.

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Renal Cell Carcinoma Presenting With Combined Cervical Lymphadenopathy and Cardiac Metastasis Without Inferior Vena Cava Involvement

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ABSTRACT

Renal cell cancer is the third most common urological malignancy following prostate and bladder malignancies. Cardiac metastases to the right side of the heart without inferior vena cava (IVC) involvement are exceedingly rare, with only a handful of cases described in the literature. Metastasis to the head and neck region is also rare, occurring in an estimated 1% of cases. Here we present a case of a patient with recurrent syncopal events secondary to renal cell carcinoma without IVC involvement, with metastases both to the right ventricle and cervical lymph nodes. To our knowledge, this is the first case that presents with both of these rare findings together and that highlights cancer screening in patients with high risk factors and new exam findings in patients with syncopal events having negative initial workup.

INTRODUCTION

Renal cell cancer (RCC) is the third most common urological malignancy following prostate and bladder malignancies.[1] The 5-year survival rate for RCC is 75% overall, which decreases to 12% among patients with distant metastatic disease.[2] The most common sites of RCC metastasis include the lung, liver, soft tissues, bones, and central nervous system; rarer sites of metastasis include the heart and the head and neck region.[3] The most common pattern of RCC spread to the heart is through inferior vena cava (IVC) involvement, which can occur in 5% to 15% of the cases.[3] Cardiac metastasis in the absence of vena cava involvement is exceptionally rare, with only a few cases reported in the literature. Metastasis to the head and neck region also is rare, occurring in an estimated 1% of cases.[4] Here we present a case with 2 extremely rare metastatic sites of RCC: cardiac metastasis without IVC involvement and metastasis to the head and neck region.

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CASE REPORT

A 61-year-old man with a past medical history of hypertension and schizophrenia with medicine nonadherence was brought to the hospital by family after an episode of syncope. The family reported that he had been having progressive left-sided neck swelling for the past 3 months, along with enlarging masses on his buttocks and left axilla. On initial presentation, he denied any complaints of pain and was adamant about going home only. His family also denied any previous syncope episodes. The patient had previously refused to seek medical care, but his family was able to convince him to come to the hospital after his syncopal episode. He had a 40 pack-year smoking history with no history of alcohol use or illicit drug use. His family denied any history of cancers in the family before. They also indicated he was getting intramuscular injections for his schizophrenia, but they were unsure about his compliance to all of his medications. After discussion with the family, he was admitted and workup was started.

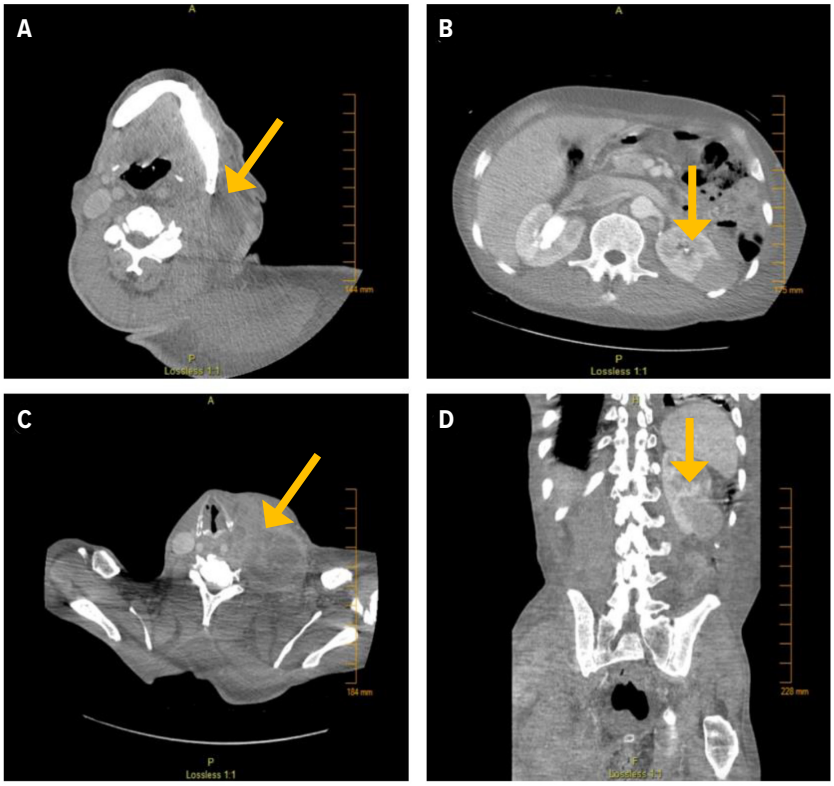
The patient's vital signs on initial presentation were as follows: blood pressure 128/96, pulse rate 92/min, respiratory rate 18/min, and temperature 36.9° C. On physical exam, he had a disheveled and cachectic appearance. He had a hard left-sided neck mass measuring 3x3 cm (Figure 1A), along with palpable diffuse left-sided axillary lymphadenopathy. Another nodular large mass measuring 11x8 cm was noted on the right lower back, about 6 cm lateral to the gluteal cleft, which was biopsied to have initial diagnosis. He also had left upper extremity swelling and erythema. The rest of his examination was unremarkable. Initially, it was sus-

pected that he had either lymphoma with distant metastases or a primary abdominal tumor with distant metastases and lymphadenopathy.

Initial electrocardiogram on presentation showed sinus rhythm with left axis deviation, without any evidence of atrioventricular blocks or bundle branch blocks. To rule out intracranial cause for syncope, computed tomography (CT) head was done and was negative for any acute findings. A left upper extremity ultrasound was significant for a nonocclusive thrombus involving the left axillary and high left brachial veins. CT with contrast of the neck revealed bulky left cervical lymphadenopathy measuring 5.4 x 6.1 cm and extending to the base of the neck, supraclavicular, axillary, and superior mediastinal regions (Figure 1C). Left axillary conglomerate lymphadenopathy measuring 9.5 x 6.0 cm was also noted. CT thorax identified a filling defect in the right ventricle extending to the apex measuring 6cm, a finding suspicious for malignancy. A mass effect on the left internal jugular vein resulted in partial occlusion. CT abdomen and pelvis was significant for multiple renal masses on the lateral aspect of the left kidney involving all poles (Figure 1B, 1D). Several of these lesions were cystic, while others were exophytic solid masses. Diffuse confluent pelvic adenopathy and massive inguinal lymphadenopathy were reported as well. Transthoracic echocardiogram was performed to further characterize the cardiac mass. A large mass measuring 4.8 cm x 3 cm extended from the apex to the mid-right ventricular cavity and right ventricular outflow tract (Figure 2). The deformation of the right ventricular free wall suggested malignant growth rather than a thrombus.

The patient's initial presentation of syncope was likely secondary to a combination of his intracardiac mass and left internal jugular occlusion leading to decreased venous return to the heart and a subsequent drop in cardiac output. CT-guided core biopsy was done from his lower back (gluteal mass), which came back as metastatic poorly differentiated carcinoma of likely renal origin. On immunohistochemistry, tumor cells expressed pancytokeratin, PAX-8, and vimentin and were negative for S-100, Melan-A, and RCC. Immunohistochemistry favored metastatic carcinoma of renal origin with a possibility of unclassified RCC. PAX-8 is a very useful marker for Mullerian carcinomas, whereas vimen-

Figure 1. Computed Tomography (CT) of Head, Neck, Abdomen, and Pelvis.



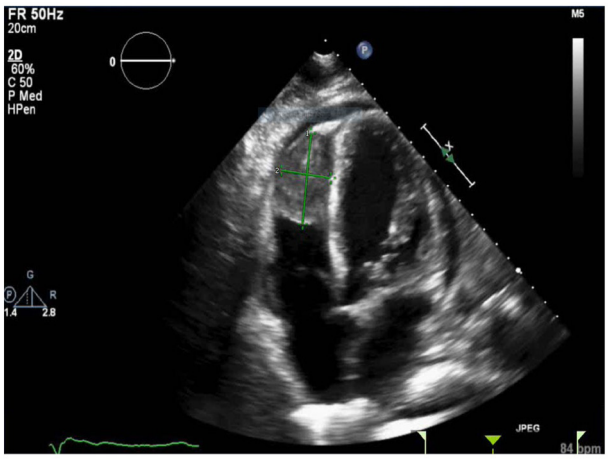
1A. CT neck. Arrow indicates 3 x 3 cm mass.

1B. CT abdomen and pelvis with contrast. Arrow indicates left renal mass.

1C. CT with contrast of the neck. Arrows indicates 5.4 x 6.1 cm bulky left cervical lymphadenopathy extending to base of the neck and supraclavicular, axillary, and superior mediastinal regions.

1D. CT abdomen and pelvis. Arrow indicates multiple renal masses on lateral aspect of left kidney involving all poles.

Figure 2. Echocardiogram: Transthoracic (TTE)



Cardiac mass 4.8 cm x 3 cm in the right ventricle.

tin helps distinguish RCC mimics. Due to unsure status of the patient about medical decision-making, his case was discussed with his family throughout the hospitalization and, after discussion with family, he was discharged with family care. Follow-up with oncology was arranged to discuss further workup and treatment options, but the patient did not follow up after discharge.

