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WMJ

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COVID-19 the Great Mask Debate

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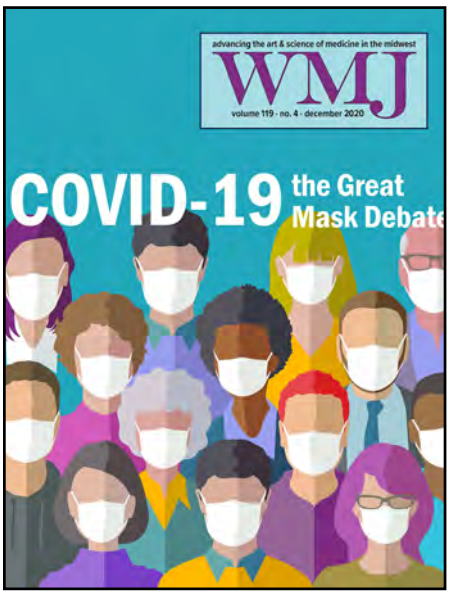

COVER THEME
COVID-19: The Great Mask Debate

As the COVID-19 pandemic continues, an increasing body of research looks at all aspects of the virus and its impact on health. This issue of *WMJ* includes several COVID-related papers, including a comprehensive review that points to the evidence in favor of community face coverings to slow the spread of COVID-19.

Cover design by Kendi Neff-Parvin

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WMJ

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

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Nine Months and Going Strong: Reflecting on an Unprecedented Year

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

As the COVID-19 pandemic enters its ninth month, Wisconsin is currently in the midst of a surge of cases, and hospitals throughout the state are full of patients with COVID symptoms. Meanwhile, research abounds looking at all aspects of this new virus and its impact on health. The *WMJ* continues to publish articles about COVID in Wisconsin written by Wisconsin researchers—papers we have posted in a special section on our website: wmjonline.org—including six new papers from this issue.

Topics in this issue include research about the early days of the pandemic, with papers describing patients who presented with COVID to the VA hospital in Milwaukee and patients with cancer presenting for surgery. In a study by Ebert et al, patients most commonly admitted for COVID-related symptoms at the VA in the spring of 2020 were Black men with hypertension.[1] At the same time, in Madison, Puckett et al report there was a very low rate of COVID among patients presenting for cancer surgery.[2] Researchers found only 2 positive tests out of the 227 patients with cancer who presented to the hospital for routine cancer surgery. These papers are examples of Wisconsin researchers studying and writing about the early stages of the pandemic, while a third paper by Singh et al describes the end of the 2018-2019 influenza season with the advent of COVID.[3] Interestingly, positive tests for influenza decreased suddenly with the occurrence of more COVID cases.

In "The Great Mask Debate," Raymond presents a comprehensive review of the evidence behind mask-wearing.[4] The paper provides ample evidence of how masks can reduce the risk of transmission of multiple viruses, including COVID, thereby making wearing them not really a debate at all.

> As 2020 comes to a close, we want to thank all of our reviewers who have dedicated their time and expertise to allow the *WMJ* to publish high-quality scholarship from local scientists. We could not publish the journal without their help.

A commentary in this issue by Hansmann et al describes how the pandemic has heightened challenges faced by rural communities.[5] Many people who live in rural areas depend on community resources for social support and interaction. Unfortunately, many of these resources (such as community centers or religious institutions) have been suspended during the pandemic. Further, internet services can be unreliable in rural areas, making it even harder for people to stay connected. In a poignant narrative essay, a primary care physician describes a morning of doing telemedicine,[6] highlighting the challenges for clinicians who have transformed their patient care days from face-to-face visits into telephone or video visits. For many clinicians, the rapport and communication with patients over the phone or a screen can be very challenging.

In addition to the COVID-related papers, this issue also includes several papers focusing on medical education. One report looks at how internal medicine residents experience writing and presenting case reports.[7] Another describes the development of a curriculum to teach residents about empathy, with the goal of reducing burnout rates.[8]

The year 2020 has been a busy one for the *WMJ*. We have received more than twice as many submissions as in the previous several years, including many about COVID. In response to the pandemic and another critical topic in 2020—the impact of race and racism on health—we have added two topic collections on the website (wmjonline.org). The first is a COVID repository, featuring 17 papers (to date) that cover a broad range of topics related to the pandemic. In addition to the papers from this issue, this section features several more case studies, brief reports, commentaries, and original research looking at the early days of the pandemic in Wisconsin, including two commentaries that explore its effect on medical student education.[9,10] In the spring of 2020, most in-person clinical experiences for medi-

cal students were halted temporarily due to the great uncertainties surrounding the pandemic. Authors discuss the educational implications of pulling students out of clinical rotations while at the same time focusing on the importance of keeping students healthy. In another commentary, authors address the pandemic's potential effects on immigrant physicians with a discussion of visa implications.[11]

As mentioned above, the second collection brings together papers that explore the impact of race and racism on health. Published over the last several years, these 17 papers explore specific issues related to race in Wisconsin. Topics covered include social determinants of health, racial disparities in breast cancer, and other health equity issues. To expand on this topic, the *WMJ* is publishing a special theme issue in early 2021. We have assembled a distinguished panel of experts to serve as a special advisory group to the editors for this issue that includes scientists from the University of Wisconsin (UW) School of Medicine and Public Health, the Medical College of Wisconsin, and UW-Milwaukee who have volunteered their time and expertise. Currently, we are soliciting artwork to include in this special issue. Visit our website for more information.

The *WMJ* also has teamed up with the UW-Madison Interprofessional Continuing Education Partnership (ICEP) to offer continuing education credit for certain original research papers published in the journal. Look for articles that display a blue "CE" button at wmjonline.org, and to register, click on the "earn continuing education credit" links or visit the ICEP website (https://ce.icep.wisc.edu/). There are no fees for participating in or receiving credit for this online enduring educational activity.

Finally, as 2020 comes to a close, we want to thank all of our reviewers who have dedicated their time and expertise to allow the *WMJ* to publish high-quality scholarship from local scientists. We could not publish the journal without their help. If you have never reviewed for the *WMJ*, please consider signing up on the website today.

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A Day in the Life of a Student-Run Free Clinic

Angela Olvera, BSE; Jorgo Lika, BS; Christie F. Cheng, BS

It's 3 AM, and everything is dark except the light flashing from the television. The weather forecaster announces a huge snowstorm, and as first-year medical student leaders of a free clinic, we must decide whether to hold clinic that day. At 7:30 AM, after a 40-minute drive that normally takes 20, we pull into the parking lot of the community health center site used every Saturday for our free student-run clinic. Patients are already lined up outside, even though it will be another 30 minutes until doors open. This scene is in stark contrast to the version of Madison we had been exposed to, describing it as a "Happening Place to Be Healthy"[1] and the third-best city to live in.[2] Unfortunately, the ease of living is not shared by many of our patients, and disparities in health care are often overlooked and unaddressed, requiring many to seek services where they can—our clinic being one of their only options.

The doors open at 8 AM, and patients fill the waiting room. On a typical day, our volunteer team of 12 students, 3 clinicians, and 2 pharmacists serves about 20 patients—most of whom are underserved, uninsured, and predominantly Spanish-speaking. On a first-come, first-served basis, we provide general medical care, physical therapy, and dermatology services. As clinic coordinators, we meet some but not all of the patients. However, in those moments we do meet, we are privy to not only their acute medical concerns but their stories and backgrounds. Every week there are different challenges and barriers, and we strive to work nimbly and expect the unexpected.

> As future physicians, we recognize that we will have both the privilege and responsibility to guide and advocate for our patients—particularly those who are otherwise ignored.

Our student volunteers come from interdisciplinary health professional fields. Some speak Spanish—a critical asset to the clinic, as they can create stronger connections with our Spanish-speaking patients through face-to-face communication.

A typical clinic visit involves student volunteers performing an initial interview and exam, presenting to the supervising provider, and returning to the patient room to confirm the plan. After that comes the hard part—getting the patient what they need. Our clinic can cover labs, x-rays, and medications, but concerns requiring a specialist are referred to community resources. Our list of community partners seems endless but nonetheless comes up short. Mental health resources are incredibly sparse, with our own free mental health clinic being the most accessible option. For physical therapy, the only resource is our own bimonthly student-run clinic. We carefully ration the few primary care new-patient referrals we have per month to patients with multiple comorbidities and complex medical needs.

As the clinic day winds down and the stack of referral paperwork grows, the student and provider volunteers gather for a wrap-up to discuss the challenges of providing care to patients with limited resources and ways to improve our clinic and better serve our patients.

The day's paperwork is handed off to our Referrals Coordinators, a team of four students who then spend the following weeks calling patients and providers to facilitate appropriate follow-up care. Their commitment to connecting our patients to resources and helping them navigate the health system is essential for overcoming health literacy barriers and ensuring we provide the best care we can.

At the end of each clinic day, we send patients off with the hope that they can follow through with their treatment plans, despite the barriers. Our services would be obsolete and unneeded in an ideal world, but the current reality is far from that. Originally, we were set up to address acute medical needs but, with increasing community need, we have become the only health care option for many uninsured patients. We see it as a privilege and a welcome challenge to adapt to patients' needs,

• • •

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advocate for expanded access to primary care for the uninsured, and connect patients to much-needed resources.

Running this clinic is a bit like managing a mini healthcare system. We have implemented new programs and learned about the complexities of setting up and optimizing protocols, interdisciplinary patient care, and communicating across language and cultural barriers. These experiences also have opened our eyes to the significant needs faced by underserved communities and the true cost of health care—a cost that extends beyond the clinic and that is elucidated as we scrounge for GoodRx coupons to help with medication costs, finagle transportation vouchers, occasionally beg our community partners to squeeze in just one more patient, and dole out everything we know about community resources like candy on Halloween. Most importantly, this clinic has taught us the importance of treating the individual holistically, addressing not only medical concerns but also evaluating and addressing social determinants of health and taking the time to connect.

As future physicians, we recognize that we will have both the privilege and responsibility to guide and advocate for our patients—particularly those who are otherwise ignored. While our experience coordinating this clinic has come with its challenges, it also highlights the realities of being a health care provider. We navigate a complex system, manage follow-up, strive to improve health, and look forward to doing it again and again. We hope for our work to shape a system in which individuals have more options than to wait for hours to be seen by students at a free clinic because we believe that Madison can live up to its title and be the "happening place to be healthy" for everyone.

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Schrager Named Editor-in-Chief

The Publishing Board for the *Wisconsin Medical Journal (WMJ)* named Sarina Schrager, MD, MS, editor-in-chief in October for a three-year term that began immediately. Dr. Schrager had served as interim editor-in-chief since May 2019, when John Frey, III, MD, retired from the position. Prior to that, she served as associate editor and as a member of the Editorial Board.

"In the last 18 months while serving as interim editor-in-chief, Dr. Schrager has done a great job at moving the journal forward. Based on our experience, we unanimously approved her as the editor-in-chief," said Publishing Board Chair William Hueston, MD, senior associate dean for Medical Education and associate provost of Education at the Medical College of Wisconsin. "The Publishing Board was very impressed with the way she managed the *WMJ* while in the interim role and was excited that she was interested in the permanent position."

Dr. Schrager is a professor in the University of Wisconsin School of Medicine and Public Health's Department of Family Medicine and Community Health. A graduate of Dartmouth College, she earned her medical degree from the University of Illinois College of Medicine at Chicago and completed her residency in family medicine at the MacNeal Hospital program in Berwyn, Illinois. She also completed a self-designed fellowship in Women's Health at MacNeal that combined graduate work in Women's Studies with clinical care in family practice. Her teaching focus is on women's health education for residents.

After working with the *WMJ* for many years, Dr. Schrager said she was interested in serving as editor-in-chief for a few key reasons.

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

"The *WMJ* is a generalist journal with a wide range of article topics. I believe in it being a venue for Wisconsin-based researchers, scholars, and learners to share their work," she said. "And much of the work we publish focuses on local populations, which makes it more meaningful to me."

"I also find joy and accomplishment in being able to mentor junior authors in their writing," she added. "This is part of my job in the Department of Family Medicine and Community Health and I have enjoyed being able to help students, residents, fellows, and junior faculty publish in the *WMJ*. This process of support, guidance, and feedback is an essential component of the editor-in-chief role and one that energizes me."

In addition to serving as editor-in-chief of *WMJ*, Dr. Schrager is medical editor of *FPM*, a peer-reviewed, indexed journal published by the American Academy of Family Physicians.

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CALL FOR PAPERS & REVIEWERS

Since 1903, *WMJ* has served as a forum for professional communication and continuing education for physicians and other health professionals. This tradition continues today, but with a broader focus that extends across the country and even around the world.

Published quarterly by the Medical College of Wisconsin and the University of Wisconsin School of Medicine and Public Health, *WMJ* is a peer-reviewed, indexed scientific journal available via printed subscription and in full text online at www.wmjonline.org and PubMed through the National Library of Medicine.

WMJ invites original research, case reports, review articles, essays and "Health Innovations"—brief reports that showcase the results of initiatives being tested to improve quality, patient safety and satisfaction, cost efficiency and more in clinics and communities throughout the Midwest.

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Good Morning Doctor; Welcome to a New Day

Marc Tumerman, MD

Alone and masked in my office, I stare at my computer screen, quietly waiting for the next camera icon to turn green. I wonder if this is the future of primary care. I look over at a packet of morning glory seeds and a small baggie of potting soil gifted to me by the employee health committee—an effort to keep up morale. I also received one bag of goldfish crackers and a piece of chocolate. I decide I will eat the crackers and chocolate, and likely do nothing with the seeds. It is the thought that counts.

Before the COVID pandemic, I shared my office with three clinicians. Two of them are at home, leaving me disconnected and staring at a screen. One was furloughed, which we're told sounds better than laid off, and one is working remotely from home. We are discovering that we can do a lot of our work remotely without ever seeing or touching a patient. This is new and strange for me, and I don't like it.

My life's work is about human touch and connection. I am saddened by the intrusion of electronics into my patient relationships. The scene of a couple out for dinner in a restaurant, away from their children, both on their cell phones, is now a common trope for the ills of our modern society. I am near retirement, so my view of all of this is certainly affected by my personal history and biography. Perhaps my younger colleagues are energized about the possibilities of technology, but I worry they will be less aware of the role that human connection plays in healing.