DISCUSSION

Metastatic disease of the heart is much more common than primary heart tumors. Cardiac tumors are often asymptomatic, but some can present with symptoms such as palpitations and syncope.[5] Metastasis from primary cancers to the heart can occur through 3 mechanisms: (1) hematogenous spread with and without IVC involvement, (2) direct spread from the IVC, and (3) intrathoracic lymphatic spread.[6,7] The most common pattern of RCC spread to the heart is through IVC involvement, which can occur in 5% to 15% of cases.[3] This mechanism of spread typically involves the right atrium. Cardiac metastasis without IVC tumor burden is rare. When IVC involvement is not present, RCC can spread to the heart hematogenously via the renal vein or through intrathoracic lymphatic spread. Hematogenous spread from the renal vein most commonly involves the right side of the heart, while lymphatic spread most commonly involves the left side of the heart.[8]

Our patient likely had hematogenous spread to the right side of the heart via the renal vein without IVC tumor burden, which became the reason for his presentation to the hospital with syncope. Moreover, he likely had lymphatic spread to the lymph nodes of the head and neck. Metastasis to the head and neck region is extremely rare and is estimated to be present in less than 1% of RCC cases.[4] Patients with solitary metastasis to the heart generally do well with surgical resection of the lesion.[9] However, because our patient had multiple sites of disease, along with bulky lymphadenopathy, he was not a candidate for surgical resection. He was referred to outpatient oncology for evaluation for palliative chemotherapy.

CONCLUSION

To our knowledge, this is the first case that presents RCC metastases to both the cervical lymph nodes and the right ventricle without IVC involvement—2 individually rare findings in 1 patient. Our patient presented with syncope, which can be related to his cardiac metastatis from RCC, as no other apparent cause of syncope was identified in his case. However, this may not occur in every case. Careful history should be taken with great detail, history of personal or family malignancies should be reviewed, and detailed physical examination and syncopal workup should be done to rule out other causes of syncope.

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Bacillus cereus: Beyond Gastroenteritis

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ABSTRACT

Introduction: *Bacillus cereus (B cereus)* has been found within the gastrointestinal flora. Due to its ubiquity, *B cereus* is usually considered a contaminant. However, it can cause serious infections in certain populations.

Case Presentation: A 39-year-old woman with refractory gastroparesis requiring gastric pacemaker with a jejunostomy tube and cervical cancer status post chemotherapy presented with fever and fatigue. Initial and repeat blood cultures (from peripheral and port-a-cath access) grew *B cereus* and the port-a-cath was removed. She was treated with appropriate antibiotics and bacteremia resolved.

Discussion: *B cereus* is often associated with toxin-mediated emetic or diarrheal gastroenteritis. However, in patients with prosthetic devices or intravenous (IV) drug users, *B cereus* can cause serious infection. Biofilms produced by *B cereus* attach to indwelling catheters, allowing persistent infection until catheter removal.

Conclusion: In patients with prosthetic devices or IV drug users, *B cereus* should be treated with appropriated antibiotics and any indwelling catheters should be removed.

INTRODUCTION

Bacillus cereus (B cereus) is a saprophytic, gram-positive, aerobic-to-facultative, spore-forming rod. Although most often associated with toxin-mediated emetic or diarrheal gastroenteritis, the spores of *B cereus* can persist in hospitals and contribute to nosocomial infections.[1] *B cereus* has been found within the gastrointestinal flora of prolonged hospitalized patients. Due to its ubiquity in nature, *B cereus* is considered a contaminant when isolated from sterile specimens.[1,2] However, in patients with prosthetic devices, neonates, those undergoing chemotherapy for leukemia, or those with a history of intravenous (IV) drug use, *B cereus* can be an important cause of infection.[2-5] Antibiotic-resistant biofilms produced by *B cereus* attach to indwelling catheters, allowing persistent infection until catheter removal.[1,6]

CASE PRESENTATION

A 39-year-old woman with history of severe refractory idiopathic gastroparesis requiring gastric pacemaker with gastrostomy and jejunostomy tube and cervical cancer status post chemotherapy presented to an outside hospital with fever, nausea, vomiting, and generalized weakness. Initial labs done at the outside hospital indicated that she had gram-positive bacteremia. She was transferred to our facility for further evaluation and treatment. Her other medical conditions included bipolar disorder, depression, systemic lupus erythematosus, and chronic pain syndrome. Her last chemotherapy was more than 5 years prior to presentation. She had undergone port-a-cath placement 7 years prior for chemotherapy and, given her history of no accessible peripheral veins, it was left in place for recurrent hydration needs. She lives alone, never smoked, and has a history of IV drug use with a urine drug screen positive for cannabinoids 3 months prior to her presentation. Upon arrival, her temperature was 98.5° F, heart rate 67 beats per minute, and blood pressure 122/75 mm of Hg. On exam, a port a-cath was noted on her left

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upper chest, no signs of infection. Gastrostomy and jejunostomy tube sites were clean. The rest of the physical exam was unremarkable. Upon further review, blood cultures from the outside hospital grew *B cereus*. Given the patient's history of angioedema due to vancomycin and penicillin allergy, she was given imipenem and levofloxacin while awaiting susceptibilities.

Susceptibility testing showed that the isolate was sensitive to sulfamethoxazole/trimethoprim, vancomycin, and imipenem and resistant to penicillin, clindamycin, and levofloxacin. The patient was switched to trimethoprim-sulfamethoxazole. Unfortunately, she developed a rash with use of sulfamethoxazole/trimethoprim, so she was switched back to imipenem. Repeat blood cultures, both peripheral and from the port-a-cath isolated the same *Bacillus*. The port-a-cath was removed as a part of source control, and the tip sent for culture grew the same isolate of *B cereus.* Repeat blood cultures obtained showed clearance of bacteremia. Transthoracic echocardiogram and transesophageal echocardiogram were performed and showed no evidence of vegetations. She was discharged to home on imipenem 500 mg IV every 6 hours for 14 days with a newly placed, peripherally inserted central venous line.

DISCUSSION

It was a commonly held belief that a positive *B cereus* culture likely represented contamination. However, an increasing number of case reports regarding non-anthrax *Bacillus* species causing systemic infection, including bacteremia and endocarditis, helps to raise awareness about *B cereus* as an important systemic pathogen. In 1963, Farrar published a review article of 12 cases of non-anthrax *Bacillus* causing serious infections.[7] Since then, multiple other cases of systemic *B cereus* infection have been reported.

Differentiation between true *B cereus* bacteremia and contamination can be challenging. A retrospective study of *Bacillus* species blood isolates of 1 hospital over 5 years found that 5% to 10% of isolates were pathogenic.[8] The incidence of bloodstream *B cereus* infection is higher in IV drug users, immunocompromised patients, and patients with central venous catheters compared to general population.[8,9] One meta-analysis done on 29 cases of *B cereus* between 2003 and 2012 at a teaching hospital in Japan showed that 69% of *B cereus* bloodstream infections were central venous catheter-related.[9] IV drug use and indwelling central venous catheters are independent risk factors for serious *B cereus* bacteremia and endocarditis.[10] *B cereus* can originate from cutaneous colonization, injection equipment, or even inhaled heroin.

The clinical presentation of *B cereus* bacteremia ranges from a mild fever to signs of sepsis like tachypnea, hypotension, persistent fever, nausea, and vomiting. The clinical course of fulminant *B cereus* septicemia is described by 2 phases: (1) a mild febrile illness lasting 6 to 14 hours with subtle symptoms of an overactive sympathetic nervous system and (2) a second short fulminant phase, marked by high fever (104° F-105.8° F) accompanied by major central nervous system disturbances, resulting in deep coma and brain stem dysfunction. Presence of an intravascular catheter is the most common feature of bacteremia caused by *Bacillus* species, and a significant proportion of patients have underlying malignancy or immunosuppression.

Endocarditis due to *B cereus* is rare and usually is associated with IV drug use, most commonly affecting the aortic or mitral valve. There has, however, been a case report of native valve *B cereus* endocarditis in a patient without any risk factors like IV drug use, immunodeficiency, or rheumatic heart disease.[11]

Treatment

B cereus bacteremia and endocarditis need to be treated with antimicrobials. Vancomycin is the preferred empiric antibiotic in suspected *B cereus* bacteremia with 100% susceptibility of isolates.[12] Penicillin and cephalosporins should not be the first choice, as many *B cereus* strains have beta-lactamase genes that are resistant to all beta-lactams other than carbapenems, although resistance to meropenem and imipenem has been encountered in the past. Interestingly, a literature review on 57 patients with *B cereus* infection showed that empirical treatment with beta-lactam antibiotics was associated with higher mortality.[12] Aminoglycosides, carbapenems, and fluoroquinolones can be used as a second line. Because there is evidence of clindamycin resistance, it can be used after sensitivity is confirmed.[13]

Although vancomycin and other antibiotics (eg, aminoglycosides, carbapenems, and fluoroquinolones) might be effective against free-floating *Bacillus*, they have poor activity against biofilm. Compared to free-floating *Bacillus*, *Bacillus* embedded in biofilm is resistant to antibiotics due to multiple mechanisms, including increased cell density, physical exclusion of the antibiotic, and physiological changes of individual bacteria.[14,15] Hence, source elimination is crucial, as infected lines and devices need to be removed.[16] In general, 7 to 14 days of antibiotic after removing the device is sufficient for *Bacillus* bacteremia.[17] Longer antibiotic course and further investigation are required for persistent bacteremia or symptoms. More complicated *Bacillus* infections, such as endocarditis, require 6 weeks of antibiotics.