• • •

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Prior to the pandemic, our very large health system set a goal of going 75% virtual for patient visits by the year 2030. We have all had a crash course in telehealth etiquette and technology. My first attempts failed as the patients could not connect from their home computer or mobile devices. I sat at my desk, in my empty office, waiting for the little camera icon on the screen to turn green.

This is the signal I am waiting for now, the one that notifies me that a nurse 100 miles away has virtually roomed a patient and that they are ready to be "seen." The first four times it never turned green.

My most recent attempt succeeded, and I watched on the screen as my patient took off his shoes and socks and tried to position his feet and iPad such that I could see the rash he had recently acquired. In the process he fell out of his chair. Is this a reportable fall event to submit to the quality oversight committee? Eventually, with the camera aimed just right, I was able to diagnose his rash and fire off an electronic prescription to his pharmacy. Magic!

Alone and masked in my office, I stare at my computer screen, quietly waiting for the next camera icon to turn green. I wonder if this is the future of primary care.

Is this the practice I want for my patients and myself? Does it matter what I want if this is what patients want, the ultimate convenience? It is our groups' goal that 75% of all visits be just like this one, perhaps without a man falling out of his chair.

For now, I continue to stare at the screen, rubbing my eyes and waiting for the next green icon. I glance at the packet of morning glory seeds one more time. Turning over the packet I see that the germination cycle for a seed is 14 days, the same time needed to quarantine a patient who has been exposed to the Coronavirus. Opening the packet, a few seeds fall onto my desk and I pick them up and roll them between my fingers. It is such a small simple thing, this seed and packet of dirt. It might be nice to grow something green in my office.

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Mind the Gaps: Supporting Key Social Safety Nets Across the Digital Divide in Rural Wisconsin

Kellia J. Hansmann, MD, MPH; Quinton D. Cotton, MSSA; Amy JH Kind, MD, PhD

The late Bill Withers succinctly and soulfully captured our human need for community and connection when he sang, "We all need somebody to lean on." Who people lean on in times of need is also known as their informal social safety net – family and community support, social networks, and community programs that help maintain financial security, health, and wellness. Before the COVID-19 pandemic, face-to-face interactions were vital to informal social safety nets for many older adults, people living in rural areas, and low-income and racial and ethnic minority communities. These groups routinely "lean on" their safety net through cooking classes at the YMCA, dinners at senior centers, bingo at the VFW Post, coffee club at the local café, conversations at the barber shop or beauty salon, and activities through faith-based organizations. But the global COVID-19 pandemic has disrupted routine behaviors and led face-to-face interactions and group gatherings to become potential health risks.

• • •

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Overlapping Gaps in Social Safety Nets and the Digital Divide

Physical distancing has been essential for limiting virus transmission and flattening the curve of new COVID-19 cases since March, but the unintended consequence of physical distance has been social distance. In times of crisis, lack of social connections can be an important predictor of higher mortality, especially for those with low socioeconomic status and the elderly, as seen during Japan's 2011 Tsunami and its aftermath.[1] Without proper planning for the unique needs of groups who are already socially vulnerable, the response to a crisis like COVID-19 can worsen health inequities. Long term, loss of social connection also has negative impacts on health, including increased risk for early mortality.[2] Physically distancing has challenged informal social connections in profound ways, especially for those with little or no access to information and communication technology (ICT).

> Physical distancing remains one of our best options for public health management of the COVID-19 pandemic, but it is also our responsibility to consider how we will manage its unintended adverse effects – social distancing, social isolation, and widening gaps in our social safety nets.

Many who rely on informal social safety nets are the same people who have inconsistent or no ICT access. Persons who are older, who live in rural areas, and who have lower incomes and less education are less likely to have Internet access and/or a video-enabled device.[3] Recent estimates from the US Census suggest that in half of Wisconsin's counties, fewer than 60% of households own a smartphone and that in 9 counties—all in rural areas of Wisconsin—at least 30% of households have no internet service at all.[4] For these communities, shifting their social connections to virtual connections

using platforms such as FaceTime or Zoom simply may not be an option. Wisconsinites in rural counties are not just facing COVID-19, they are also struggling with new gaps in their social safety nets.

Supporting Social Safety Nets and Bridging Divides

As public health officials continue to recommend physical distancing to reduce risk of virus transmission, we will also need to anticipate the unintended consequences of social distancing. This is particularly important for Wisconsinites living in rural counties – especially older or otherwise vulnerable adults who are most likely to rely on informal social supports but less likely to have access to smart devices and broadband internet. Strategies to shore up new gaps in the social safety net will need to have short- and long-term plans for connecting with those who have limited access to ICT going forward.[5] Public health outreach and related health improvement strategies will need to meet both the requirements of safe physical distancing and provide options for those with limited or no ICT.

Traditional strategies to address social isolation have involved bringing people together to participate in community activities, support groups, or group classes.[6] However, the pandemic has necessitated a shift. Since March, communities across the country have begun creatively using guidance about how to prevent the spread of COVID-19 to identify alternative ways to meet their basic needs and maintain social connections safely. Neighbors have organized chalk art into sidewalk and driveway art galleries[7] and taken bingo nights outside to balconies and patios.[8] In Wisconsin, local 4-H organizers have been sending supplies for craft projects to members' homes.[9] Faith-based organizations have developed action plans to adapt spiritual gatherings and volunteer ministries to meet public health and safety guidelines.[10] Although these are important examples, more needs to be done by Wisconsin leaders to ensure systematic outreach with consistent messaging to those who rely on informal social safety nets and whose needs go unmet through virtual connections alone.

The more we learn about the best practices for slowing the spread of COVID-19, the better equipped we are to work with those at higher risk for infection and social isolation – to develop specific strategies for safely maintaining and promoting social connection. In rural areas of Wisconsin, this could involve helping local groups organize winter clothes and gear drives to help residents bundle up for colder weather hiking, bird watching, and more. When weather is inclement, coffee clubs, churches, and other social groups can organize into phone trees to continue regular check-ins and updates. Social supports can also help people address their basic needs. Family members, neighbors, or volunteers can help vulnerable individuals avoid face-to-face interactions in enclosed spaces by picking up groceries and medications. Ultimately, a comprehensive and systematic approach will be needed to address the needs of all medically and socially vulnerable individuals.

Physical distancing remains one of our best options for public health management of the COVID-19 pandemic, but it is also our responsibility to consider how we will manage its unintended adverse effects – social distancing, social isolation, and widening gaps in our social safety nets. The permanent solutions for addressing these gaps and the Digital Divide will require new approaches to health and social care financing and delivery. However, as we continue to respond to this global pandemic, we must not forget – especially during a crisis – we all need somebody to lean on.

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The Great Mask Debate: A Debate That Shouldn't Be a Debate at All

John R. Raymond, Sr., MD

ABSTRACT

Background: Despite a rapidly growing and evolving literature, there continues to be a vigorous public debate about whether the community use of face coverings can mitigate the spread of COVID-19 ten months into the pandemic.

Objectives: This article describes a semi-structured literature review of the use of face coverings to prevent the spread of coronaviruses and similar respiratory pathogens, with a focus on SARS-CoV-2 (COVID-19).

Methods: The author conducted a semi-structured literature review using search terms "COVID-19" or "SARS-CoV-2" crossed with "mask/s" or "face covering/s." Articles were evaluated through October 30, 2020 for inclusion, as were key references cited within the primary references and other references identified through traditional and social media outlets.

Results: There is strong evidence to support the community use of face coverings to mitigate the spread of COVID-19 from various laboratory, epidemiological, natural history, clinical, and economic studies, although there was only 1 high-quality published randomized controlled trial of this topic at the time of review.

Conclusions: The evidence in favor of community face coverings to slow the spread of COVID-19 is strong. Although most of the benefit of wearing a face covering is conferred to the community and to bystanders, a face covering also can protect the wearer to some extent, both by reducing the risk of COVID-19 infection, and perhaps by reducing the severity of illness for those who contract a COVID-19 infection.

INTRODUCTION

Ten months into the SARS-CoV-2 (COVID-19) pandemic, in the midst of a surge of cases across the Midwest that is spreading across the United States, there is ongoing debate about the utility of wearing face coverings in the community—especially paper masks or cloth coverings over the nose and mouth, hereafter referred to as masks. Early in the pandemic, inconsistent information from the Centers for Disease Control and Prevention (CDC) and the World Health Organization created confusion inasmuch as neither organization initially recommended wearing masks in community settings. The CDC reversed its position and advocated for community masks on April 3, 2020.[1] The World Health Organization advocated for community masks much later, on June 5, 2020.

The debate about masks to prevent community spread of COVID-19 has become increasingly partisan, pitting personal liberty against the common good. Indeed, public health officials who have imposed public mask mandates and other public health interventions have been criticized and threatened, causing some to resign out of concern for their safety.[2] A poll conducted by CBS News and reported on June 28, 2020, highlighted the political divide about masks – with 76% of Democrats polled calling the decision to wear a mask a "public health responsibility," whereas 59% of Republicans called it a "personal choice."[3] The debate has been further complicated by a glut of poorly curated information, disinformation, and opinion science about COVID-19.

Surprisingly, the same debate about masks played out over a hundred years ago during the Spanish Flu epidemic of 1918 and 1919 (see Figure), pitting public health officials and elected officials against an Anti-Mask League Coalition of tavern and the-

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Figure. Images of Mask Wearing During the Spanish Flu Pandemic

1A. San Francisco streetcar conductor refusing non-masked rider during Spanish Flu pandemic. From the US National Archives (identifier 45499311).

1B. "Conductorettes" in New York City during Spanish Flu pandemic. From the US National Archives (identifier 45499323).

1C. Cincinnati barbers wearing masks to prevent the spread of Spanish Flu. From the US National Archives (identifier 45499317).

ater owners, partiers, and people concerned about the economy and personal liberty.[4,5]

Politics aside, health care providers have an obligation to understand the scientific literature, to use critical thinking for the benefit of our patients and communities, and to communicate clearly so that our patients, communities, and elected and appointed leaders have the best information available to guide their decisions. This is especially important in that only 41.2% of individuals leaving grocery stores in Wisconsin during May and June 2020 (during which masks were voluntary) were observed to be wearing face coverings.[6]

This review covers evidence of 3 types of benefit from the community use of masks to mitigate the spread of COVID-19 – protection of bystanders (source control), protection of mask wearers, and reduction of the severity of illness for those who become infected with COVID-19.

METHODS

This semi-structured review is not a comprehensive review nor a meta-analysis, but it reflects a rapidly expanding literature about masks to mitigate the spread of COVID-19. The author conducted a literature review of the PubMed database maintained by the US National Library of Medicine of the National Institutes of Health, using key word search terms "COVID-19" or "SARS-CoV-2" crossed with "mask/s" or "face covering/s" on September 19, 2020. This strategy obtained 572 matches. A similar search of the preprint servers operated by Cold Spring Harbor Laboratory–bioRxiv and medRxiv–was conducted, identifying another 32 articles. The abstracts or full articles were assessed for inclusion, giving preference to articles that included "mask/s" or "face covering" in the title or abstract. Articles that focused primarily on manufacturing, decontamination, or reuse of personal protective equipment or that evaluated the use of masks in surgical settings or invasive medical procedures were excluded. The author then conducted a "snowballing search" of references cited within the primary references from the search. The author also reviewed Twitter, LinkedIn, Instagram, and Reddit posts to identify further relevant studies and articles. In addition, the author performed daily scans of various mainstream media sources including, but not limited to *The New York Times, The Wall Street Journal, Chicago Tribune,* Reuters*, Politico*, *National Review, Forbes, The Washington Post, The Hill, The Daily Telegraph, Daily Mail, The Guardian, Fox News*, and *CNN* through November 10, 2020.

Evidence Supporting Masks to Slow the Community Spread of COVID-19

Although there was only 1 high-quality, randomized controlled study of the efficacy of masks to mitigate the spread of COVID-19 at the time of this review, there is strong evidence that wearing masks outside of the household slows the spread of COVID-19, both for source control and for protecting the mask wearer. The first evidence of the effectiveness of masks to slow the spread of respiratory pathogens in community settings came from the Spanish Flu epidemic of 1918.[4,5] Because COVID-19 is transmitted from person to person like influenza—primarily through large respiratory droplets and aerosols[7]—masks could reduce the

spread by trapping the infectious exhalations from the source or by blocking inhalations from bystanders. In a contemporary meta-analysis of 172 observational and comparative studies involving the transmissibility of coronaviruses SARS-CoV-1, SARS-CoV-2, and MERS-CoV, Chu and colleagues estimated that masks reduce the risk of person-to-person transmission from 17.4% to 3.1%.[8] Further, they showed that N95 respirators were the most effective face coverings, followed (in order of efficacy) by paper surgical masks, multilayer cotton masks, and single-layer cotton masks.

The US Navy Bureau of Medicine and CDC studied the spread of COVID-19 among sailors on USS Theodore Roosevelt.[9] A convenience sample of 382 sailors showed that masks reduced transmission from 80.8% to 55.8%. The authors concluded that masks reduce transmission of COVID-19 even in tight quarters.

Leung et al studied 246 people with upper respiratory tract infections and found that masks significantly reduced coronavirus RNA in aerosol exhalations and trended toward reduced detection in respiratory droplets.[10]

Wang and colleagues performed a retrospective cohort study in Beijing, China, of 335 people in 124 families in households with a least 1 person who had laboratory-confirmed COVID-19.[11] Because at the time of the study (February 27 until March 17, 2020) most of the transmissions of COVID-19 in China were occurring inside households, there was widespread use of masks within homes—even for asymptomatic individuals. Although the secondary transmission rate was 23%, the authors showed that face mask use by the primary case and family contacts reduced transmission by 79%. It is noteworthy that masks were not significantly protective after the onset of symptoms in the primary case, emphasizing the importance of the prophylactic use of masks. Similarly, a case control study of transmission of SARS-CoV-1 showed that mask use was strongly protective for the wearer; always wearing masks when leaving the home reduced risk by 70% compared with never wearing a mask.[12]

Other evidence that masks can prevent the community spread of respiratory pathogens comes from the observation that mask wearing and other interventions early in the COVID-19 pandemic dramatically reduced the incidence of influenza and other respiratory illnesses in Singapore,[13] Taiwan,[14] Thailand,[15] and in Shanxi province of China[16] when compared with previous years, and when comparing before and after mask interventions in 2020.

One real-world illustration of the effectiveness of masks was provided when 2 stylists at a salon in Springfield, Missouri tested positive for COVID-19.[17] One of the stylists had provided services to numerous customers, despite feeling under the weather. Of 139 clients exposed in the salon, none developed symptoms, and 46 who agreed to be tested for COVID-19 tested negative. Public health officials attributed the results to strict adherence to masks for the stylists and their clients and to other measures, such as distancing and sanitization.

Multiple studies of respiratory droplet ejecta produced by talking or simulated cough have shown that masks dramatically reduce the spread of respiratory droplets and, to lesser extent, of aerosols.[18,19] Verma and colleagues demonstrated that droplets produced by a simulated cough can travel up to 12 feet without a mask. Homemade stitched cloth masks reduced the forward movement of the droplet jet to just 2.5 inches. Single-layer cotton bandanas or handkerchiefs were less effective but still reduced the distance traveled by the droplets by more than 70%.[18] Several similar studies confirmed that various types of masks reduce the spread of droplets and that multiple cloth layers are more effective than a single layer.

At the time of submission of this manuscript, the CDC did not recommend the use of neck gaiters due to insufficient and conflicting research. Indeed, 2 studies suggested that neck gaiters and single-layer cloth bandanas might not be as effective as multilayer cloth masks and surgical masks,[20,21] although 2 unpublished studies from Virginia Tech and University of Georgia supported the use of neck gaiters. If neck gaiters or bandanas are used as face coverings, multilayer fabrics are recommended.[22] Masks with valves should not be used because they can concentrate and focus the exhaled stream of respiratory droplets.

Several studies in hospitals associated with the University of Paris, Mass General Brigham, and Duke Health demonstrated that the use of surgical masks is associated with reduced COVID-19 in health care workers.[23-25]

Population-based studies also support masks to mitigate the community spread of COVID-19. One such study compared the trends and mitigation measures in Wuhan, China; Italy; and New York City from January 23 to May 9, 2020.[7] Officials in Wuhan intervened quickly with simultaneous implementation of social distancing, stay-at-home, and masking strategies, whereas the interventions in New York and Italy were more gradual and sequential. The authors were able to separate the effects of each mitigation measure from background pandemic trends. They estimated that mandatory masks reduced the number of infections by more than 78,000 in Italy between April 6 and May 9, 2020, and by over 66,000 in New York City between April 17 and May 9, 2020. They concluded that masks are the most effective intervention to slow the interhuman community transmission of COVID-19 and that other mitigation measures, such as physical distancing, are inadequate by themselves.

Lyu and Wehby examined daily COVID-19 case counts and county-level growth rates before and after masking mandates in 15 US states between March 31 and May 22, 2020.[26] They concluded that mandatory masks resulted in declining COVID-19 growth rates that were more pronounced the longer the mandates were in force, by 0.9% if the mandates were in force for 1 to 5 days, by 1.1% for 6 to 10 days, by 1.4% for 11 to 15 days, by 1.7% for 16 to 20 days, and by 2.0% for 21+ days. Their study provides evidence that US states that mandated public masking had greater declines in daily COVID-19 growth rates than those states that did not.

The nonprofit Institute of Labor Economics (IZA) investigated the spread of COVID-19 in the German city of Jena before and after masks were introduced on April 6, 2020, after which infections fell rapidly. They estimated that masks reduced the spread of COVID-19 by 40% to 60% and that masks were particularly effective in mitigating the spread in people over the age of 60.[27]

Stutt and colleagues performed a modelling study showing that masks lower the reproductive number of COVID-19 (a measure of contagiousness) to less than 1.0 and that there would be vastly less spreading even if masks reduced viral inoculum by only 50%.[28] They concluded that masks used in combination with stay-at-home mandates and distancing are highly effective strategies to attenuate the COVID-19 pandemic. Other models predicted that even limited mask use can slow the spread of COVID-19 and could reduce the need for more drastic shutdowns.[29-32] Chermozhokov and colleagues modeled the impacts of masks, policies, and behavior early in the COVID-19 pandemic and concluded that voluntary and mandated mitigation behaviors had equivalent beneficial effects on the spread of COVID-19 and that mask mandates appear to be more effective than business closures and stay-at-home orders, although layered interventions have added benefit.[32]

In a multivariate analysis of data from 198 countries early in the pandemic, Leffler and colleagues showed that in countries with cultural norms or government policies supporting public mask-wearing, the per capita COVID-19 mortality increased by an average of just 7.2% each week, compared with 55.0% each week in the remaining countries.[33]

A group from Vanderbilt University studied statewide COVID-19 hospital admission data and showed that Tennessee counties with mask mandates had a dramatically slower rise of hospitalizations than counties without mask mandates from July 1 through early August 2020.[34] Similarly in Kansas, 15 counties that implemented mask mandates had improvements in COVID-19 cases per capita, whereas 90 counties without mask mandates showed no decreases in per capita COVID-19 cases between late June and early August 2020.[35]

A study showed that mask mandates in Arizona, coupled with other mitigation measures such as limiting attendance at public events, quickly blunted widespread community surges of COVID-19 in June 2020 and resulted in a rapid decline of new cases about 2 weeks after implementation.[36] Similarly, a German study of nearly 7,000 people demonstrated that mask mandates moderately enhanced mask compliance compared to voluntary masking and that the mask mandates correlated well with other protective behaviors.[37]

Interestingly, even banking giant Goldman Sachs has publicly supported face masks both to reduce transmission of COVID-19 and to protect the economy. Their analysis suggests that a federal face mask mandate could prevent as much as a 5% reduction of the US gross domestic product.[38] Similarly, in early September 2020, US Federal Reserve Chairman Jerome Powell said in an interview, "There's actually enormous economic gains to be had nationwide from people wearing masks and keeping their distance," and that masks allow people to "go back to work and not get sick."[39]

Do Masks Reduce the Severity of COVID-19 Infections?

Over the course of the pandemic, many have speculated that the percentage of asymptomatic patients or mildly symptomatic patients with COVID-19 has increased. Some of this trend could be explained by increased availability of testing and better contract tracing, allowing for detection of more asymptomatic or mildly symptomatic patients. A systematic review of studies published early in the pandemic before masking was prevalent showed an average rate of 20% for asymptomatic COVID-19 infections in 79 eligible studies.[40] A more recent narrative review of 16 studies suggested that the rate of asymptomatic cases was 40% to 45%.[41] Although there are several possible reasons for the difference in the estimates of asymptomatic patients between both reviews, one explanation is that there was more widespread use of masks later in the pandemic. This idea raises the intriguing hypothesis that in addition to reducing the transmission of COVID-19, masks might reduce the severity of symptoms in people who become infected.

In that regard, Gandhi and colleagues noted that countries that encouraged early and widespread masking, such as Japan, Hong Kong, Singapore, South Korea, Vietnam, and the Czech Republic, have had lower rates of severe COVID-19-related illness and death than other countries that did not as readily embrace masking as a mitigating strategy.[42] Gandhi also championed the emerging concept that masks might reduce the severity of COVID-19 infections by reducing the dose of virus to which an individual is exposed, thus allowing the immune system to more effectively quell or limit the infection. In other words, breathing in a small amount of virus may lead to no infection or a milder COVID-19 infection. This concept is not new, dating back over 80 years.[43] Indeed, this idea underlies the earliest attempts to protect individuals from smallpox by inoculation or variolation of a healthy person with a low dose of pathogen.

Recent viral challenge studies in healthy human subjects have demonstrated clearly that lower doses of influenza A result in milder symptoms and less severe illness.[44] Although no similar challenge studies of COVID-19 have been performed in human subjects, there is growing epidemiological evidence that masks might reduce the severity of COVID-19 infections. One approach compares the amount of asymptomatic or mild infections between settings with various degrees of mask-wearing in congregate living or close-working situations. For example, on the Diamond Princess cruise ship in January and February 2020 where masks were not used, 18% of the 700 passengers and crew who tested positive for COVID-19 infections were asymptomatic.[45] In contrast, in mid-March 2020, during an outbreak on the Antarctic-

bound Greg Mortimer cruise ship where surgical masks were given to all passengers and N95 respirators to the crew, 81% of 128 who tested positive for COVID-19 were asymptomatic.[46]

An indoor festival in Gangelt, Germany was a COVID-19 super-spreading event. Those infected at the festival did not practice distancing or wear masks. After the festival, the community initiated several nonpharmacological interventions, including mask-wearing. People infected with COVID-19 at the festival had more severe symptoms than those infected in the community after the festival and had a lower percentage of asymptomatic infections (15.9% vs 35.7% asymptomatic).[47] Similarly, during an outbreak of COVID-19 among 3 companies of young and otherwise healthy Swiss soldiers in March and April 2020, implementation of mask wearing, handwashing, and distancing reduced the rate of infection from 62% to 15% and increased asymptomatic infections from 60% to 100%.[48] Additionally, 95% of COVID-19 cases from food processing plants in Oregon (Pacific Seafoods) and Arkansas (Tyson) were asymptomatic, which was much higher than expected. Both outbreaks happened at facilities in which masks were required.[49,50]

Other evidence suggesting that masks reduce the severity of COVID-19 infections comes from animal studies. Watanabe and colleagues showed that severity of illness from SARS-CoV-1 is dependent on initial viral dose in mice.[51] Correspondingly, when uninfected hamsters were exposed to hamsters infected with SARS-CoV-2 in an adjacent cage, 66% of previously uninfected hamsters became infected. When a surgical mask was placed between the cages, the infection rate dropped to 25%, and newly infected hamsters in the adjacent cage became less ill.[52]

Perhaps the most compelling evidence supporting the idea that larger inocula of COVID-19 result in more severe disease was provided by a study showing that patients with high upper respiratory tract genomic COVID-19 loads were twice as likely to be intubated or to die than those with lower COVID-19 viral loads.[53] Those effects were independent of any comorbidities, age, or severity of illness at presentation. That study supports the idea that strategies to reduce the initial inoculum of COVID-19, such as wearing a mask, could reduce the severity of COVID-19 symptoms and improve outcomes.

What About Evidence That Does Not Support the Utility of Masks?

Not all studies support the utility of masks to reduce the spread of COVID-19. Several systematic reviews failed to detect a beneficial effect of community masks to prevent the spread of respiratory viral pathogens. For example, the authors of a streamlined, structured review of 18 randomized controlled trials and 21 observational studies of masks for respiratory virus infections concluded that the evidence of the effectiveness of masks to prevent respiratory infections is stronger in health care settings than in the community.[54] They noted, however, that compliance with mask wearing in the community was low. In addition, none of the studies involved community masking specifically for COVID-19.

A recent rapid systematic review of facemasks to prevent respiratory illnesses concluded that "the evidence is not sufficiently strong to support widespread use of facemasks as a protective measure against COVID-19." However, the review included evidence suggesting that wearing a facemask "can be very slightly protective against primary infection from casual community contact" and modestly protective against intrahousehold spread when both infected and noninfected members wear facemasks. The authors also highlighted key weaknesses of the review—that is that poor compliance among mask wearers and mask use among controls could obscure the benefits of wearing a mask. In that regard, it is important to consider that even a small effect can be beneficial during the exponential growth phase of a pandemic.[55]

A small meta-analysis of 9 randomized controlled trials of masks to prevent the community spread of viral respiratory illnesses found no benefit for facemasks or facemasks plus handwashing.[56] Another systematic review of the effectiveness of personal protective equipment to prevent influenza in nonhealthcare settings found limited effectiveness of handwashing, touch surface sanitization, respiratory etiquette, or face coverings.[57] That review included 10 randomized controlled studies of the use of masks to prevent laboratory-confirmed influenza from the years 1946 through 2018. Pooled analyses of those studies showed no benefit in a variety of settings, including residence halls, a hajj pilgrimage, and households. However, the authors conceded that most of the studies were underpowered and that adherence to mask wearing was questionable. Interestingly, the 2 largest randomized clinical trials in the meta-analysis showed that a combination of handwashing and masks significantly reduced transmission of influenza and that masks alone had a beneficial effect that was not statistically significant. Another study cited in the review showed that facemasks and hand hygiene reduced household transmission of influenza if started within 36 hours of symptoms. Thus, even within a rigorous systematic review of randomized controlled studies that failed to detect a beneficial effect of masks to slow the community spread of respiratory viruses in a broad array of different settings, there was evidence that masks do reduce the spread of respiratory viruses in several community settings. Unfortunately, although randomized clinical trials are considered the "gold standard" for clinical intervention trials, they are difficult to perform in community settings due to the complexities of human behavior, ethical issues, and questionable adherence to the intervention.

Not all systemic reviews have concluded that masks are ineffective in slowing the spread of respiratory viruses. A rigorous Cochrane review of physical interventions to reduce the spread of respiratory viruses concluded that "simple mask wearing was highly effective," and that "surgical masks or N95 respirators were the

most consistent and comprehensive supportive measures" based on 7 case-control studies.[51] Two additional reviews presented evidence that supports the use of masks to prevent community spread through source control and protection of the mask wearer[52,53] or by reducing the viral inoculum to which an uninfected person could be exposed.[53] The authors of those reviews emphasized that inconsistent adherence to wearing masks is an important variable that must be considered when evaluating the effectiveness of mask wearing to mitigate the spread of COVID-19 in community settings. Furthermore, they stated that experiments of the impact of specific public health interventions may be impractical. Therefore, decisions about nonpharmacological interventions for COVID-19 should be based on the total body of evidence.

Some have noted that the COVID-19 transmission rate (reproductive number) and daily deaths in the first wave of the pandemic stabilized more rapidly than predicted by models and that those trends do not seem to be directly linked to government mandates of nonpharmacological interventions. One group of investigators analyzed the trends of reproductive numbers and death rates during the first wave of the pandemic in 25 US states and 24 countries that had more than 1,000 deaths from COVID-19 by July 22, 2020. They noted that the transmission rate decreased and deaths stabilized within 30 days, irrespective of government interventions. They concluded that "the role of region-specific nonpharmacological interventions implemented in this early phase of the pandemic is likely overstated."[54] The authors did not state that masks are ineffective. Rather, they posited that it is possible that people take spontaneous actions, including mask wearing, that slow the transmission of COVID-19. They also proposed another idea that slowing transmission through nodes of social networks can decrease the transmission of COVID-19 more profoundly than would be predicted by more random interactions across a population. In either case, these data do not specifically refute the effectiveness of masks. There are some weaknesses of the work. The work specifically studied the "first wave of COVID-19" and might not be applicable to the second wave and third waves that were surging in late 2020 in Europe and the United States, respectively. The work also did not measure hospitalizations. Nevertheless, the study is provocative and should be addressed more deeply in terms of the effectiveness of government mandates in mitigating the spread of COVID-19.