CONLCUSION

This case demonstrates the capacity of *B cereus* in serious infection and the importance of not dismissing it as a contaminant when isolated in blood cultures of bacteremia patients with prosthetic devices. Although more commonly a cause of self-limited gastroenteritis, recognizing *B cereus* as a pathogen in bacteremia and beginning appropriate antibiotic therapy with source removal is crucial to prevent morbidity and mortality due to resulting systemic infections.

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Encephalopathy of Unclear Etiology: A Diagnostic Dilemma

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ABSTRACT

Introduction: Drug reaction with eosinophilia and systemic symptoms (DRESS) is a potentially fatal condition caused by drug exposure resulting in hypersensitivity reaction with involvement of different organ systems.

Case Presentation: We present a case of a 65-year-old man with a recent history of right total knee arthroplasty complicated by wound infection on a regimen of vancomycin who was transferred to our hospital for further management of fever, rigors, altered mental status, acute hypoxic respiratory failure, acute kidney injury, and development of an erythematous rash.

Discussion: DRESS syndrome was considered definite in this patient according to the European Registry of Severe Cutaneous Adverse Reaction Criteria, also known as RegiSCAR. To our knowledge, metabolic encephalopathy associated with multiorgan dysfunction resulting from vancomycin-induced DRESS syndrome has not been reported.

Conclusion: A thorough analysis of recent medication history is essential for the prompt identification and management of this condition.

INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a potentially fatal drug-induced hypersensitivity reaction with a long latent period from exposure to disease manifestation.[1] The reported mortality ranges from 3% to 10%,[2] and its prevalence has been reported at 2.18 per 100,000 patients.[2,3] Patients exhibit dermatological symptoms, fever, hematological abnormalities, and internal organ involvement.[4-7] Common culprits include but are not limited to antiepileptic drugs, antibiotics, sulfonamides, and antiviral medications.[1-9] The pathophysiology of DRESS is not fully understood, but is believed to be due to genetic predisposition in individuals exposed to the offending agents.[1,5] Reactivation of human herpes viruses (HHV) and other viruses also have been implicated in disease pathogenesis.[1,5,10-12]

We present a case of a 65-year-old man who experienced multiorgan failure and metabolic encephalopathy after vancomycin treatment. A thorough medication review is warranted for patients exhibiting neurological symptoms, multiorgan failure, and rash for prompt identification and treatment of DRESS.

CASE REPORT

A 65-year-old man was transferred to our facility for management of altered mental status, fever, rigors, acute hypoxic respiratory failure, acute renal failure, and diffuse maculopapular rash. Past medical history included nonocclusive coronary artery disease, major depressive disorder treated with venlafaxine and trazodone, and recent right total knee arthroplasty 2 months prior to the index visit.

One month after his arthroplasty, the patient developed wound dehiscence and drainage managed by washout and an intravenous (IV) regimen of vancomycin prior to discharge. He presented to an outside facility a month after initiating vancomycin with altered mental status, fever, and malaise. Shortly after, he developed acute respiratory distress, and an initial chest x-ray revealed bilateral pulmonary edema (Figure 1). He was intubated and mechanically ventilated. Based on his recent surgical history, the care team suspected septic arthritis and added meropenem

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Figure 1. Chest X-ray Revealing Extensive Interstitial and Alveolar Pulmonary Edema

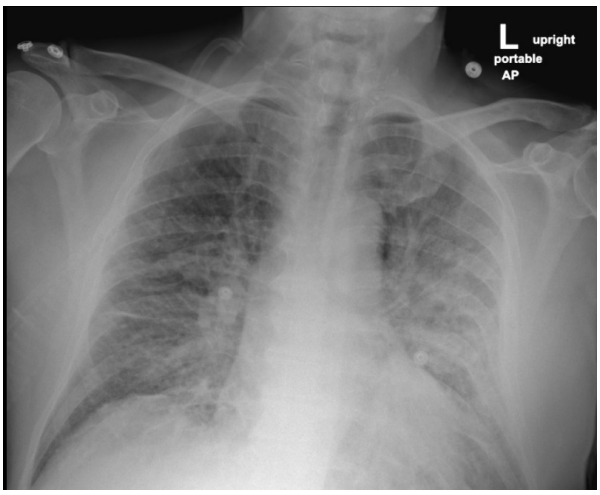
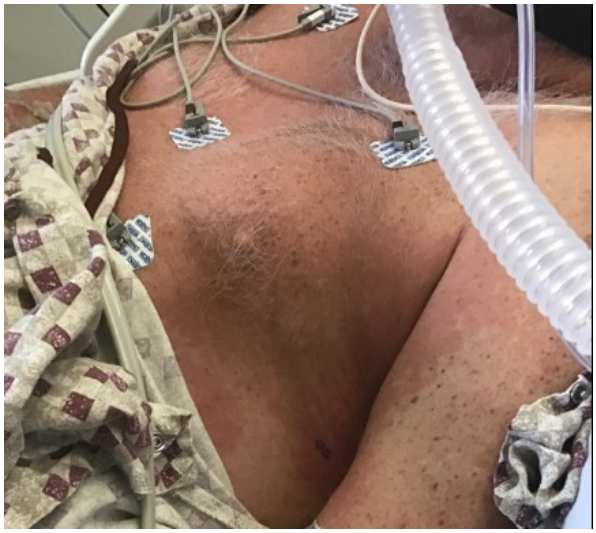


Figure 2. Photo of Index Patient's Chest and Left Arm



Erythematous, blanchable, poorly demarcated patches can be seen over the patient's chest and extremities with more pronounced erythema in the axilla. There are no areas of erosions, ulcerations, vesicles, or pustules seen.

to his preexisting vancomycin regimen. Despite being on broad-spectrum antibiotics, he continued to have altered mental status, fevers, and rigors. Serotonin syndrome was suspected due to long-term venlafaxine use and the presence of rigidity and clonus on physical examination. On his third day of hospitalization, the patient developed an erythematous rash with blanchable macules that coalesced into confluent patches involving his face, chest, and upper extremities, with more pronounced erythema in the axilla as well as desquamation involving the face, chest, and upper extremities. He had petechial macules and purpuric patches that were poorly demarcated on bilateral hands and feet, as well with surrounding significant pitting edema of the hands. There were no ulcerations, vesicles, or pustules on exam (Figure 2). This generalized rash initially was thought to be due to meropenem, which was discontinued and replaced with a regimen of piperacillin and tazobactam (Zosyn). He continued to be on vancomycin and was then transferred to our institution's medical intensive care unit.

At our facility, the patient received cyproheptadine for suspected serotonin syndrome, and his venlafaxine and trazodone were discontinued without resolution of symptoms. Laboratory analysis of blood and serum revealed elevated liver enzymes, creatinine, and procalcitonin levels as well as eosinophilia. His diffuse maculopapular rash persisted despite meropenem discontinuation and was thought to be "red man syndrome," which is a hypersensitivity reaction caused by degranulation of mast cells and basophils resulting in histamine release.[13] Thus, vancomycin was discontinued. However, he became agitated on his second day of hospitalization at our facility and continued to have decreased cognitive function.

A complete neurological workup on his third day of hospitalization included electroencephalogram and cerebrospinal fluid (CSF) analysis for infection and paraneoplastic syndromes. The electroencephalogram showed moderate diffuse slowing in a generalized fashion indicative of a generalized cerebral dysfunction and encephalopathy with no seizure activities observed. CSF analysis revealed pleocytosis with neutrophilic (72%) and eosinophilic (16%) predominance, as well as detectable numbers of red blood cells (Table 1); CSF cultures were negative for microbial infection. Serum and CSF paraneoplastic panels were also unremarkable, and there was no evidence of antinuclear antibodies and antineutrophil cytoplasmic antibodies. Magnetic resonance imaging of the brain was negative for encephalitis yet showed chronic microvascular changes. Arthrocentesis of the knee was negative for malignant

Table 1. Cerebrospinal Fluid Cell Count and Differential

Result	Value/Units	Normal/Units
Total nucleated cells	19/µL	05/µL
Red blood cells	7,100/µL	0–0/µL
Blast	0%	0–0%
Neutrophils	72%	0–6%
Lymphocytes	5%	40–80%
Monocytes	7%	15–45%
Eosinophils	16%	0–0%
Glucose	65 mg/dL	40–70 mg/dL
Total protein	37 mg/dL	15–45 mg/dL
Color	Colorless	
CSF-immunoglobulin	2.6 mg/dL	0.0–6.6 mg/dL
CSF-albumin	22.3 mg/dL	15.0–32.0 mg/dL
IgG/albumin	0.12	0.0–0.27

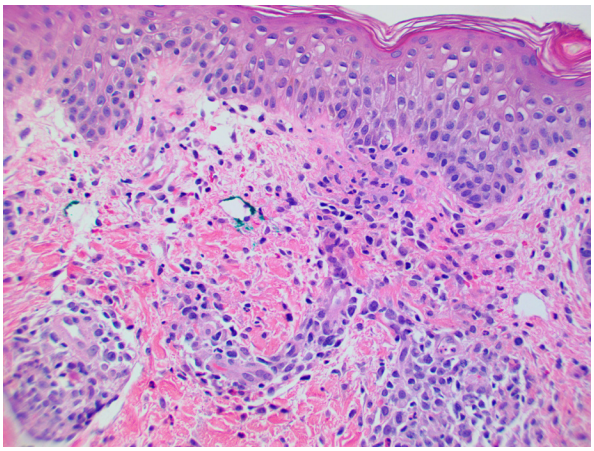
Abbreviation: CSF, cerebrospinal fluid

Table 2. European Registry of Severe Cutaneous Adverse Reaction (RegiSCAR) Patient Score