Another study that has been widely misconstrued was a case control study of community and close contact exposures of adults with symptomatic COVID-19 infections.[55] The study, which was performed at 11 health centers in the United States during July 2020, retrospectively examined behaviors of symptomatic patients who were tested for COVID-19. Patients who tested positive were matched with demographically similar patients who tested negative for COVID-19. The authors noted that patients who tested positive were more likely to have had a documented exposure to a patient with COVID-19 or to have eaten on site at a restaurant or to have gone to a bar or coffee shop in the 2 weeks preceding illness. On the other hand, there were no differences in self-reported mask wearing between COVID-19 positive and negative patients. Seventy-one percent of case patients and 74% of control self-reported always wearing cloth face coverings in public in the 2 weeks prior to the onset of illness. This later finding was incorrectly interpreted in *The Federalist* as meaning that masks are not effective in preventing the spread of COVID-19, even for those who consistently wear them. There are several problems with this interpretation. First, the study only involved symptomatic patients for both cases and controls and may not represent the population at large. Second, the patients might have had recall bias as to whether they had worn masks frequently and correctly. Most importantly, COVID-19-positive patients had a much higher level of exposure than control subjects inasmuch as they were 3 times more likely to have been exposed to a COVID-19-positive patient and twice as likely to have eaten or imbibed on site at a bar, restaurant, or coffee shop, where they likely removed their masks for a prolonged period of time to eat or drink in public than were COVID-19-negative controls. The best interpretation of this study is that removing masks in high-risk settings (crowded indoor venues for more than 15 minutes) or being exposed closely to an infected patient increases the risk of a COVID-19 infection, even when masks are worn most of the time.

Finally, a single randomized controlled study of mask wearing did not find a statistically significant beneficial effect of community use of masks to mitigate the spread of COVID-19.[56] The DANMASK-19 study randomized community-dwelling adults in 5 regions of Denmark without symptoms or diagnosis of COVID-19 to wear masks (or not) for a month between April 3 and June 2, 2020. Of 4,862 subjects who completed the study, COVID-19 infections occurred in 40 (1.8%) of the participants in the mask group and 53 (2.1%) participants in the group that was asked to abstain from wearing masks. The difference was not statistically significant. Some have concluded that this study demonstrates that masks do not protect the wearer from COVID-19 infections. However, the authors concluded that "the 95% confidence intervals are compatible with a possible 46% reduction to 23% increase in infections among mask wearers. These findings do offer evidence about the degree of protection mask wearers can anticipate in a setting where others are not wearing masks and where other public health measures, including social distancing, are in effect. The findings, however, should not be used to conclude that a recommendations for everyone to wear masks in the community would not be effective in reducing SARS-CoV-2 infections, because the trial did not test the role of masks in source control of SARS-CoV-2 infection." Although this was a well-designed study, it had several key limitations. During the study period, there was a low burden of community COVID-19 infections in Denmark, and the study intervention only lasted for 1 month. Cafés and restaurants were closed for the first half of the study (through May

18, 2020). Mask adherence relied on retrospective self-reports. Participants in the mask group had more documented household COVID-19 infections (n = 52) than in the control group (n = 39). The antibody test used for diagnosis of COVID-19 infection had a sensitivity of only 82.5%. Finally, there was a trend toward protection in the mask group, which could have been significant had more subjects been recruited to the study or if the community burden of COVID-19 had been higher. Those limitations aside, this study is interesting and highlights the need for more community-based studies. It bears repeating that community-based randomized controlled trials of behavioral interventions are difficult to perform due to the complexities of human behavior and questionable adherence to the intervention being studied.

Concerns About Negative Effects of Wearing Masks

Several concerns have been raised about the community use of masks for COVID-19. Because the supply chain for personal protective equipment has been disrupted, there have been calls to preserve N95 respirators for frontline health care providers and first responders. Those calls have been misinterpreted and generalized to include all types of masks, whereas the shortages of paper surgical masks and cloth masks are not as critical, and the supply chains for various types of personal protective equipment have improved since the beginning of the pandemic.

One frequently mentioned concern about wearing masks is that they increase face-touching and, therefore, might increase COVID-19 transmission through fingers and hands contaminated by respiratory droplets that land on touch surfaces, such as door handles and elevator buttons. However, studies demonstrate that mask wearing decreases face touching in community and health care settings.[64,65] This concern highlights the importance of reminding people who wear masks to avoid touching their face or mask and to wash hands frequently.

Another idea promoted for not wearing masks is that they cannot effectively filter COVID-19 because the virus is 100 times smaller than the pore size of masks (60-140 nm vs 100 μm). Indeed, a similar view was raised in 1919 by neurologist and psychiatrist James Crichton Browne about the effectiveness of gauze masks against the Spanish flu. Crichton-Browne stated, "The fact that the influenza organism is so infinitely minute that it can make its way through porcelain throws doubt on the value of the mask. Its use in the streets with the addition of goggles as has been proposed would, I believe, be futile, and would probably, if resorted to on a large scale, produce panic, which has always contributed to the spread of epidemic disease."[66] However, this persistent concern is not valid in that we do not exhale "naked virus," rather COVID-19 is expelled within large respiratory droplets when talking, singing, or shouting and, to a lesser extent, in smaller aerosolized particles that can be captured efficiently by masks worn by the infected individual (source control) or by uninfected bystanders. Additionally, droplets do not move in straight lines, and their Brownian motion and electrostatic charges can increase the likelihood of being trapped by masks.

The community use of masks might be especially difficult for those with hearing loss. Masks could undermine speech communication for hearing-impaired individuals to understand the spoken word by muffling speech and obscuring facial expressions and lip movements. This problem could be overcome in certain settings by using clear face masks.

Masks can cause a subjective impression of increased work of inspiration. This can be a limiting factor for a small set of patients who cannot tolerate them. Some have claimed that surgical masks induce hypoxia, but the literature suggests no decreases or minor decreases in oxygen saturation with N95 respirators.[67] Because paper surgical masks and cloth masks are looser fitting and more porous than N95 respirators, there is little likelihood that they meaningfully reduce oxygen saturation when worn in community settings.[68] There is some evidence that N95 respirators can increase respirator dead space and transcutaneous CO_2 levels leading to mild hypercapnia,[69] but there is little evidence that paper surgical or cloth masks cause CO_2 retention.[70] Therefore, there is little evidence that masks cause significant respiratory problems for most people.

Critics of community masks claim that masks cause reinfection or reinhalation of pathogens. Unfortunately, this largely unsupported claim was reinforced by an imprecise statement made by US Surgeon General Jerome Adams, who on March 2, 2020, said, "You can increase your risk of getting it (COVID-19) by wearing a mask if you are not a health care provider. Folks who don't know how to wear them properly tend to touch their faces a lot and actually can increase the spread of coronavirus."[71] Although the risk of masks increasing COVID-19 transmission is not supported by evidence, Dr Adams' statement reinforces the need to wear clean masks and to avoid touching one's face, mouth, nose, and eyes.

The claim that masks weaken the immune system is not well-supported and has been consistently refuted by public health officials and professional societies.

Some concerns about masks are legitimate. It is possible that masks might create a false sense of security. Yan and colleagues used anonymized cell phone data to show that when communities were ordered to wear masks in public, people left their homes more frequently and stayed away longer, often visiting restaurants and hardware stores.[72] This trend could undermine the benefits of community masks and highlights the importance of continued diligence for physical distancing. On the other hand, another community study showed that mask wearing increased adherence to social distancing.[73]

Young Black men have expressed concerns that wearing a face covering will make them a target for suspicion,[74] which is unfortunate inasmuch as Black people and African Americans are more likely than other groups to contract COVID-19 and to have poor

outcomes.[75] The CDC estimated that non-Hispanic Black people have an age-adjusted risk of hospitalization from COVID-19 that is disproportionately higher than that of non-Hispanic White people.[76] According to the Wisconsin Department of Health Services, as of October 30, 2020, Black people accounted for 11.3% of Wisconsin COVID-19 deaths, despite constituting only about 6.2% of the population.[77]

Masks can be inconvenient, warm, and uncomfortable. They can fog glasses. Masks can cause rashes at contact areas, such as on ears and the bridge of the nose. Mask wearers may experience a minor sensation of difficulty inhaling because of increased resistance from the fibers of the mask or increased reactive nasal resistance. Health care professionals can develop headaches from long-term use of personal protective equipment, such as N95 respirators and goggles. Headaches could be secondary to external compression of sensitive facial and scalp nerves from tight-fitting masks or their straps. Alternatively, altered cerebral hemodynamics could be responsible for the headaches, although this effect is not a limiting factor for health care worker performance. One study suggested that headaches could be associated with minor acute increases in middle cerebral artery blood flow and end-tidal carbon dioxide levels in health care workers wearing N95 respirators,[78] but these minor alterations were not shown to affect performance of the health care workers.[79] This minor concern about N95 respirators is not likely to be a limiting factor for community use of masks.

Are there legitimate medical exemptions from wearing masks? According to the CDC, "cloth masks should not be placed on young children under age 2, anyone who has trouble breathing, or is unconscious, incapacitated, or otherwise unable to remove the mask without assistance."[80] There may be other limited instances for which a face mask would be inadvisable, such as significant facial burns or certain mental health conditions, but specific exemptions should be carefully considered by a patient's health care provider.

Studies That Have Been Misinterpreted or Taken Out of Context

In a *New England Journal of Medicine* Perspective article early in the pandemic, Klompas and colleagues stated, "We know that wearing a mask outside health care facilities offers little, if any, protection from infection."[81] This statement has been widely interpreted as proof that masking is ineffective in slowing the community spread of COVID-19. However, the statement was made before the significance of spread by respiratory droplets was well-established, and the authors were referring to passing encounters outside of health care settings. Also, the authors admitted in that article that masks, coupled with other nonpharmacological interventions, could reduce the spread from asymptomatic individuals infected with COVID-19. In a follow-up letter, they clarified, stating, "We understand that some people are citing our Perspective article as support for discrediting widespread masking. In truth, the intent of our article was to push for more masking, not less. It is apparent that many people with SARS-CoV-2 infection are asymptomatic or presymptomatic yet highly contagious and that these people account for a substantial fraction of all transmissions. Universal masking helps to prevent such people from spreading virus-laden secretions, whether they recognize that they are infected or not."[82]

Evidence Supporting Face Shield Use to Slow Community Spread of COVID-19

Masks are thought to mitigate the spread of COVID-19 by reducing the inoculum contained in large respiratory droplets and aerosols and possibly by serving as a visual cue to increase physical distancing between individuals. Because of the concerns about masks highlighted in the previous section, some have speculated that clear face shields extending below the chin and covering the eyes laterally might provide some of the advantages of masks without the disadvantages. Two recent editorials speculated about the possible merits of face shields.[83,84] Those benefits include less physical and respiratory discomfort, protecting the eyes, preventing fogging of glasses, and allowing for visualization of facial expressions and lip movements. Face shields are more durable than masks and are easier to clean. The face shield wearer may be less likely to touch face, eyes, mouth, or nose. The most important disadvantage of a face shield is that it provides no filtration.

Chu suggested that goggles or face shields could reduce transmission by up to 70%, similar in magnitude to the beneficial effect of masks.[8] Interestingly, a small study from China showed that people who wore glasses regularly were less likely to be hospitalized for COVID-19, although the degree of protection was less than that of goggles or face shields.[85] Lindsley used a simulator to provide evidence that face shields could protect the wearer by reducing droplet inhalation by 68% to 96% immediately after a simulated cough, but that face shields were less effective in reducing aerosol inhalation.[86] On the other hand, Verma et al showed that face shields are ineffective for source control, inasmuch as face shields could block the initial forward motion of a simulated cough jet, but that the expelled droplets can move around the visor with relative ease and spread out over a large area.[27] Modeling studies by Fugaku, the world's fastest supercomputer, suggested that face shields alone are inferior to face coverings and are not particularly effective for source control.[87]

Interestingly, during a small outbreak of COVID-19 at a hotel in the Swiss village of Pontresina, employees and guests who wore only plastic visors became infected with COVID-19; no one who wore a mask—alone or in addition to a face shield—contracted COVID-19, suggesting that face shields do not provide the same level of protection for the wearer as do masks.[88]

These findings suggest that face shields alone are not as effective as masks to mitigate the community spread of COVID-19, but further work will need to be done. Because face shields redirect the respiratory ejecta downward rather than filtering droplets, face shields probably should be used as an adjunct to masks.

CONCLUSION

Although the literature about the utility of masks to slow the spread of COVID-19 in community settings is expanding rapidly, there is copious evidence that community masking reduces the transmission of COVID-19. Although most of the benefit of wearing a mask is conferred to the community and to bystanders through source control, a mask also can protect the wearer from infection to some extent (guidance from Centers for Disease Control and Prevention, November 10, 2020). There also is emerging evidence that masks can reduce the severity of COVID-19 by decreasing the dose of viral inoculum to which a bystander is exposed. Cloth face masks and paper surgical masks provide significant protection that increases as the percentage of people in the community who wear masks increases. Multilayer masks provide the adequate protection to mitigate the spread of COVID-19 in the community, and masks are preferred to bandanas, neck gaiters, and face shields.

The debate about the usefulness of masks to mitigate the spread of COVID-19 shouldn't be a debate at all. On balance, the benefits of community mask wearing to mitigate the spread of COVID-19 outweigh the risks. As trusted leaders of our communities, physicians and other health care providers should communicate clearly about what the literature tells us regarding the utility of masks in mitigating the community spread of COVID-19.

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Choosing a Vasopressor for a Prehospital Emergency Medical System: Consideration for Agent Selection and Review of Pharmacologic Profiles, Efficacy, and Safety in Treatment of Shock

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ABSTRACT

Introduction: Prehospital medical teams encounter patients with varying states of shock that require the use of vasopressors for hemodynamic support during transport. Selection of a vasopressor is challenging due to the absent comparative literature in prehospital medicine, as well as practical limitation of use in an ambulance.

Areas Covered: This article discusses specific challenges in the delivery of vasopressor support for hemodynamically compromised patients in the prehospital environment. Discussion includes the current state of vasopressor use in prehospital medicine, use of a patient-specific agent selection or "one-vasopressor-fits-all" modality, as well as considerations for each vasopressor based on practical, pharmacologic, and comparative evidence-based evaluations.

Conclusions: There are currently many limitations to assessment of shock etiology in the prehospital setting. A "one-vasopressor-fits-all" strategy may be most feasible for most prehospital emergency medical services (EMS) systems. No clear difference in extravasation exists amongst agents. Based on current evidence, norepinephrine may be more efficacious and have a better safety profile than other vasopressors in cardiogenic, distributive, and neurogenic shocks. Due to its suitability for most shocks, norepinephrine is a reasonable agent for EMS systems to employ as a "one-size-fits-all" vasopressor.

BACKGROUND

Shock is one of many conditions encountered by Emergency Medical Services (EMS) and is defined by the dysfunction of oxygen delivery from a state of circulatory failure. Circulatory support with vasoactive medications plays a vital role in treatment of shock.

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While prehospital providers often encounter varying states of shock, vasopressors are utilized infrequently.[1,2] A possible contributor to this infrequent use may be the challenges created in selecting the appropriate prehospital agent given the wide array of vasoactive agents and shock etiologies. According to data from the National EMS Information System (NEMSIS), dopamine was the most commonly used prehospital vasopressor in the United States in 2017.[3] However, other countries like France show norepinephrine as the predominantly used agent.[4]

In addition to safety and efficacy, there are many factors to consider when choosing a vasopressor for a prehospital formulary. Lack of invasive monitoring capabilities, difficult conditions for drug preparation, shelf life of unused drugs, and potential harms associated with unmonitored or peripherally administered medications all play a role in agent selection. The purpose of this article is to discuss specific challenges in the delivery of protocol-based vasopressor support for hemodynamically compromised patients in the prehospital environment. The article will provide considerations for agent selection based on practical, pharmacologic, and evidence-based evaluations.

ADMINISTRATION METHOD: BOLUS VASOPRESSORS OR INFUSION

Bolus- or "push-dose" vasopressors refer to the use of syringes with phenylephrine, epinephrine, or ephedrine given in intermittent boluses for the management of hypotension. Two studies and 1 case series exist describing the use of prehospital bolus-dose vasopressors.[5-7] One study reported efficacy and safety

after 100 administrations of push-dose epinephrine (10 mcg per dose) during the critical care transport of patients after return of spontaneous circulation (ROSC) (n = 24), in septic (n = 9) or cardiogenic shock (n = 3), or other patients (n = 7). The rate of dosing errors was 6.0%, and rate of effective hypotension resolution after correctly dosed bolus was 58.5%. No significant patient harm occurred from use; however, 1 patient experienced an extreme episode of transient hypertension after bolus administration.[5] Another large retrospective case-control study evaluated the effect of 100 mcg epinephrine boluses for up to 4 doses for hypotension. Of 571 patients, 62% required additional dosing after a single bolus. While blood pressure remained elevated compared to matched controls, the bolus-dose epinephrine group had more episodes of hypertension > 220 mmHg, recurrent hypotension, and cardiac arrest after administration. Patients treated with epinephrine required a vasopressor infusion in 65% of cases. No safety events or dose errors were reported among the 571 patients.[6] One case series also describes the use of bolus-dose vasopressors in the peri-intubation period for 2 patients. No adverse effects occurred in the patients who received these doses.[7]

The majority of data regarding use of these push-dose vasopressor agents are derived from anesthesia data that use precompounded products in the controlled environment of the operating room.[8] There is a paucity of data within the emergency department (ED) setting where these agents are used for peri-intubation hypotension, medication-related hypotension, or as a bridge to a long-term vasopressor.[8-12] Recurrence of hypotension is more likely with bolus doses of vasopressors compared to infusions given the short duration of action, which often necessitate additional vasopressor as demonstrated by up to 65% of patients requiring infusions after a bolus dose.[6,9,11] Furthermore, complex dilutions often are needed to prepare these medications, which may lead to higher rates of error.[10,12]

Given the concern for compounding error and data supporting frequent vasopressor infusions after bolus doses, the infusion strategy may be a more definitive option in the prehospital setting. However, there is a lack of comparative safety and efficacy data with bolus dosing compared to infusion. More evaluation is needed to determine the role of push-dose vasopressors in the prehospital setting. Safety considerations and guidelines for safe use of bolus-dose vasopressors in the ED were published recently.[10]

EXTRAVASATION RISK

Data comparing vasopressors for their relative risk of extravasation are lacking, and rates of prehospital extravasation of vasopressors have not been studied. Vasopressors carry varying ratios of vasodilatory β and vasoconstrictive α adrenoreceptor effect. There are theoretical advantages for agents with more vasodilatory β2 effect than α1 effect, as they may cause less vasoconstriction in the setting of extravasation. However, no clinical data are evident to support this.

Studies evaluating complication rates of peripherally run vasopressors (primarily phenylephrine or norepinephrine) cite complication rates between 2.0% and 5.5%.[13-18] If vasopressor extravasation occurs, catheter site placement, duration of infusion, drug concentration, and volume of drug contribute to the degree of tissue injury from extravasation.[14] Local tissue injury events occur more often with peripheral infusions of more than 4 hours in catheters placed distal to the antecubital or popliteal fossae.[15]

As prehospital teams continue to transport critically ill patients, the need for prehospital vasopressors is unlikely to diminish. No data support a stronger safety profile for any single agent. Further study is needed to evaluate the risk of extravasation by vasoactive agent and site of administration in the prehospital setting. Additionally, study of the clinical impact of prehospital extravasation, such as rate of injury or impact on clinical outcomes, is warranted.

CHALLENGES IN PREHOSPITAL AGENT SELECTION

Shock is manifested by a dysfunction in one or more components of the cardiovascular system, cardiac preload, afterload, or cardiac output. Based on the underlying deficit and subsequent compensatory changes in afterload, preload, or cardiac output, shock can be characterized into 3 primary phenotypes: cardiogenic (and cardiogenic obstructive), distributive (and neurogenic distributive), and hypovolemic. Treatment for each shock state is based on correcting the underlying hemodynamic derangement that caused the compensatory changes.[18] Table 1 summarizes shock phenotypes and guideline-recommended treatments.

Each vasopressor has a unique effect on cardiac output and afterload. Selection of an agent tailored to an individual's hemodynamic profile may maximize benefit while limiting harmful side effects.[19] In contrast to an ED or intensive care unit (ICU) setting, prehospital transport teams often lack tools like ultrasound, arterial lines, or pulmonary artery catheters that aid in identifying the specific hemodynamic derangement. This severely limits the ability to tailor vasopressor selection. Misdiagnosis and possible undue harm may come to a patient who receives an inappropriate vasopressor for their shock state.

AGENT SELECTION STRATEGY: ONE VASOPRESSOR FITS ALL

One strategy for agent selection would be to choose an agent that meets the needs of the most frequently encountered causes of prehospital shock. The most commonly coded scenario in the NEMSIS database in 2017 that required vasopressor administration was cardiac arrest, respiratory arrest, or cardiac rhythm disturbance (1212 documented occurrences) followed by hypovolemia and shock (428 occurrences).[3] Traditionally, vasopressors have a very limited role in hypovolemic shock and may increase mortality

Table 1. Shock Phenotypes and Guideline Recommended Treatment

Shock subtype	P	CO	SVR	Guideline recommended treatments
Septic[23] (Distributive)	↓	↔ Or ↑	↓	Surviving sepsis campaign recommendations • 30 ml/kg crystalloid fluid (preload correction) • Norepinephrine 1st line (afterload correction) • Vasopressin OR epinephrine 2nd line • Dopamine only in bradycardia with low risk of arrhythmia • Dobutamine if persistent hypotension despite adequate fluid
Hypovolemic	↓	↓	↑	Hemorrhagic[21] • Replacement of lost blood volume, minimal roll of vasoactive agents Dehydration • Replacement of lost fluids
Neurogenic[42]	↔	↓	↓	Consider vasopressor agents with both α- and b-adrenergic activity if high cervical/thoracic injury
Cardiogenic shock[25]	↑	↓	↑ or ↔	Abbreviated American Heart Association recommendations • Norepinephrine is associated with fewer arrhythmias and may be the vasopressor of choice in many CS patients. ***Recommendations by phenotype:*** Classic wet and cold (Low CO, high preload, high SVR), or euvolemic cold and dry (Low CO, normal preload, high SVR) • NE if high HR or pro-arrhythmic, DA if low HR however, arrhythmia risk higher, inotropic agent when stabilized and after revascularization (MI only) Vasodilatory warm and wet or mixed cardiogenic and vasodilator (low CO, low SVR) • Norepinephrine and invasive hemodynamics-guided therapy

Abbreviations: CI, cardiac index; CO, cardiac output; CS, cardiogenic shock; DA, dopamine; HR, heart rate; MI, myocardial infarction; NE, norepinephrine; P, preload; SVR, systemic vascular resistance (afterload).

in hemorrhagic shock, as volume expansion through blood products or intravenous (IV) fluids is the preferred treatment modality.[19-21] Post cardiac arrest patients with ROSC—the most common indication for need of vasopressors—provides a cornerstone for prehospital therapy selection.

Cardiogenic shock may be present in ROSC patients due to both post cardiac arrest myocardial dysfunction and interventions performed, such as defibrillation.[22] Additionally, etiologies of cardiac arrest cause cardiogenic shock states such as pulmonary embolus, myocardial infarction, or cardiac tamponade. Utilizing a vasopressor that is highly functional in cardiogenic shock would be ideal in a prehospital setting. One that is effective in distributive shock present in patients with sepsis, anaphylaxis, or post cardiac arrest reperfusion injury would be optimal to address most prehospital patients who need pressor support.

Numerous society guidelines recommend specific vasopressors for cardiogenic and distributive shock.[23-25] Additionally, many studies of patients in EDs and critical care units have evaluated comparative hemodynamic effects of vasopressors and clinical outcomes based on the specific shock subsets. Though the available data may have diminished application during shorter EMS transport times, safety and efficacy outcomes in these patient populations should be considered when selecting an agent for prehospital use.

VASOPRESSOR CONSIDERATIONS

To critically evaluate the benefits and challenges of vasopressor agent use in the prehospital setting, below is a review of the pharmacology, safety, efficacy, and practical considerations pertaining to individual medications. As there is little role for vasopressors in hypovolemic shock, discussion will focus on efficacy in cardiogenic and distributive forms of shock.

Narrative Evidence Review Search Strategy and Selection Criteria

Two authors (RF and MS) individually conducted a literature search to assess articles for inclusion. PubMed and MEDLINE were searched with the terms "vasopressor" or "norepinephrine" or "phenylephrine" or "epinephrine" or "dopamine" and "shock" and "prehospital." Abstracts were reviewed for relevance of inclusion. A manual review of reference lists from identified articles also was conducted. English language retrospective or prospective human trials comparing 2 vasopressors in adult patients were included. The search resulted in 36 individual articles; none met criteria for inclusion.

The same search was then carried out with removal of the term "prehospital." Literature reviewed were adult English language retrospective or prospective human trials comparing 1 vasopressor against historical controls or 2 or more vasopressors in adults within cardiogenic, distributive, or neurogenic shock states. Outcomes of interest included rates of mortality, refractory shock, arrhythmia, specific significant differences in hemodynamic parameters, and metabolic abnormalities. Four hundred sixty-four individual articles were identified, of which 29 met inclusion criteria, including 19 prospective randomized interventional or crossover trials, 2 prospective observational cohort studies, and 8 retrospective reviews. Table 2 includes a summary of findings comparing and contrasting data.

Comparative Hemodynamic and Pharmacologic Effects

Each vasopressor has differing effects of β1, β2, and α1, which have varying effects on cardiac output and systemic vascular resistance. Drugs with a predominance for β1 (epinephrine, dopamine) lead to increased heart rate (chronotropy) and stroke volume (inotropy), causing increased cardiac output. Drugs with a predominance for α1 (norepinephrine, phenylephrine) stimulation increase systemic vascular resistance more so than cardiac output. Table 3 provides a summary of the hemodynamic effects of each agent.

Norepinephrine: Stimulates β1, β2, and α1 receptors with a

Table 2. Vasopressor Pharmacologic Profile and Comparative Outcomes

Agent	Hemodynamics CO (β1)	Hemodynamics SVR (α1)	Pro	Con
Norepinephrine	+	+++	• 1st line in septic and cardiogenic shock due to large evidence base supporting safety and efficacy[23,25]	• Less HR and CI increase compared to DA or EP[15,27,28,30,34]
Dopamine	+++	++	• Increases HR if bradycardic, increases CO more than NE[27,29] • Long shelf life	• Concern for increased mortality in cardiogenic shock[44] • More arrhythmogenic than NE[50,51] • May be less effective than NE in septic shock[44,45]
Epinephrine	+++	+++	• Increases HR if bradycardic, increases CO more than NE or DA[28,30,34] • 1st line in anaphylaxis[37] • 2nd line recommendation in septic shock[23]	• Possible increase in mortality or refractory shock in cardiogenic shock and prehospital transport[6,33,54] • Increased lactate production may confound resuscitation[31,32,35,36,46]
Phenylephrine	-	+++		• May decrease cardiac output through reflex bradycardia or reduced stroke volume[38,52] • Limited utility in undifferentiated shock

Abbreviations: CO, cardiac output; DA, dopamine; EP, epinephrine; HR, heart rate; NE, norepinephrine; SVR, systemic vascular resistance.

higher affinity for α1 than β. Smalls studies have shown the primary vasoactive effects of norepinephrine to be through an increase in systemic vascular resistance while maintaining cardiac output.[26] Compared to dopamine, norepinephrine maintains mean arterial pressure without as large of an increase in cardiac index or myocardial oxygen demand.[27-30] It causes significantly less cardiac output increase compared to epinephrine.[31,32]

Dopamine: Stimulates dopamine receptors and the adrenergic receptors β1, β2, and α1 with a predominant effect on β1. The resultant increase in mean arterial pressure is primarily through an increase in cardiac output, as opposed to increasing systemic vascular resistance.[26-29] It has a greater effect on cardiac output than norepinephrine, though it appears to be less than that of epinephrine.[27,29]

Epinephrine: Stimulates β1, β2, and α1 receptors. In comparison to norepinephrine, it has greater affinity for β1 and β2 stimulation, leading to a larger increase in cardiac output with similar increase in systemic vascular resistance. It also increases lactate production and may be associated with a lower pH and more metabolic derangement than norepinephrine during resuscitation.[31-36] Its affinity for β2 stimulation may be of benefit in anaphylactic conditions due to increased bronchiolar dilation.[37]

Phenylephrine: Stimulates only α1 receptors, increasing mean arterial pressure through an increase in systemic vascular resistance. In patients with myocardial dysfunction, it has been shown to increase systemic vascular resistance and reduce cardiac output and stroke volume,[38] giving this agent the potential to worsen cardiogenic shock.