RegiSCAR Item		RegiSCAR Item Score if Present		RegiSCAR Item Score if Absent	RegiSCAR Item Score in Index Patient	Score in Index Patient
Fever ≥38.5° C		0		-1	Yes	0
Enlarged lymph nodes (>1 cm size, at least 2 sites)		1		0	No	0
Eosinophilia						
≥700 or ≥10%	≥1,500/μL ≥20%	1	2	0	Yes (3,400 cell/μL)	2
Atypical lymphocytes		1		0	No	0
Rash ≥50% of body surface area		1		0	Yes	1
Rash suggestive (≥2 of facial edema, purpura infiltration, desquamation)		1		0	Yes	1
Skin biopsy suggesting alternative diagnosis		-1		0	No	0
Disease duration >15 days		0		-2	Yes	0
Organ involvement						
1 organ	≥2 organs	1	2	0	Yes (≥ organ systems)	2
Investigation for alternative cause (blood cultures, antinuclear antibodies, serology for hepatitis viruses, mycoplasma, chlamydia) ≥3 done and negative		1		0	Yes	1
Total						7

*Total score <2: excluded; 2-3: possible; 4-5: probable; ≥6: definite.

Figure 3. Punch Biopsy From Left Lateral Chest With Hematoxylin and Eosin Staining Revealing Patchy Rocal Interface Dermatitis With Scattered Eosinophils and Neutrophils. (Magnification: 200x)



cells or infection. On day 4 of hospitalization, the patient was extubated to bilevel positive airway pressure, and dexmedetomidine was continued for his agitation. Since his symptoms were not consistent with serotonin syndrome, cyproheptadine was discontinued. In response to progressively worsening renal function and eventual acute renal failure secondary to acute tubular necrosis, he received continuous renal replacement therapy.

Due to the persistence of rash, multiorgan dysfunction, and eosinophilia, DRESS syndrome was suspected. A punch biopsy from the patient's lateral chest revealed patchy focal interface dermatitis with scattered eosinophils and neutrophils in the superficial to mid-dermis (Figure 3). His RegiSCAR (Registry of Severe Cutaneous Adverse Reaction) Criteria score was calculated (Table 2) and suggested a definite diagnosis of vancomycin-induced DRESS syndrome. Vancomycin was discontinued, and he was treated with high-dose IV methylprednisolone. This treatment was gradually tapered and replaced with a regimen of oral corticosteroids for 4 to 6 weeks to avoid relapse. With these measures, the patient's symptoms resolved completely, and follow-up neurological evaluation revealed a full recovery of his cognitive function and return of renal, pulmonary, and liver function back to baseline. He was discharged 27 days after hospital transfer.

DISCUSSION

DRESS syndrome is an uncommon but potentially life-threatening drug-induced hypersensitivity reaction.[1-9] Its clinical presentation is highly variable and, as a result, diagnosis requires a high index of clinical suspicion. DRESS is usually supported by a history of exposure to a high-risk medication within 2 to 8 weeks of systemic symptoms; appearance of a progressively morbilliform, erythematous, or exfoliative dermatitis; associated hematological abnormalities; and systemic organ involvement.[6,14] Delayed presentation after initiation of the offending medication is usually longer than most drug eruptions, which is 4 to 9 days for morbilliform drug eruptions and about 1 to 4 weeks for Stevens-Johnson syndrome/toxic epidermal necrolysis.[7,15]

Due to the atypical features of respiratory distress, altered sensorium, and multiple organ dysfunction before the rash appeared, DRESS syndrome initially was not considered. Given the patient's history of knee replacement with subsequent wound dehiscence, sepsis complicated with acute respiratory distress syndrome, and multiorgan dysfunction, metabolic or infectious encephalopathy was suspected. However, there was no identified infectious source. Our patient's rigidity, which initially raised concerns for serotonin syndrome, was considered to be secondary to his toxic metabolic encephalopathy secondary to multiorgan dysfunction. Persistence of these symptoms following several days of discontinuation of venlafaxine combined with cyprohep-

tadine administration and the development of a generalized skin rash made serotonin syndrome very unlikely.

Other inflammatory causes of disease also were considered, though such diagnoses were less consistent with his physical signs, symptoms, and negative results for autoimmune disease, infection, and paraneoplastic conditions. The patient also was evaluated for Stevens-Johnson syndrome and toxic epidermal necrolysis, which are associated with epidermal necrosis and mucosal involvement on at least 2 sites in 80% of cases.[14] However, eosinophilia is uncommon, and our patient's biopsy findings did not match the full-thickness epidermal necrosis generally seen with these conditions. Acute generalized exanthematous pustulosis, which usually starts <3 days after drug exposure, also did not fit the patient's clinical profile. Discontinuation of vancomycin corresponded to cognitive and functional improvements and supports our final diagnosis of DRESS syndrome.

CONCLUSION

A high index of clinical suspicion for DRESS is warranted for patients with a recent history of vancomycin who exhibit neurologic and pulmonary symptoms, multiorgan dysfunction, and no evidence of infectious or neoplastic disease with latent development of rash.

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Heart Disease, Advanced Age, Minority Race, and Hispanic Ethnicity Are Associated With Mortality in COVID-19 Patients

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ABSTRACT

Background: The objective of this study was to determine the associations between heart disease, obesity, and demographic factors and increased COVID-19 mortality.

Methods: We extracted deidentified patient-level data from the Froedtert Health System and Children's Hospital of Wisconsin and used descriptive statistics and multivariable logistic regression to characterize relationships between heart disease, obesity, age group, sex, race and ethnicity, and mortality following COVID-19 diagnosis.

Results: We found heart disease (adjusted odds ratio [AOR] 2.85; 95% CI, 2.11-8.83) and other demographic factors are significant predictors of increased mortality in COVID-19 patients. However, obesity was not a significant predictor of mortality (AOR 1.04; 95% CI, 0.53- 3.10).

Discussion: These unique results indicate some comorbid conditions and patient demographics contribute more strongly to mortality in COVID-19 patients.

INTRODUCTION

COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an ongoing global pandemic since its emergence in late 2019. While vaccines against SARS-CoV-2 are now widely available, the virus continues to spread, resulting in a profound impact on our health care system. Evidence suggests SARS-CoV-2 disproportionately affects certain populations, especially those with comorbid conditions[1-3] and some minority racial and ethnic groups.[4] While studies show comorbid conditions and patient demographics (eg, age, sex, race, ethnicity) are independently associated with poor health outcomes,[1-4] it is unclear which of these contributes more strongly to mortality in COVID-19 patients. Understanding these relationships is important for providing care as it informs which patients are potentially predisposed to poor outcomes following a COVID-19 diagnosis.

The purpose of this study was to explore the associations between mortality in COVID patients and comorbidities—specifically heart disease and obesity—and other demographic factors in a sample of patients in the Milwaukee, Wisconsin greater metropolitan area to understand further how the state has been affected.

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METHODS

Data Source

Data for this study were obtained from the Clinical and Translational Science Institute (CTSI) of Southeast Wisconsin's Clinical Research Data Warehouse (CRDW). The CRDW contains patient-level information for all encounters, including demographics, diagnoses, and diagnostic results. Institutional contributors to this database include the Froedtert Health System and Children's Hospital of Wisconsin (CHW). The database is maintained and updated weekly by the biomedical informatics team at the CTSI. TriNetX (a pharma-sponsored cohort query and analysis tool) was used to identify eligible patients. The Honest Broker data extraction tool was used to extract deidentified patient demographic data from TriNetX.

Patient Cohort

The study population included all patients with an encounter in the Froedtert Health System or CHW and a subsequent diagnosis

of COVID-19 based on International Classification of Diseases, Tenth Revision (ICD-10) code U07.1 between January 1, 2020 and November 18, 2020. Within this population, the 3 most common ICD-10 codes for each condition were used to classify individuals as having heart disease (I50, I50.9, I51.9) and/or obesity (E66, E66.9, E66.0).

Demographic data including shifted birth date, vital status (alive or deceased as of November 18, 2020), sex, race, and ethnicity, were extracted. Because of low numbers, individuals who identified as American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiracial, other, and patients who chose not to disclose their race were grouped into a single "other" category.

Statistical Analysis

Descriptive statistics were used to report patient characteristics, including *t* tests to describe differences between alive and deceased patients for normally distributed data. Multivariate logistic regression was used to identify relationships between mortality and each predictor, while also controlling for each predictor analyzed. All statistics were performed using R version 1.31093. For all statistical analyses, 2-sided *P* values were used ($P < .05$ was statistically significant).

Table 1. Patient Characteristics

Characteristic	Alive (n=8567) No. (%)	Deceased (n=243) No. (%)	*P* value
Age			<0.001
0 – 24	1094 (12.8)	2 (0.8)	
25 – 44	3127 (36.5)	10 (4.1)	
45 – 64	2676 (31.2)	37 (15.2)	
65 – 84	1426 (16.6)	125 (51.4)	
85+	244 (2.8)	69 (28.4)	
Comorbidity			
Heart disease	883 (10.3)	126 (51.9)	<0.001
Obesity	2441 (28.5)	95 (39.1)	<0.001
Sex			<0.001
Female	5241 (61.2)	113 (46.5)	
Male	3325 (38.8)	130 (53.5)	
Race			0.04
White/Caucasian	5534 (65.2)	142 (58.4)	
Black/African American	2060 (24.3)	77 (31.7)	
Asian	206 (2.4)	8 (3.3)	
Other	684 (8.1)	16 (6.6)	
Ethnicity			0.52
Non-Hispanic	7725 (93.1)	19 (7.8)	
Hispanic	572 (6.9)	224 (92.2)	

T test for significance was performed to assess the difference between groups. $P < .05$ was considered significant.

RESULTS

Categorical Data

A total of 8810 patients who fit the inclusion criteria were seen in the Froedtert Health System or CHW between January 1, 2020 and November 18, 2020. Of the 8810 COVID-19 patients, 1009 (11.5%) were diagnosed with heart disease and 2536 (28.8%) were diagnosed with obesity. A total of 243 (2.8%) patients in the study died.

Among the COVID-19 patients in the study, deceased patients were more likely to be over 65, have heart disease and be obese (all $P < .0001$) (Table 1). Deceased patients also were more likely to be male ($P < 0.001$) and White or Caucasian ($P = 0.04$). However, it is important to note that 65% of all patients and 58.4% of all deceased patients were White or Caucasian. Additionally, only 24.5% of all patients in the study were Black or African American, yet 31.7% of all deceased patients were Black or African American.

Logistic Regression

In unadjusted analyses (Table 2), ages 45-64 years (odds ratio [OR] 7.56; 95% CI, 1.82-31.40), 65-84 years (OR 47.95; 95% CI, 11.85-194.05), and 85+ years (OR 154.68; 95% CI, 37.71-634.55) were significant predictors of death following a COVID-19 diagnosis. Additionally, both heart disease (OR 9.37; 95% CI, 7.22-12.17) and obesity (OR 1.61; 95% CI, 1.24-2.09), along with male sex (OR 1.81; 95% CI, 1.40-2.34) and Black or African American race (OR 1.46; 95% CI, 1.10-1.93), were significant predictors of death.

In the adjusted analysis (Table 2), obesity was no longer independently associated with increased mortality, while Asian race and Hispanic ethnicity became significant. The adjusted analysis showed similar increases in likelihood of death with increased age and male sex. Patients with heart disease were 2.85 times more likely (adjusted odds ratio [AOR] 2.85; 95% CI, 2.11-3.83) to die following a COVID-19 diagnosis than those without heart disease. Additionally, Black patients were 2.11 times more likely (AOR 2.11; 95% CI, 1.55-2.90) and Asian patients were 3.96 times as likely (AOR 3.96; 95% CI, 1.77-8.86) to die compared to White patients. Hispanic patients were 2.67 times more likely (AOR 2.67; 96% CI, 1.18-6.07) than non-Hispanic patients to die. The Figure shows a forest plot indicating the adjusted odds ratio for each predictor variable.

DISCUSSION

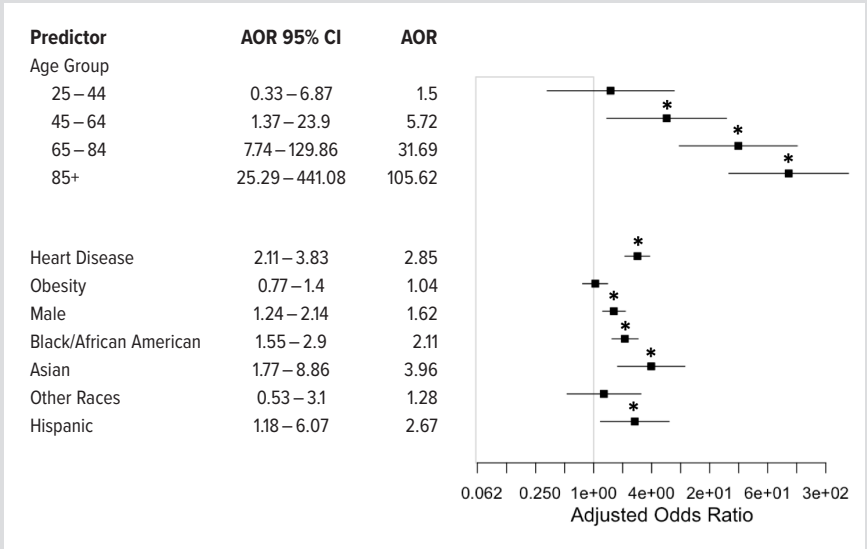
In this study, we found significant associations between heart disease, advanced age, male sex, minority race, and Hispanic ethnicity and increased mortality in COVID-19 patients. While other studies indicate obesity is associated with poor outcomes in COVID patients,[3,5] obesity was not a significant independent predictor of mortality when controlling for other factors in our study. These findings are unique, as we show underlying heart disease is more strongly associated with mortality than obesity in patients diagnosed with COVID-19. This suggests that comorbidities contribute in different ways to poor outcomes in COVID-19 patients, but much of these relationships is yet to be delineated. Characterizing and quantifying these relation-

Table 2. Logistic Regression Predicting Death Among COVID-19 Patients (N=8810)

Variable	Unadjusted *P* Value	Unadjusted Odds Ratio (95% CI)	Adjusted *P* value	Adjusted Odds Ratio (95% CI)
Age				
0 – 24	Referent		Referent	
25 – 44	0.47	1.75 (0.38 – 7.99)	0.6	1.50 (0.33 – 6.87)
45 – 64	< 0.05	7.56 (1.82 – 31.40)	0.016	5.72 (1.37 – 23.9)
65 – 84	< 0.001	47.95 (11.85 – 194.05)	< 0.001	31.69 (7.74 – 129.86)
85+	< 0.001	154.68 (37.71 – 634.55)	< 0.001	105.62 (25.29 – 441.08)
Comorbidity				
No heart disease	Referent		Referent	
Heart disease	<0.001	9.37 (7.22 – 12.17)	< 0.001	2.85 (2.11 – 3.83)
No obesity	Referent		Referent	
Obesity	< 0.001	1.61 (1.24 – 2.09)	0.78	1.04 (0.77 – 1.4)
Sex				
Female	Referent		Referent	
Male	< 0.001	1.81 (1.40 – 2.34)	<0.001	1.62 (1.24 – 2.14)
Race				
White/Caucasian	Referent		Referent	
Black/African American	< 0.05	1.46 (1.10 – 1.93)	< 0.001	2.11 (1.55 – 2.90)
Asian	0.26	1.51 (0.73 – 3.13)	< 0.001	3.96 (1.77 – 8.86)
Other	0.73	0.91 (0.54 – 1.54)	0.58	1.28 (0.53 – 3.10)
Ethnicity				
Non-Hispanic	Referent		Referent	
Hispanic	0.58	1.15 (0.71 – 1.84)	0.019	2.67 (1.18 – 6.07)

A univariate and multivariate logistic regression was performed with age group, underlying health condition, sex, and race as predictors of mortality following a COVID-19 diagnosis.

Figure. Forest Plot of Logistic Regression (N=8810)



Underlying health conditions and patient demographics as predictors of mortality following COVID-19 diagnosis. We report each predictor's adjusted odds ratio (AOR) (black boxes) and their respective 95% CI (bars) (*P< 0.05) compared to each predictor's referent.

ships indicates which comorbidities clinicians should be aware of while providing appropriate care for COVID patients.

Our patient demographic results are valuable as they indicate which characteristics in COVID patients more strongly contribute to mortality. While it is known that advanced age is associated with COVID-19 mortality,[3] our analyses show how different age groups are significantly affected. Similar to other studies, our findings show that Hispanic ethnicity and Black/African American and Asian races are associated with increased mortality in COVID-19 patients.[6-8] However, our findings uniquely depict how this relationship is stronger for Asian race. In fact, besides advanced age, Asian race is the strongest predictor of mortality in COVID-19 patients for this patient population.

In a similar study of the greater Milwaukee region, Egede and colleagues report Hispanic patients, but not non-Hispanic Black patients, were more likely to die from COVID-19 than White patients, and they propose this may be a product of Milwaukee's long history of structural racism.[7,9,10] We believe our results indicating Hispanic ethnicity and Asian race as significant predictors of death from COVID-19 could be similarly explained by structural racism. Our findings, in combination with those of Egede and colleagues,[7] amplify the need for future studies to investigate the roots of racial disparities in Milwaukee to develop alleviation strategies.

Limitations

One major limitation of our results lies in the data extraction method. We extracted data on patients with a COVID-19 ICD-10 code. Although all patients had COVID-19, it is unknown whether the viral infection itself was their final cause of death. Moreover, due to the nature of the CRDW data extraction from the electronic medical record, there may be patients in this data set who died but whose record was not updated at the time of data extraction.

Additionally, our use of COVID-19 diagnosis, rather than positive polymerase chain reaction (PCR) test, may be a limitation. We were unable to obtain data on patients who tested positive for SARS-CoV2 but never obtained a COVID-19 diagnosis, which includes patients who either recovered or developed worsening symptoms and died in their homes.

Another important limitation to consider is the nature of studying heart disease and obesity in the same multivariate model, as these conditions are often associated with one another thereby

explaining the lack of significance observed with obesity when examining both heart disease and obesity. This could be considered an overcorrection if heart disease is an intermediate step in the causal pathway from obesity to death, but this complex relationship has yet to clearly be delineated. Based on our unadjusted odds ratios, we conclude obesity is still associated with COVID-19 mortality, but the multivariate model indicates heart disease is a more significant predictor, warranting increased caution and vigilance in clinical scenarios.