Guideline Recommendations for Vasopressor Use

Norepinephrine: Carries a recommendation as a preferred vasopressor in cardiogenic shock under multiple guidelines and is the first-line recommended agent for septic distributive shock.[23,25,39-41]

Dopamine: Carries low levels of evidence recommendation as an alternative to norepinephrine in septic shock only in those with bradycardia and low risk of arrythmia. It carries recommendations to avoid use in ischemic cardiogenic and neurogenic shock.[23-25,39,41,42] It is also recommended as a possible agent in cardiogenic shock with a low heart rate, with the caveat that it may be more arrhythmogenic (Table 2).

Epinephrine: There are no recommendations listed in societal guidelines for or against the use of epinephrine in the management of cardiogenic shock. Epinephrine is recommended as a preferred agent for anaphylactic shock due to theoretical increased β2 dilation of airways and possible immunomodulation of mast cells.[37] It is recommended as a second-line agent after norepinephrine in the treatment of sepsis.[23]

Phenylephrine: Recommended for consideration in initial vasoactive management of cardiogenic shock due to aortic stenosis, mitral stenosis, or dynamic left ventricular outflow tract (LVOT) obstruction due to theoretical disease-specific advantages rather than clinical data.[24] Although previously recommended for use in 2012 surviving sepsis guidelines in the setting of cardiac dysrhythmias or refractory shock, current sepsis guidelines make no recommendation on phenylephrine use.[23,43] Avoidance of phenylephrine is suggested in the setting of spinal cord injury shock with higher spinal column injuries.[42]

Narrative Literature Review of Efficacy and Safety

A brief summary of comparative efficacy trials identified during literature review are provided below. Table 3 contains key points regarding hemodynamic effects, safety, and efficacy extracted from these trials.

Cardiogenic Shock

Norepinephrine vs Dopamine: A large prospective trial of ICU

patients requiring vasopressors (N = 1679) compared dopamine to norepinephrine. In the subgroup analysis of cardiogenic shock patients, dopamine (n = 135) had greater 28-day mortality than norepinephrine (n = 145) (incidence not reported, $P = 0.03$).[44]

Norepinephrine vs Epinephrine: A randomized trial compared norepinephrine (n = 30) to epinephrine (n = 27) in patients with ischemic cardiogenic shock. Norepinephrine had significantly lower rates of refractory shock (37.0% vs 7.0%, $P = 0.008$) and a lower composite outcome of 7-day mortality or need for extracorporeal life support (37.0% vs 13.0%, $P = 0.045$) compared to epinephrine.[33]

Phenylephrine: No comparative data exist evaluating phenylephrine in cardiogenic shock. One prospective case series of phenylephrine administration in patients with heart disease demonstrated a further reduction in cardiac output when phenylephrine was administered.[38]

Summary: In cardiogenic shock, norepinephrine has shown reduced mortality, or rates of refractory shock compared to dopamine or epinephrine. Data comparing dopamine and epinephrine was not found. Phenylephrine may worsen cardiogenic shock.

Distributive Shock

Norepinephrine vs Dopamine: Small trials of septic shock demonstrate norepinephrine outperformed dopamine in ability to maintain hemodynamic goals and increase oxygen delivery efficiency.[27,29,30,44,45] There was no significant difference in mortality between norepinephrine or dopamine in a subgroup analysis of septic patients from a large trial of ICU patients requiring vasopressors.[44]

Norepinephrine vs Epinephrine: In a randomized control trial of epinephrine (n = 169) vs norepinephrine +/- dobutamine (n = 161) in septic shock, there was no difference in mortality or arrhythmia. Epinephrine-treated patients had significantly lower pH and higher lactate during treatment.[46] Subanalysis of septic shock patients in a large randomized trial (N = 277) showed no difference in mortality or time to therapeutic goal between epinephrine (n = 76) and norepinephrine (n = 82).[35]

Norepinephrine vs Phenylephrine: Small trials of norepinephrine (n = 16) vs phenylephrine (n=16) in septic patients found phenylephrine increased lactic acid production and reduced creatinine clearance compared to norepinephrine, but there was no significant difference in hemodynamic parameters.[47,48] In a large multicenter evaluation of septic patients when there was a shortage of norepinephrine and alternatives were used, an increase in mortality was detected compared to historical controls.[49]

Summary: In distributive shock, small studies support that norepinephrine may outperform dopamine in maintenance of hemodynamics, through no difference in mortality has been seen in large trials. Norepinephrine appears equivalent to epinephrine but causes less metabolic derangements. Very little prospective data exists to support use of phenylephrine. Data were not found comparing dopamine, epinephrine, or phenylephrine to each other.

Safety

Norepinephrine: In a retrospective trial, hypokalemia and metabolic acidosis were more common in the norepinephrine-treated cohort compared to dopamine ($P<0.05$).[50] Norepinephrine has been shown to cause less metabolic derangement (lactic acid production, gastric malperfusion, metabolic acidosis) than both epinephrine and phenylephrine.[29,31,32,34-36,46,48]

Dopamine: Dopamine has been shown to cause more arrhythmia than norepinephrine in numerous trials of cardiogenic shock.[44,50,51] Dopamine use was associated with an increase in cardiac complication (ventricular tachycardia, troponin elevation, atrial fibrillation, heart rate > 130 or < 50) in an analysis of patients treated for shock related to spinal cord injury.[52] A similar analysis showed dopamine was associated with increased adverse effects in a subset of patients > 55 years.[53]

Epinephrine: Patients receiving 100 mcg boluses of epinephrine had a higher incidence of 24-hour mortality and cardiac arrest than historical case controls who would have qualified for treatment. This effect remained after adjustment for confounding variables.[6] Epinephrine has demonstrated more frequent metabolic disturbances compared to norepinephrine in numerous trials.[31-36] In a prospective observational cohort of patients requiring vasopressors for cardiogenic shock, epinephrine was the only vasopressor independently associated with increased 90-day mortality (OR 5.3; 95% CI, 1.88-14.7; $P = 0.002$).[54]

Phenylephrine: Phenylephrine use was associated with an increase in cardiac complication (ventricular tachycardia, troponin elevation, atrial fibrillation, heart rate > 130 or < 50) in an analysis of patients treated for shock related to spinal cord injury.[52,53]

Summary: Norepinephrine appears to cause less arrhythmia than dopamine. It also appears to have less effect on metabolic parameters, such as lactate production, than epinephrine. Phenylephrine and dopamine have been associated with higher rates of adverse effects in neurogenic shock.

Practicality

Norepinephrine: Can be purchased as a premix bag from compounding pharmacies or may be reconstituted to the desired concentration via a vial or ampule injected into an infusion bag. Premade infusions could be compounded at concentrations of 4 mcg/ml (1 mg in 250 ml) and 16 mcg/ml (4mg in 250 ml) and are stable in dextrose 5% or saline for 7 days at room temperature and ambient light.[55]

Dopamine: Available as an infusion directly from the manufacturer at varying concentrations, dopamine may be utilized without drug compounding. The shelf life of the premade bag is 18 months.[56]

Alternatively, an infusion may be compounded using stock vials and infusion bags to desired concentrations. Compounded infusions of 2 mg/ml, 10 mg/ml, and 30 mg/ml in normal saline, dextrose 5%, and dextrose 10% are stable for up to 84 hours under room temperature and ambient light.[57]

Epinephrine: Can be purchased as a premix bag from compounding pharmacies or may be reconstituted to the desired concentration via a vial or ampule injected into an infusion bag. Premade bags can be compounded at concentrations of 25 mcg/ml (5 mg in 250 ml), 50 mcg/ml (10 mg in 250 ml), and 100 mcg/ml (20 mg in 250 ml) in dextrose 5% or saline. These concentrations are stable for 30 days at room temperature and in ambient light.[58]

Phenylephrine: Can be purchased as a premix bag from compounding pharmacies or may be reconstituted to the desired concentration via a vial or ampule injected into an infusion bag. Phenylephrine is stable for 60 days at room temperature and light with concentrations of 200 mcg/ml (50 mg in 250 ml) and 400 mcg/ml (100 mg in 250 ml) in normal saline.[59]

DISCUSSION

Numerous factors must be considered when selecting a prehospital vasopressor. The agent should have utility in multiple shock states. Phenylephrine is limited in that it only stimulates $\alpha 1$, which may worsen cardiogenic shock.[38] Coupled with sparse clinical efficacy data, phenylephrine may be a less than ideal option as a "one-size-fits-all" vasopressor. This leaves agents such as dopamine, norepinephrine, and epinephrine. Premixed agents may be easier to administer in an uncontrolled ambulance environment. Premixed dopamine with a long shelf life is available from the manufacturer; however, all agents are available as premix solutions from compounding pharmacies. Ease of use should be balanced with pharmacologic profiles, efficacy, and safety data for each agent. While prehospital outcome data are lacking, extrapolation from inpatient shock management can provide initial direction.

Available evidence supports that norepinephrine has lower rates of refractory shock, mortality, and arrhythmia compared to dopamine.[44,43,44,50,51] Dopamine has the benefit of a more significant increased cardiac output compared to norepinephrine, which would be of benefit in bradycardic or cardiogenic shock. Despite this theoretical benefit, outcomes appear to be worse with dopamine in this shock type.[44] Worse outcomes with dopamine compared to norepinephrine in cardiogenic shock have been supported by other literature reviews as well. An English and Chinese language meta-analysis, which includes 5 studies not listed in this review, found dopamine-treated cardiogenic shock patients had higher 28-day mortality (RR 1.611; 95% CI, 1.219–2.129; $P < .001$) and higher risk of arrhythmia (RR 3.426; 95% CI, 2.130–5.510, $P < .001$) than norepinephrine.[60] Dopamine's inferior efficacy and concerning safety data may offset any benefit of its longer shelf life.

Epinephrine offers utility in numerous shock states, including septic, anaphylactic, and cardiogenic shock. Similar to dopamine, its pharmacologic profile provides a theoretical benefit in cardiogenic shock due to increasing cardiac output more than norepinephrine or dopamine. However, a small prospective trial has shown higher rates of refractory shock with epinephrine than norepinephrine in this population.[33] Epinephrine's association with increased mortality in cardiogenic shock also has been supported by other meta-analysis.[61] While it appears similar to norepinephrine in distributive shock, it more consistently causes metabolic derangement, such as lactate elevation, which may confound resuscitation.[31,32,35,36,46] Epinephrine's theoretical advantages in some shock etiologies, such as anaphylaxis, are difficult to reconcile against emerging data showing increased mortality in cardiogenic shock and prehospital transport patients.[6,33,54] Norepinephrine's large amount of supportive data, utility in all shock states, lower rates of arrhythmia, and ease of use with premixed infusions, make it a good option for use within an EMS system as a "one-size-fits-all" vasopressor.

One barrier to moving beyond a "one-size-fits-all" vasopressor strategy is the limited ability to evaluate the etiology of shock during medical transport. Patient evaluation is currently limited to paramedic assessment and physical exam findings. Advances in prehospital care may help revolutionize the assessment and management of shock patients in this setting. Prehospital ultrasound is currently being studied as a potential additional tool, which may help the prehospital provider better assess cardiac function and volume status.[62] Point-of-care testing also may be an option in certain EMS systems, which would allow for assessment of lactate, mixed venous oxygen partial pressure.[63] Expedient initiation of vasopressors for hemodynamic support has been associated with better neurologic outcomes in patients experiencing out-of-hospital cardiac arrest.[64] Advances in diagnostics, coupled with more sophisticated telemedicine, may lead to earlier identification of shock and initiation of hemodynamic support.[65] Future studies should attempt to characterize the types of shock frequently identified by EMS systems, as well as the shock states unlikely to survive to hospital admission without early vasopressor intervention.

Finally, the largest barrier to identifying an optimal vasopressor for nontraumatic prehospital shock is the complete absence of comparative evidence within prehospital populations. Comparative studies need to be completed evaluating clinical outcomes, such as survival to hospital admission, 30-day survival, rate of survival with good neurologic outcome, rates of cardiac arrhythmia, rearrest, and refractory shock in the prehospital setting. Current EMS systems that utilize multiple vasopressors should generate retrospective comparative data to aid in identifying an optimal agent. Data can be prospectively or retrospectively generated from EMS systems with a single vasopressor formulary that has changed to a different vasopressor. Like evaluations done in the ICU setting, retrospective outcome evaluations could be conducted amongst

cohorts of patients treated during times of different formulary vasopressor use.[50] Safety data surrounding the use of a vasopressor in an uncontrolled prehospital setting should also be generated. Rates of extravasation and dosing errors with infusions should be compared against other administration methods such as bolus dosing. There is still significant discovery to be made in the field of prehospital shock management. Those involved in EMS systems should evaluate their current practices to ensure they are providing the highest quality of care to their critically ill community members.

CONCLUSIONS

The robust evidence for use of norepinephrine in cardiogenic, distributive, and neurogenic shock from both efficacy and safety perspectives, numerous guideline recommendations, and ease of preparation make it a good option for prehospital use. More study is needed to identify an optimal strategy for prehospital hemodynamic support.

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Clinical Features of COVID-19 Infection in Patients Treated at a Large Veterans Affairs Medical Center

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ABSTRACT

Introduction: During recent months, reports describing the characteristics of COVID-19 patients in China, Italy, and the United States have been published. Military veterans represent another unique population affected by COVID-19. This report summarizes the demographics and baseline clinical comorbidities in veterans testing positive for COVID-19 in Milwaukee, Wisconsin.

Methods: Patient evaluations were conducted at the Zablocki VA Medical Center, Milwaukee, Wisconsin between March 11, 2020 and June 1, 2020. Patient demographics, baseline comorbidities, home medications, presenting symptoms, and outcomes were obtained via electronic medical record.

Results: Ninety-five patients (88 men, 7 women) tested positive for COVID-19 and were evaluated. Fourteen required mechanical ventilation; 50 and 31 patients were treated in the hospital without ventilation or were discharged to home isolation, respectively. Discharged patients were younger than patients hospitalized. Most patients with COVID-19 were African American (63.2%). Patients whose disease progressed to mechanical ventilation had, on admission, more dyspnea, higher heart and respiratory rates, and lower oxygen saturation than other patients. COVID-19 patients who required mechanical ventilation had a longer length of stay and higher mortality than other groups and were more likely to have a history of hypertension and hyperlipidemia than patients who were discharged to home quarantine (85.7% and 78.6% vs 48.4% and 45.2%, respectively; $P < 0.05$ for each).

Conclusion: COVID-19-positive veterans are predominantly African American men with hypertension and hyperlipidemia receiving beta blockers or ACEi/ARB. COVID-19-positive veterans who presented with dyspnea, tachypnea, tachycardia, and hypoxemia were more likely to require endotracheal intubation and mechanical ventilation, had longer hospital length-of-stay, and experienced greater mortality than comparison groups.

INTRODUCTION

The first confirmed case of coronavirus disease 2019 (COVID-19) in the United States was identified in the state of Washington on January 31, 2020. At this writing (October 6, 2020), more than 7.6 million cases and 212,485 deaths have been reported in the US alone.[1] Clinical reports recently have appeared in the medical literature, most often originating from countries with the greatest numbers of cases, including China,[2,3] Italy,[4,5] and the US,[6-9] that describe the risk factors, clinical features, and treatment of patients with COVID-19. Despite the similarities in the disease presentation across different cultures, ethnicities, and socioeconomic situations, the goals of reports differ, making each report unique. For example, investigators from New York City reported on the most common comorbidities associated with hospital admission with COVID-19 and found a higher prevalence of hypertension, obesity, and diabetes.[8] Another study of COVID-19 patients in Chicago focused on risk factors for severe respiratory complications and noted that elderly diabetic males were the population at highest risk.[9]

Military veterans represent another unique population that has been affected by COVID-19. Patients treated at Veterans Affairs (VA) hospitals are known to have more medical comorbidities and psychiatric conditions of prolonged chronicity and greater severity versus those in the civilian population.[10] VA patients are predominately older men who are more likely to be unemployed, financially disadvantaged, have less medical knowledge, and more

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often belong to a minority group than those treated in other institutions.[11,12] The authors reviewed their experience with COVID-19 at the Clement J. Zablocki VA Medical Center in Milwaukee, Wisconsin, and compared the demographic characteristics, comorbid conditions, treatment, and outcome of these patients with those described in other US general hospital populations.

METHODS

Patients treated for COVID-19 between March 11, 2020 and June 1, 2020 were included in the evaluation, which was approved by the Clement J. Zablocki VA Medical Center Institutional Review Board. Only patients with confirmed COVID-19 infection identified using the reverse transcriptase polymerase chain reaction test of nasopharyngeal or oropharyngeal swabs were included. The VA clinical pharmacy conducted these tests. Patients admitted to the hospital or those presenting to the emergency department with signs or symptoms consistent with COVID-19 (eg, fever, sore throat, dyspnea, cough), those with known exposure to subjects who were COVID-19 positive, or those who had a high index of clinical suspicion of infection were tested. Veterans with COVID-19 were classified into 3 groups: those requiring mechanical ventilation for respiratory failure, those admitted to the hospital but not requiring mechanical ventilation, and those who were evaluated in the emergency department and discharged to home isolation. Patient demographics, chronic medical conditions, medications, presenting signs and symptoms, treatment, and outcomes were recorded from the hospital's electronic medical record system.

Descriptive statistics were used to characterize each group of patients. Categorical variables were compared using chi-square or Fisher exact probability test as appropriate. Continuous variables were compared using one-way analysis of variance followed by application of Student *t* test with Bonferroni correction for multiplicity. The null hypothesis was rejected when the probability value was less than 0.05.

Table 1. Demographics, Vital Signs, and Presenting Symptoms

	Mechanical Ventilation	Hospital Admission	Home Isolation	Total
Number (%)	14 (14.7%)	50 (52.6%)	31 (32.6%)	95
Men/women	14/0	47/3	27/4	88/7
Age (years)	678	7±11	57±14[a,b]	65±13
Height (cm)	180±6	178±8	178±10	178±8
Weight (kg)	96±22	94±22	99±25	96±23
Body mass index (kg/m^2)	30±6	29±6	31±7	30±6
Racial Ethnicity				
White (%)	4 (28.6%)	22 (44.0%)	8 (25.8%)	34 (35.8%)
African American (%)	10 (71.4%)	28 (56.0%)	22 (71.0%)	60 (63.2%)
Asian American (%)	0 (0.0%)	0 (0.0%)	1 (3.2%)	1 (1.1%)
Vital Signs				
Heart rate (beats per minute)	103±16	92±17[a]	85±13[a,b]	92±17
Systolic arterial pressure (mmHg)	133±24	136±20	143±26	137±23
Diastolic arterial pressure (mmHg)	79±17	76±12	81±12	78±13
Respiratory rate (breaths per minute)	28±11	22±7[a]	18±3[a,b]	22±8
Oxygen saturation (%)	86±9	94±5[a]	97±2[a,b]	94±6
Presenting Symptoms				
Fever (%)	8 (57.1%)	33 (66.0%)	12 (38.7%)[b]	53 (55.8%)
Chills (%)	3 (21.4%)	15 (30%)	9 (29.0%)	27 (28.4%)
Cough (%)	7 (50%)	30 (60%)	20 (64.5%)	57 (60.0%)
Dyspnea (%)	12 (85.7%)	27 (54.0%)[a]	12 (38.7%)[a]	51 (53.7%)
Malaise (%)	7 (50%)	20 (40%)	8 (25.8%)	35 (36.8%)
Myalgias (%)	5 (35.7%)	6 (12%)	15 (48.4%)[b]	26 (27.4%)
Headache (%)	2 (14.3%)	12 (24%)	10 (32.3%)	24 (25.3%)
Gastrointestinal complaints (%)	3 (21.4%)	11 (22.0%)	10 (32.3%)	24 (25.3%)
Loss of smell or taste (%)	1 (7.1%)	6 (12.0%)	5 (16.1%)	12 (12.6%)

Data are numbers (percentages) or mean±standard deviation.
[a]Significantly ($P<0.05$) different from mechanical ventilation.
[b]Significantly ($P<0.05$) different from hospital admission.

RESULTS

A total of 95 patients (88 men, 7 women) tested positive for COVID-19 and were included in this evaluation (Table 1). Fourteen patients required mechanical ventilation, whereas 50 and 31 patients were treated in the hospital without ventilation or were discharged to home isolation, respectively. Discharged patients were younger (age 57 years +/- 14 years) than those who were intubated (age 67 years +/- 8 years) or hospitalized (age 70 years +/- 11 years). The majority of patients with COVID-19 were African American (63.2%); no differences in racial ethnicity were observed between treatment groups. COVID-19-positive patients receiving mechanical ventilation had higher initial heart rate and respiratory rate and lower oxygen saturation (assessed coincident with COVID-19 testing) than those who did not have respiratory failure (103±16 beats/minute, 28±11 breaths/minute, and 86±9% vs 92±16 beats/minute, 22±7 breaths/minute, and 94±5%, respectively; $P<0.05$ for each). Hospitalized patients had similar derangements in vital signs compared with those who were discharged. No differences in systolic or diastolic arterial pressure were observed between treatment groups. COVID-19 patients who subsequently required mechanical ventilation were more likely to report dyspnea as a presenting symptom (85.7%) than those who did not. Patients released to home isolation were less likely to present with fever but more likely to complain of myalgias versus those who were hospitalized. No differences in other presenting symptoms were observed between groups.

COVID-19 patients who required mechanical ventilation were more likely to have a history of hypertension and hyperlipidemia than their counterparts who were discharged to home isolation

Table 2. Medical History and Medications

	Mechanical Ventilation	Hospital Admission	Home Isolation	Total
Medical history				
Coronary artery disease (%)	5 (35.7%)	10 (20.0%)	2 (6.5%)	17 (17.9%)
Hypertension (%)	12 (85.7%)	42 (84.0%)	15 (48.4%)[a,b]	69 (72.6%)
Hyperlipidemia (%)	11 (78.6%)	28 (56.0%)	14 (45.2%)[a]	53 (55.8%)
Diabetes mellitus (%)	9 (64.3%)	26 (52.0%)	11 (35.5%)	46 (48.4%)
Peripheral vascular disease (%)	3 (21.4%)	4 (8.0%)	1 (3.2%)[b]	8 (8.4%)
Stroke (%)	1 (7.1%)	1 (2.0%)	0 (0.0%)	2 (2.1%)
Chronic kidney disease (%)	3 (21.4%)	15 (30.0%)	1 (3.2%)	19 (20.0%)
COPD (%)	4 (28.6%)	5 (10%)	2 (6.5%)	11 (11.6%)
Obstructive sleep apnea (%)	6 (42.9%)	13 (26.0%)	5 (12.3%)	24 (25.3%)
Obesity (%)	5 (35.7%)	25 (50.0%)	9 (29.0%)	39 (41.1%)
Tobacco use disorder (%)	10 (71.4%)	37 (74.0%)	22 (71.0%)	69 (72.6%)
Psychiatric disorder (%)	9 (64.3%)	26 (52.0%)	18 (58.1%)	53 (55.8%)
Medications				
Beta blocker (%)	7 (50%)	24 (48.0%)	4 (12.9%)[a,b]	35 (36.8%)
ACE/ARB (%)	8 (57.1%)	24 (48.0%)	8 (25.8%)[a]	40 (42.1%)
Calcium channel blocker (%)	4 (28.6%)	22 (44.0%)	7 (22.6%)	33 (34.7%)
Diuretic (%)	2 (14.3%)	6 (12.0%)	4 (12.9%)	12 (12.6%)
Nitrate (%)	2 (14.3%)	3 (6.0%)	0 (0.0%)	5 (5.3%)
Hydralazine (%)	1 (7.1%)	2 (4.0%)	0 (0.0%)	3 (3.2%)
Insulin (%)	4 (28.6%)	15 (30.0%)	2 (6.5%)[b]	21 (22.1%)
Oral hypoglycemic (%)	7 (50%)	17 (34.0%)	8 (25.8%)	32 (33.7%)
Statin (%)	8 (57.1%)	32 (64.0%)	13 (41.9%)	53 (55.8%)
Inhaled bronchodilator (%)	7 (50%)	16 (32.0%)	15 (48.4%)	38 (40.0%)

Abbreviations: COPD, chronic obstructive pulmonary disease; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers.
Data are numbers (percentages) or mean ± standard deviation.
[a]Significantly ($P<0.05$) different from mechanical ventilation.
[b]Significantly ($P<0.05$) different from hospital admission.

Table 3. Treatment of Hospitalized Patients

	Mechanical Ventilation	Hospital Admission	Total
Intensive care unit admission	14 (100%)	16 (32.0%)[a]	30 (31.6%)
Medications and interventions			
Antibiotic (%)	10 (71.4%)	23 (46.0%)	33 (34.7%)
Antiviral (%)	2 (14.3%)	1 (2.0%)	3 (3.2%)
Antimalarial (%)	10 (71.4%)	24 (48.0%)	34 (35.8%)
Inhaled bronchodilator (%)	2 (14.3%)	7 (14.0%)	9 (9.5%)
High-flow nasal cannula (%)	5 (35.7%)	0 (0.0%)[a]	5 (5.3%)
Anticoagulant (%)	5 (35.7%)	0 (0.0%)[a]	5 (5.3%)
Steroid (%)	1 (7.1%)	0 (0.0%)	1 (1.1%)
Mechanical ventilation duration (hours)	186 ± 149	--	186 ± 149
Length of stay (days)	16 ± 8	7 ± 4[a]	9 ± 6
Mortality (%)	4 (28.7%)	0 (0.0%)[a]	4 (4.2%)

Data are numbers (percentages) or mean ± standard deviation.
[a]Significantly ($P<0.05$) different from mechanical ventilation.

(85.7% and 78.6% vs 48.4% and 45.2%, respectively; $P<0.05$ for each, Table 2). No differences in other medical or psychiatric comorbidities were observed between treatment interventions. Hospitalized patients were more likely to be chronically treated with beta blockers, angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARB), and insulin than those who were discharged. Treatment of COVID-19-positive patients with antibiotics and antiviral and antimalarial medications was similar and independent of the need for intubation and mechanical ventilation (Table 3). Ventilated patients were more likely to be initially treated with humidified high-flow nasal cannula oxygen therapy (Vapotherm, Exeter, New Hampshire) and receive systemic anticoagulation than those who did not require endotracheal intubation. The duration of mechanical ventilation was 186 ± 149 hours. Hospital length-of-stay and mortality were greater for COVID-19-positive patients who were ventilated compared with those who were not (16 ± 8 days and 28.7% vs 7 ± 4 days and 0%, respectively; $P<0.05$ each).

DISCUSSION

The results of our study indicate that COVID-19-positive veterans were predominantly African American men. Individual health factors and medical treatments more often associated with a veteran infected with COVID-19 were hypertension, hyperlipidemia, and receiving a beta blocker or an ACEi/ARB. The COVID-19-positive veterans who presented with dyspnea, tachypnea, tachycardia, and hypoxemia were more likely to require endotracheal intubation and mechanical ventilation, had longer hospital length-of-stay, and experienced greater mortality. In contrast, the afebrile COVID-19-positive patients with normal oxygen saturation and myalgias upon presentation were more likely to convalesce and isolate at home.