Future Directions

In this study, we established heart disease as an important predictor of mortality in patients with COVID-19. However, there are many other chronic conditions that may increase susceptibility to death from COVID-19, such as diabetes, chronic respiratory illnesses, autoimmune diseases, and many others. Future studies should investigate the roles of other chronic conditions, in addition to heart disease and obesity, in COVID-19 mortality to better understand which conditions predispose patients to worse health outcomes. Moreover, they should incorporate additional demographic factors, such as income and ZIP code to improve our understanding of the social determinants of health as it pertains to COVID-19. Delineating these relationships will aid clinicians in considering factors that may predispose their patients to worse COVID-19 outcomes.

CONCLUSION

In this brief report, we have demonstrated heart disease, but not obesity, is significantly associated with mortality in COVID-19 patients. Additionally, we characterized the significant associations between advanced age, minority race, and Hispanic ethnicity and COVID-19 mortality. Future studies are needed that include more comorbid conditions, such as diabetes and chronic respiratory illnesses, and demographic factors, such as ZIP code and income.

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Effect of Genicular Nerve Radiofrequency Ablation for Knee Osteoarthritis: A Retrospective Chart Review

Brody Fitzpatrick; Matthew Cowling, DO; Michelle Poliak-Tunis, MD; Kathryn Miller, MD

ABSTRACT

Background: Genicular nerve block and radiofrequency ablation improve pain and function in patients with knee osteoarthritis. We aimed to evaluate the efficacy of these procedures and to identify factors predicting outcomes.

Methods: We conducted a chart review of 18 patients referred for these procedures from our clinic. Pain scores were collected before and after the procedure and at a follow-up visit. Functional measures were recorded before the procedure.

Results: Both procedures reduced pain in the post-procedure and follow-up settings, and the Western Ontario and McMaster Universities Osteoarthritis Index correlated with the paired differences of pre- and follow-up pain scores.

Discussion: These procedures provided significant pain relief, and the Western Ontario and McMaster Universities Osteoarthritis Index may help identify appropriate candidates for these procedures.

INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis and is a leading cause of disability in the United States.[1] Thirty-five million people in the US are 65 and older, and over half of them have radiographic evidence of osteoarthritis in at least 1 joint.[1] In addition to an aging population, approximately two-thirds of US adults are overweight. Obesity is the largest modifiable risk factor of knee osteoarthritis (KOA) and can complicate its management.

To address the needs of people suffering from this condition, international management guidelines have been developed to recommend evidence-based care for osteoarthritis.[2] These guidelines are in agreement that first-line care for KOA should prioritize the appropriate exercise and weight loss prior to medications, injections, and joint replacement. Despite the existence of well-developed osteoarthritis management guidelines, the characteristic management of osteoarthritis is not concordant with these recommendations, suggesting that the majority of people do not receive appropriate care.[3] In an effort to address this evidence/practice gap, there is growing international interest in the development and dissemination of coordinated osteoarthritis management programs designed specifically to ensure that patients are supported in receiving quality KOA care.

As osteoarthritis progresses, a total knee arthroplasty has been shown to be an effective treatment.[4] However, patients with body mass index (BMI) ≥ 40 are often excluded from joint replacement due to higher surgical risk. In the last decade, the genicular nerve block (GNB) and radiofrequency ablation (RFA) have been shown to improve outcomes in KOA by reducing pain and improving function.[5] During these procedures, the patient initially receives injections with an anesthetic (usually lidocaine) under fluoroscopic guidance to block the superior medial, superior lateral, and inferior medial genicular nerves. If they report a satisfactory response to the GNB (≥50% pain reduction), they may go on to receive an RFA, wherein alternating current is used to deliver thermal energy to an area of nerve tissue. This causes cell death, thus decreasing pain signals from that area. Patients who undergo RFA may receive up to 12 months of pain relief.[6]

Studies evaluating the efficacy of GNB and RFA have shown

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Studies evaluating the efficacy of GNB and RFA have shown promise in pain management in KOA; however, it is not known if these procedures are beneficial to patients receiving high-quality care and little is known regarding patient factors (eg, BMI, functional status) that predict outcomes of these procedures. It is also unknown if patients who receive guideline-recommended care for KOA will receive additional benefit from GNB and RFA. Therefore, we aimed to evaluate the efficacy of these procedures in a population of patients meeting all KOA quality care indicators and to identify factors predicting outcomes.

METHODS

We conducted a retrospective chart review on 21 patients with primary KOA who were referred for a GNB or RFA from an osteoarthritis management program between October 1, 2017 and May 31, 2019. Patients seen in this program have higher levels of pain and dysfunction compared to the general KOA population. In addition, unlike patients managed in typical care, patients seen in this program receive guideline-based care. Ultimately, 18 patients completed a procedure; therefore, only the information from these patients' charts was utilized for statistical analyses.

Information obtained from medical charts included demographics; BMI; tobacco smoking status; prior treatments; procedure type and date; numeric rating scale (NRS) scores; osteoarthritis indices, including Knee Injury and Osteoarthritis Outcome (KOOS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC); Veterans RAND (VR)-12 scores; and functional tests, including timed up-and-go, single-leg stance, and 30-second chair rise.

NRS scores were collected in the peri- and post-procedural settings within the hospital. Scores also were collected at a follow-up visit, with a median of 46 (range 1-279) days post-procedure. Of the VR-12, osteoarthritis indices, and functional measures collected from the patients' medical records, only those completed immediately prior to a GNB or RFA were included in statistical analyses.

Data was summarized by mean (SD) or N (%). Comparison of NRS scores over time between groups utilized mixed effects ANOVA with time (pre, post, and follow-up), procedure (GNB or RFA), and their interaction as fixed effects and subject identification as a random effect. The mixed effects ANOVA model controlled for surgery number and leg (right, left, bilateral) as fixed covariates. *T* tests were used for single time point comparisons between procedural groups; correlations (95% CI) were calculated based on Pearson's correlation coefficient. Analyses were conducted using R for statistical computing version 3.5; all tests were 2-tailed tests with $\alpha = 0.05$.

RESULTS

Of the 18 patients who underwent a GNB, 5 (27.8%) proceeded to undergo an RFA following 1 or more GNBs. In summation, the patients completed 26 GNBs and 7 RFAs. There were no statistically significant differences between ages, BMIs, VR-12, osteoarthritis indices, or functional measures of the procedure groups (Table 1). There were also no statistically significant differences in the NRS scores between nonmorbidly obese (BMI < 40) and morbidly obese (BMI ≥ 40) patients at any of the measurement intervals, nor were there any differences in the average NRS reduction in the post-procedural and follow-up intervals between these groups. Lastly, there were no statistically significant correlations comparing the differences in the pre- and post-procedural NRS scores to BMI, VR-12, osteoarthritis indices, or functional measures.

Table 1. Patient Characteristics by Group[a]

	Genicular Nerve Block (n = 26)	Radiofrequency Ablation (n = 7)
Unique patients (n = 18)	18 (100%)	5 (27.8%)
Leg		
Bilateral	12 (46.2%)	1 (14.3%)
Left	6 (23.1%)	3 (42.9%)
Right	8 (30.8%)	3 (42.9%)
Age – year	61.7 (15.2)	61.6 (6.7)
Body mass index	38.8 (8.1)	41.6 (5.7)

[a]Reported as mean (SD) or N (%)

When comparing the pre- and post-procedure NRS scores of patients who underwent a GNB, the average NRS score decreased from 6.6 to 1.6 ([difference] -5.0; 95% CI, -6.1 to -3.9; $P < 0.001$). In addition, the average pre-procedure and follow-up NRS scores decreased from 6.6 to 4.5 (-2.1; 95% CI, -3.3 to -0.9; $P = 0.001$). Similar results also were found for patients who underwent an RFA, with average pre- and post-procedure NRS scores decreasing from 8.1 to 5.4 (-2.7; 95% CI, -4.8 to -0.7; $P = 0.010$) and average pre-procedure and follow-up NRS scores decreasing from 8.1 to 5.1 (-3.1; 95% CI, -5.5 to -0.6; $P = 0.016$). While not statistically significant ($P = 0.052$), there was a trending interaction when comparing the differences in the average post-procedural change in NRS scores between procedure groups, demonstrating a 23% greater reduction in NRS scores for patients who underwent a GNB compared to those who underwent RFA. (See Table 2.)

Collection of functional measures was rather incomplete, with most variables having data for ~12 to 15 GNB and 1 to 2 RFA patients. Therefore, for correlation analyses of these variables with change in NRS, we grouped GNB and RFA patients together. The relationship between WOMAC total score and the paired differences of pre- and follow-up NRS scores for GNB and RFA demonstrated a significant correlation of -0.668 (95% CI; -0.932 to -0.008), signifying that patients who had higher (worse) WOMAC scores tended to receive more pain reduction from a GNB or RFA than patients with lower (better) WOMAC scores. (See Table 3.)

Table 2. Summary of Numeric Rating Scale Over Time Between Groups[a]

Procedure	Time	Mean (95% CI)	Difference (95% CI)	*P* value	Interaction	*P* value
GNB	Pre	6.6 (5.5 to 7.7)	–		Post change difference	
	Post	1.6 (0.5 to 2.7)	-5.0 (-6.1 to -3.9)	<0.001	-2.3 (-4.6 to 0.02)	0.052
	Follow-up	4.5 (3.3 to 5.7)	-2.1 (-3.3 to -0.9)	0.001		
RFA	Pre	8.1 (6.1 to 10)	–		Follow-up change difference	
	Post	5.4 (3.4 to 7.4)	-2.7 (-4.8 to -0.7)	0.010	1.0 (-1.8 to 3.7)	0.484
	Follow-up	5.1 (2.6 to 7.5)	-3.1 (-5.5 to -0.6)	0.016		

Abbreviations: GNB, genicular nerve block; RFA, radiofrequency ablation.
[a]Reported as mean (95% CI) from mixed effects ANOVA controlling for surgery number and leg (left, right, or bilateral).

Table 3. Correlation (95% CI) of Functional Variable Prior to Surgery and Change in Numeric Rating Scale as Post and Follow-up Time Points

	Postoperative Correlation			Follow-up Correlation		
Variable	**N**	**Correlation (95% CI)**		**N**	**Correlation (95% CI)**	
VR-12 - MCS	25	-0.162	(-0.523 to 0.249)	18	0.166	(-0.326 to 0.588)
VR-12 - PCS	25	0.248	(-0.164 to 0.585)	18	-0.120	(-0.555 to 0.368)
KOOS - pain	14	-0.264	(-0.697 to 0.310)	13	0.182	(-0.410 to 0.666)
KOOS - symptoms	18	-0.296	(-0.670 to 0.198)	13	0.157	(-0.431 to 0.652)
KOOS - ADL	10	-0.242	(-0.757 to 0.457)	10	0.620	(-0.016 to 0.899)
KOOS - sport	9	0.236	(-0.508 to 0.778)	6	-0.121	(-0.849 to 0.766)
KOOS - QOL	9	-0.213	(-0.769 to 0.525)	7	-0.462	(-0.902 to 0.446)
WOMAC - stiffness	17	0.190	(-0.320 to 0.614)	12	0.129	(-0.480 to 0.654)
WOMAC - function	9	0.067	(-0.625 to 0.700)	9	-0.617	(-0.909 to 0.080)
WOMAC - total	9	0.159	(-0.565 to 0.744)	9	-0.668	(-0.923 to -0.008)
TUG	14	-0.003	(-0.533 to 0.529)	12	0.298	(-0.333 to 0.744)
Single leg balance - right	7	0.443	(-0.465 to 0.897)	6	-0.758	(-0.972 to 0.140)
Single leg balance - left	8	0.505	(-0.310 to 0.892)	7	-0.510	(-0.912 to 0.395)
Chair rise	14	-0.019	(-0.544 to 0.517)	12	0.031	(-0.553 to 0.594)
Body mass index	33	0.186	(-0.168 to 0.498)	23	0.139	(-0.290 to 0.521)

Abbreviations: VR, Veterans RAND; MCS, mental component score; PCS, physical component score; KOOS, Knee Injury and Osteoarthritis Outcome; ADL, activities of daily living; QOL, quality of life; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; TUG, timed up-and-go.

DISCUSSION

This study replicated previous studies by demonstrating that both GNB and RFA were successful in reducing pain in the post-procedural and follow-up settings.[5] Notably, patients who received a GNB reported lower post-procedural pain and a greater absolute pain reduction than patients who received an RFA. While peculiar, this result also has been reported in prior studies. The authors postulated that there may be an incongruence between the area anesthetized by lidocaine during a GNB and the area subsequently lesioned during an RFA that may account for the discrepancy.[7] Overall, although the efficacy of these procedures has been well documented, to our knowledge, this is the first time they have been shown to provide pain relief for nonsurgical candidates with severe knee osteoarthritis after receiving care at a multidisciplinary clinic.

Statistical analysis did not demonstrate a relationship between BMI and the NRS scores at any point before or after receiving a GNB or RFA. This contradicts 2 prior studies demonstrating an association between increased BMI and increased likelihood of knee pain.[8,9] In our study, our ability to compare pain scores stratified by BMI classes may have been limited by group sample sizes, as most of our patients had BMI > 40.0. Despite this result, patients tended to receive similar pain relief regardless of BMI. Therefore, although we do not completely understand the relationship between BMI and osteoarthritic knee pain, GNBs and RFAs provide significant benefit for patients with severe KOA.

To date, there have not been any well-established guidelines for when to refer patients for a GNB or RFA, although some authors have recommended standardized protocols for patient selection.[5,10] Therefore, one goal of this study was to identify variables influencing treatment outcomes of these procedures. Patients who had higher (worse) WOMAC total scores tended to have a higher likelihood of receiving benefit from these procedures. Ultimately, we want to utilize patient-specific variables to develop an algorithm to help guide patient selection and referral processes for GNB and RFAs.

The primary limitation of this study is small sample size. In order to be included in the study, patients must have visited our clinic and have been referred for, and subsequently completed, a GNB or RFA between October 2017 and May 2019. Due to our clinic's time and resource restrictions, and because GNB and RFAs are second- or third-line therapies for osteoarthritic knee pain, only 18 patients met inclusion criteria. Therefore, this study is underpowered to detect many statistically significant results; of those that are significant, interpretations and generalizations are limited. Thus, larger studies will be needed in the future to identify significant differences and allow for stronger interpretations of significant results. Lastly, due to the inability to standardize data collection protocols with a retrospective chart review, many functional measures obtained could not be used for statistical analyses. Therefore, future studies should consider conducting a prospective trial with standardized protocols for data collection.

CONCLUSION

This retrospective chart review demonstrated clinically meaningful pain relief with GNB and RFA for nonsurgical candidates with

severe primary knee osteoarthritis being referred from a multidisciplinary osteoarthritis clinic. Additionally, the WOMAC may be valuable in the evaluation of primary knee osteoarthritis and referral protocol for GNB and RFA in the future.

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Joseph E. Kerschner, MD

Knowledge Changing Life: A History of the Medical College of Wisconsin, 1893-2019

Joseph E. Kerschner, MD

"When the time comes to write a full history of medical education in Milwaukee, it will be said of the medical schools in Milwaukee that the night seemed darkest before the dawn."[1(pv)]

This prophetic statement, published in an editorial in the *Wisconsin Medical Journal* in January 1913 – more than 108 years ago – provides the epigraph to the newly published *Knowledge Changing Life: A History of the Medical College of Wisconsin, 1893-2019*, and refers to the precarious situation faced by the Medical College of Wisconsin's (MCW) for-profit predecessor institutions in late 1912. At that time, the Wisconsin College of Physicians and Surgeons (founded in 1893) and the Milwaukee Medical College (founded in 1894) faced closure due to financial losses and accreditation downgrades. But the perseverance of Milwaukee's civic leaders, working with Marquette University to transfer the student bodies and physical assets of the two medical schools into the newly formed Marquette University School of Medicine, helped ensure the coming of the dawn.

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In 1967, Marquette ended its sponsorship of the Medical School, which became a private freestanding institution renamed the Marquette School of Medicine. In 1970, the institution was renamed the Medical College of Wisconsin, but still faced financial challenges; however, leaders and philanthropists throughout the region and state came together to help solve these difficulties. In 1978, MCW moved to the Milwaukee Regional Medical Center campus – its current home – and began a period of extraordinary growth which continues to this day.

> It is impossible to capture the richness of the book's anecdotes, tidbits of information, "portraits" of historical figures and decade-by-decade discussions of achievements, triumphs and challenges – but MCW alumni in particular will find this a fascinating walk down memory lane.

Woven throughout *Knowledge Changing Life's* 720 pages, meticulously researched and written by MCW's chief historian, Richard N. (Dick) Katschke, are rich tales of MCW's 125+ years of accomplishments, challenges and controversies, as well as the institution's critical relationships with Marquette, Milwaukee County, Milwaukee's hospitals and health care facilities, and a wide range of philanthropists and donors. The book also serves as a foundation for MCW's future as we actively reimagine our institution – thinking generatively and creatively about how to educate the next generation of health and science thought leaders, how research is conducted and applied, how healthcare is delivered, how we engage with our community, and how to collaborate and partner.

Throughout its history, MCW has created new knowledge that has changed lives through training the next generation of physicians, scientists and other healthcare professionals, through biomedical research, clinical excellence, specialty expertise and transformative clinical breakthroughs, and through bidirectional interaction with the communities we serve.

The *Wisconsin Medical Journal's* January 1913 editorial also wisely noted, "Of course, it

is not possible to create a Class A+ medical school in the twinkling of an eye. The evolution of the medical department of Marquette University from the chaos of this revolution into a thoroughly satisfactory school will take time. But the spirit in which the work is being undertaken is so earnest and sincere that there is every reason to hope for a bright and creditable future for it."[1(p22)]

And a bright and creditable future it has been! As noted in the Preface, written by John R. Raymond, Sr., MD, MCW's president and chief executive officer:

> MCW is an institution that surmounted financial deficits [and] accreditation challenges…to become a jewel in the crowns of Wisconsin and the nation. MCW attributes its triumphs over adversity to the supportive citizens of the Milwaukee area and throughout the state; dedicated civic leaders and elected officials; generous donors; strong academic and clinical partners; and loyal alumni, students, faculty and staff. These individuals supported MCW during the difficult times, but also during the promising times when MCW had opportunities to transform medicine both locally and globally. As a result, MCW has harnessed the knowledge and talents of its faculty physicians, staff, healthcare professionals and scientists to improve the quality of health and the lives of those we serve.[1(p ix)]

The Wisconsin Medical Society is mentioned in numerous places throughout the book. On page 55, Katschke notes that MCW's Graduate School of Biomedical Sciences traces its origins to the first basic science graduate degrees awarded on June 17, 1936. On that date, Stanley J. Seeger received a Master of Science degree from the Marquette University School of Medicine after having earned his MD degree at Marquette years before. Seeger was a prominent Milwaukee pediatrician who went on to become chief of staff at Columbia Hospital and then president of the Wisconsin Medical Society.[1(p55)]

On page 59, Katschke shares that the Marquette University School of Medicine joined with the University of Wisconsin School of Medicine and the Wisconsin Medical Society in 1934 to successfully lobby against three bills to ban animal research, and another bill that would have required the burial of unclaimed bodies instead of their release to the medical schools.[1(p59)]

On page 91, Katschke writes that at the beginning of the 1950s, Medical School faculty members began teaching brief, postgraduate courses at local hospitals under the sponsorship of the Medical Society of Milwaukee County. The program expanded, and the Medical School faculty members created "circuit sites" across the state where they taught courses in partnership with the University of Wisconsin Medical School and the Wisconsin Medical Society.[1(p91)]

Perhaps most importantly, in 1969, at the height of the Medical School's financial crisis, the Wisconsin Medical Society purchased full-page newspaper ads in 10 Wisconsin cities which alerted the public, saying, "Unless the Marquette School of Medicine gets financial help now…it may be forced to close its doors!"[1(p124)]

And, most enduring, at MCW's first White Coat Ceremony in 1999, the Wisconsin Medical Society began the tradition of giving the white lab coats to first-year medical students – which continues to this day. [1(p294)]

It is impossible to capture the richness of the book's anecdotes, tidbits of information, "portraits" of historical figures and decade-by-decade discussions of achievements, triumphs and challenges – but MCW alumni in particular will find this a fascinating walk down memory lane. *Knowledge Changing Life* is now available for purchase at www.mcw.edu/historybook.

As Katschke concludes: "Clearly the dawn has arrived for the Medical College of Wisconsin. By the end of the 21st century's second decade, MCW has emerged as a national and international leader in health science education, research, patient care and community engagement. Its more than 18,000 alumni have elevated medical care in almost every county in the state, and every state in the nation. MCW faculty members and alumni have made major discoveries in every specialty and sub-specialty of medicine and have been selected by their peers to lead the nation's major health organizations. MCW faculty physicians and alumni have developed new patient care treatments and strategies that have saved countless lives worldwide." [1(p624)]

Acknowledgements: Dr Kerschner gratefully acknowledges the assistance of Sara L. Wilkins, editor of *Knowledge Changing Life,* in preparing this column.

REFERENCE

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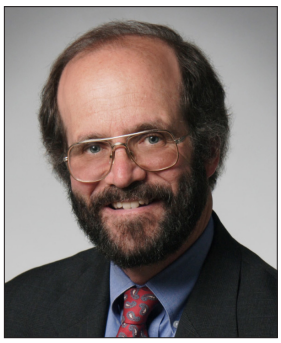

Robert N. Golden, MD

David O'Connor, PhD

The First COVIDecade

Robert N. Golden, MD; David O'Connor, PhD

Predicting the future is risky business. In 2007, the CEO of Microsoft declared, "There's no chance that the iPhone is going to get any significant market share. No chance." Predictions made in a fast-changing landscape are at the greatest risk of being spectacularly flawed.

Predictions from only a few months ago have not aged well, both in Wisconsin and globally. In November 2020, people expressed little, if any, concern that SARS-CoV-2 variants would impact vaccination campaigns, and experts predicted that India was on its way to "ending" its epidemic until, tragically, it surged to catastrophic levels. Such forecasts are fraught and illustrate how little we know about COVID-19. Often, we don't even know what we don't know! Nonetheless, experiences over the last year and from past pandemics allow us to squint into the horizon, anticipating some of the scientific and social issues that lie ahead.

1. The COVID-19 pandemic will be the defining societal event of this decade throughout the world. It is one of the rare events that has touched nearly everyone's life. It is this decade's Word War II or 9/11. Beyond its immediate impact on health, it has forever changed art, media, technology, sports, and other facets of life. Many cultural landmarks will be immediately binned into "before COVID" and "after COVID" categories, akin to pre-9/11 movies in which people rush to an airport gate to bid farewell to a paramour without encountering security checks or the early Superman episodes that rely on ubiquitous telephone booths for his transformation from a mild-mannered reporter into the Man of Steel. Moreover, lingering chronic health impacts of COVID-19 infection that are difficult to predict and treat may be felt for a generation or longer, similar to the chronic respiratory illnesses and other diseases that the 9/11 first responders continue to struggle with.
2. COVID-19 will continue to feature prominently in global geopolitics. Many decisions made in the earliest days of the pandemic will reverberate long into the future. For example, in 2003, the President's Emergency Plan for AIDS Relief exemplified the United States' moral authority by making lifesaving treatment for HIV widely available. Two decades later, China and Russia have joined the United States as major international leaders in the COVID-19 crisis, supplying precious supplies, such as vaccines, as well as scientific and medical expertise. COVID diplomacy will be a major instrument of exerting soft power in resource-constrained countries.
3. Borrowing from George Harrison, all things will pass, including front-page concern about COVID-19. The 20th century witnessed a huge reduction in mortality from infectious diseases in developed countries, as mortality from cancer and cardiovascular diseases gained prominence. Now, the general public's focus on infectious diseases has skyrocketed, similar to the way concerns about terrorism became dramatically elevated after 9/11. Eventually,

Experiences over the last year and from past pandemics allow us to squint into the horizon, anticipating some of the scientific and social issues that lie ahead.

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people will adapt and stop thinking about COVID-19 on a daily basis. At the start of the 20th century, people attended school, visited their families, and lived their lives in a world where infectious disease mortality was a constant threat. This does not mean we will suddenly return to a pre-pandemic "normal." Rather, we hope we will emerge from the pandemic with a greater, enduring appreciation of the importance of public health measures (vaccines, masks, social distancing) and public health funding.

4. COVID-19 will increase awareness of the global village and the reality that virulent pathogens do not require visas or passports to spread across the world. In other parts of the world, infectious diseases have never ceased to be a major cause of mortality, often as a result of inadequate infrastructure, including limited access to clean water, nutrition, and health care. Acceptance or denial of the reality of disadvantaged populations sets the stage for future pandemics that can spread quickly to wealthy nations, as well.
5. Global travel will resume, but unfettered international travel will be a distant memory. Outright travel bans will become less common, but ongoing quarantine requirements may not. Some of this will reflect legitimate concerns about importing more contagious, vaccine-resistant variants, but quarantine policies may also be sustained by xenophobia or political considerations.
6. Variants will continue to emerge and spread throughout the next decade. People have significant reasons to worry that the first batch of variants will increase contagiousness, potentially heighten virulence, and may overcome natural and vaccine-induced immunity. If "second-generation" COVID-19 can possess such worrisome biological properties, what will "20th-generation" and "50th-generation" viruses look like?
7. The rapid development of vaccines will embolden a sense of triumphalism, that future threats from SARS-CoV-2 and other emergent viruses can be brought to heel by quickly developed vaccines. If scientists can generate vaccines to protect against SARS-CoV-2, they should be able to adapt them to variants. Yet, we have no guarantee that vaccine immunogens that match circulating variants will elicit antibodies with the same efficacy as vaccines against "first-generation" SARS-CoV-2. We also have no guarantee that repeated vaccination will allow our immune systems to stay "up-to-date," or that the current resistance to vaccination among "anti-vaxxers" may grow to include others who develop "vaccination fatigue."
8. COVID-19 will have a seismic impact on education. Coping with the loss of an in-person school year will be a challenge for a generation of students and will exacerbate inequities. As a silver lining, talented students coming-of-age during the pandemic and fascinated by infectious disease will become the next generation's leaders to fight COVID-19 and other global infectious disease threats, such as influenza, HIV, tuberculosis, and malaria. The next decade will usher in a renaissance in our understanding of infectious disease forecasting, prevention, and treatment.
9. COVID-19 will catalyze access to free and ubiquitous high-speed internet throughout the United States and other developed countries. The need for remote schooling demonstrated that internet access is a public utility, as fundamental to modern life as electricity and running water. At the same time, the pandemic has highlighted the pernicious effects of misinformation about health and safety via social media, endangering efforts at masking, social distancing, testing, and vaccinations. Public policy needs to address the epidemic of dangerously false information.
10. Another pandemic will occur in the next 10 years. In the 2010s, Zika virus emerged in the Americas, and the most explosive Ebola outbreak in history occurred in West Africa. A camel-borne coronavirus known as Middle East respiratory syndrome, or MERS, disrupted the Middle East and South Korea. SARS-CoV-2 is simply the most recent member of the "new virus club" to threaten human health, but it will not be the last. The systems we put in place to respond to COVID-19, belatedly and at huge expense, will stand us in good stead against the next pandemic threat. We must remain patient, however, and accept that being ready for unknown future threats necessitates indefinitely supporting resources—the people, infrastructure, and plans—that we can rapidly mobilize when an unpredictable event occurs at an unpredictable time in the future.

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