Our findings in veterans are similar, but not identical to those reported in other populations. Older age, male sex, obesity, congestive heart failure, and chronic kidney disease were previously cited as risk factors in a large analysis of hospitalized COVID-19-positive patients in New York City.[13] A study of COVID-19 patients in Chicago reached conclusions similar to those reported here and merits attention because of Chicago's geographic proximity to the Milwaukee metropolitan area from which most of our veterans originate. Multivariable logistic regression analysis identified age, sex, respiratory rate, oxygen saturation, history of diabetes, and shortness of breath as factors predictive of intubation.[9] Our results confirmed the importance of signs and symptoms of respiratory compromise as risk factors for the need for mechanical ventila-

tion in COVID-19-positive veterans, whereas obesity and diabetes were not uniformly implicated. The association of obesity with outcomes may be due to fundamental alterations in respiratory mechanics[14,15] and the presence of proinflammatory cytokines known to inhibit the immune response.[16,17] Coronary artery disease, diabetes, stroke, and chronic kidney disease were not associated with an increased risk of acquiring COVID-19 in our veteran patients, whereas these diseases have been identified as risk factors for the development of adult respiratory distress syndrome requiring intensive care and mortality in other larger studies.[8,9,13,18] Our results did concur with previous findings suggesting that chronic obstructive pulmonary disease and asthma had less influence on hospitalization rates.[13] It is possible that our relatively small sample size precluded us from distinguishing other reported risk factors, including obesity, that have been observed in larger epidemiological surveys, but we believe the difference may be something unique to our veteran population.

The study from the Chicago area reported an intubation rate of 28% in hospitalized COVID-19 patients, which was very similar to our observation in veterans (14 of 64, 22%). A second report from the New York area described a mortality rate of nearly 10% in hospitalized patients and 24% mortality in mechanically ventilated patients.[8] Our data indicate a mortality rate of 29% in mechanically ventilated patients. Additionally, there was 0% mortality in hospitalized patients not intubated.

Our results also indicated that hypertension and hyperlipidemia were primary risk factors for hospitalization with or without mechanical ventilation in veterans. The proportion of our COVID-19-positive veterans with hypertension (72.6%) substantially exceeded the prevalence of this disease (10%-25%) in other reports[2,19] and has been linked to adverse outcomes.[20,21] Our results further indicated that the use of ACEi/ARB was more frequently associated with the need for mechanical ventilation in veterans. The use of these medications has been linked to upregulation of the membrane receptor angiotensin converting enzyme 2 (ACE2),[22] and acute respiratory distress syndrome associated with another coronavirus results from viral binding to ACE2 expressed on the surface of alveolar endothelium.[23,24] Whether a causative link exists between use of ACEi/ARB and severe COVID-19 respiratory disease has yet to be definitively established.[20,25] This question will need to be addressed in future clinical trials.[26]

Our results should be interpreted within the constraints of several potential limitations. As mentioned, our sample size was relatively small and only included patients treated at a single VA medical center. Whether our findings can be extrapolated to other VA facilities caring for COVID-19 patients cannot be ascertained. Several patients in our population were still hospitalized when our data were analyzed. As a result, final clinical outcomes, including duration of mechanical ventilation, hospital length-of-stay, and mortality could not be established for the purposes of this analysis. The specific criteria for endotracheal intubation and mechanical ventilation were not standardized and differed to some degree between health care providers. We incorporated prone positioning in the treatment of our hospitalized COVID-19 patients when preliminary findings suggested that this intervention was beneficial for oxygen exchange. We did not quantify the number of patients who underwent proning or the duration of prone treatment, nor did we assess the relative efficacy of this technique in our evaluation.

CONCLUSION

Our evaluation describes the clinical features of COVID-19-positive patients treated during a two-and-a-half month period at the Clement J. Zablocki VA Medical Center in Milwaukee, Wis. Our results indicated that COVID-19-positive veterans at our facility are predominantly African American men. We found COVID-19-positive patients had a prevalence of hypertension and hyperlipidemia, and many patients were receiving beta blockers or ACEi/ARB. Our COVID-19-positive veterans who presented with dyspnea, tachypnea, tachycardia, and hypoxemia were more likely to require endotracheal intubation and mechanical ventilation, had longer hospital length-of-stay, and experienced greater mortality. In general, our findings mirror those reported in the populations from US hospitals treating the COVID-19 pandemic.

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Continuous Engagement in a Weight-Loss Program Promotes Sustained Significant Weight Loss

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ABSTRACT

Background: Significant weight loss improves health but regain is common.

Objective: The objective of the study was to determine if 2,346 members of Take Off Pounds Sensibly—a national, low-cost, peer-led weight-loss program—achieved and maintained significant weight loss with 7 consecutive annual renewals.

Methods: This study was a retrospective cohort design. For each renewal, the cumulative change from baseline weight was calculated. Weight change was placed into 1 of 3 categories: significant weight loss, loss ≥ 5%; weight stable, loss of 0 to < 5%; or weight gain, any amount above baseline weight.

Results: The cohort included 2,346 individuals. Fifty-one percent (n=740) of participants were in the significant weight-loss category all 7 years; 256 (18%) were in the significant weight-loss category at year 1 but moved into at least 1 other category during years 2 through 6; 359 (25%) were in the weight stable category at year 1; and 98 (7%) were in the weight gain category at year 1.

Conclusions: Over 60% of the population achieved significant weight loss by year 7. Since continuous, long-term engagement in a weight-loss program can lead to significant weight loss, even if significant weight loss is not initially achieved, participation should be encouraged.

INTRODUCTION

Overweight and obese individuals are at greater risk for virtually every chronic health disease, including Type 2 diabetes, coronary artery disease, dyslipidemia, and various forms of cancer.[1-4] On the other hand, individuals who experience significant weight loss—defined as weight loss ≥ 5% of baseline weight—reduce or eliminate their risks for these conditions.[5] Unfortunately, the health benefits of significant weight loss diminish when weight is regained.[6,7] While weight-loss programs are effective at weight loss, maintaining significant weight loss over the longer term is a critical challenge. For example, a meta-analysis of weight-loss programs found approximately 80% of weight lost is regained after 4 to 5 years.[8] However, few studies describe what percentage of individuals maintain significant weight loss for more than 2 years.[9-11]

Objective

The objective of this research is to describe the percentage of Take Off Pounds Sensibly (TOPS) participants with significant weight loss over 7 consecutive years of membership. Fully described elsewhere,[12] TOPS is a nonprofit, peer-led behavioral health promotion program designed to help its members lose weight by eating healthier and increasing physical activity. Previous studies of TOPS showed that the average weight loss for those consecutively renewing their membership was 7% to 8% of baseline weight.[12] The purpose of the study is to determine if individuals with 7 consecutive annual TOPS renewals stay in the significant weight loss category.

TOPS Program Details

TOPS is a health promotion program with over 115,000 members in more than 6,000 chapters located in communities throughout the United States. Chapters start with at least 4 interested com-

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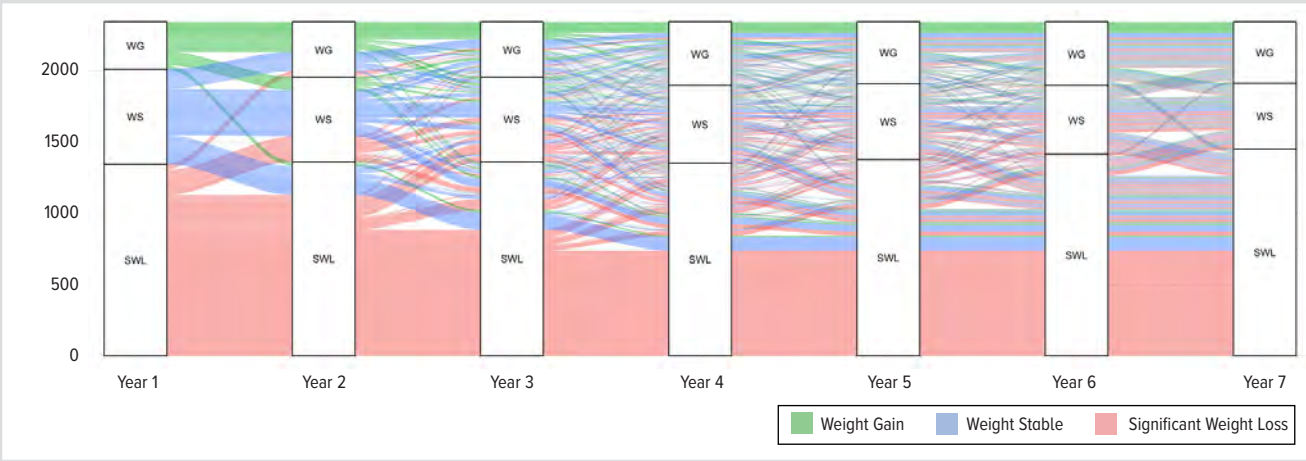
Figure. Weight-Change Categories Over 7 Years



munity members. A TOPS "chapter advocate" assists new chapters with initial paperwork, organization, and programming ideas. TOPS provides the administrative and educational materials. The program recommends one of two nutrition plans: the American Academy of Nutrition and Dietetics Food Exchange System[13] or the US Department of Agriculture (USDA) My Plate Program.[14] Participants also learn about recommended physical activity levels based on the US Department of Health and Human Services Physical Activity Guidelines.[15]

Weigh-in Procedures

Prior to each weekly meeting, a weight recorder documents members' weights during a private weigh-in, then there is a group educational program. TOPS has specific weight measurement and recording procedures described in its chapter manual. For example, no members or officers are allowed to measure or record their own weights. Additionally, participants with medical equipment – such as casts or braces – must have a signed statement from a health care provider about the weight of the equipment, which is deducted from the participant's recorded weight. There are also procedures for dealing with common variances when a chapter gets a new scale and when members transfer to new chapters.[16,17] Although members are expected to weigh in each week, weight measurements are sent to the national office when members join and at the time they renew their annual membership. The data for this study were obtained from the national database.

Once individuals achieve their goal weights, they enter the maintenance phase of the program, Keep Off Pounds Sensibly (KOPS). Weight-loss and weight-maintenance phases are nearly indistinguishable because TOPS and KOPS members attend the same weekly meetings and weigh-ins.

METHODS

This is a retrospective cohort design to describe weight change for TOPS' members who renewed their annual membership for 7 consecutive years. After obtaining Institutional Review Board approval, the TOPS national office shared deidentified information for members enrolling from January 2005 through December 2011. This study included only participants who (1) joined the program from January to December 2005 and (2) who renewed their annual membership for 7 consecutive years.

Weight Change

Weight change was calculated as percentage change from baseline weight at initial TOPS enrollment. For each year, cumulative weight change relative to baseline weight was placed into one of three categories: (1) significant weight loss (SWL, cumulative weight loss ≥5% of baseline weight); (2) weight stable (WS, cumulative weight loss of 0 to <5% of baseline); and (3) weight gain (WG, cumulative weight change >0). Mean and standard deviations (SD) of the weights were calculated for the cohort. An alluvial figure (Figure 1) was created to show the change in weight categories across all 7 years of participation in the TOPS program. Data were analyzed using SAS v. 9.4 (Cary, NC) and R 3.1.3 (Vienna, Austria).

RESULTS

Of the 35,661 individuals who joined TOPS during 2005, the cohort contained 2,346 – less than 7% – who renewed their membership for 7 consecutive years. The mean baseline weight for the cohort was 97.5 kg (SD 20.8); 2,197 (94%) were women and 149 (6%) were men. Table 1 shows the cohort's average cumulative weight change. Over the course of the study, the cohort's cumulative average weight change was clinically significant at each of the 7 annual renewals.

Weight Change Categories Compared to Baseline Weight at Each Renewal

Table 2 shows the percentage of participants in each category over the 7 years. The percentage of participants with significant weight

loss ranged from 57% at year 1 renewal to 62% at year 7 renewal. The percentage of individuals in the WS category ranged from 20% at year 7 renewal to 28% at year 1 renewal. The percentage of participants in the WG category ranged from 14% at year 1 renewal to 19% at year 4 and 6 renewals.

Table 1. Average Cumulative Weight Change (kilograms and percentage) at Annual Renewals

	Starting Weight	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
Weight change, mean kg (SD)	97.5 (20.8)	-7.0 (8.2)	-7.5 (9.6)	-7.3 (9.7)	-7.2 (10.0)	-7.5 (10.4)	-7.8 (10.7)	-8.2 (11.0)
Weight change, mean % (SD)		-7.1 (7.8)	-7.6 (8.8)	-7.4 (8.9)	-7.3 (9.2)	-7.4 (9.5)	-7.8 (9.7)	-8.2 (10.1)

Table 2. Weight Categories From Starting Weight at Annual Renewal, N=2,346 [a]

Category	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
Significant weight loss, n (%)	1347 (57%)	1365 (58%)	1363 (58%)	1355 (58%)	1380 (59%)	1417 (60%)	1453 (62%)
Weight stable, n (%)	667 (28%)	593 (25%)	595 (25%)	544 (23%)	532 (23%)	482 (21%)	463 (20%)
Weight gain, n (%)	332 (14%)	388 (17%)	388 (17%)	447 (19%)	434 (19%)	447 (19%)	430 (18%)

Significant weight loss: ≥5% loss; weight stable: 0 to <5% loss; weight gain: >0.
[a] Column percentages may not total 100% due to rounding.

Figure 1 shows how individuals either stayed within or moved between weight-change categories for years 1 through 7. The majority (64%) of participants moved between categories during the study period, whereas 36% remained in the same category all 7 years (ie, 740 [32%] in SWL, 20 [1%] in WS, and 78 [3%] in WG). At the year 7 renewal, 1,453 (62%), 463 (20%), and 430 (18%) were in the SWL, WS, and WG categories, respectively. Seven hundred-forty participants (51%) were in SWL for all 7 years; 256 (18%) were in SWL at year 1 but moved into at least one other category during years 2 through 6. Three hundred fifty-nine (25%) were in WS at year 1, while 98 (7%) were in WG at year 1.

Twenty participants (4%) were in the WS category all 7 years; 139 (30%) were in WS at year 1 but moved into at least one other category during years 2 through 6. Two hundred eighteen (47%) were in the SWL category at year 1; 86 (19%) were in the WG category. Seventy-eight (18%) were in the WG category all 7 years; 70 (18%) were in WG at year 1 but moved into at least one other category during years 2 through 6. One hundred forty-nine (35%) were in WS at year 1; and 133 (31%) were in SWL at year 1.

DISCUSSION

Over 60% of individuals who consecutively renewed their membership in a peer-led weight-loss program for 7 years achieved significant weight loss by year 7, with half staying in the SWL category for all 7 years. The implication is that continuous engagement in a weight-loss program helps participants maintain significant weight loss. It is also important to note that individuals who were in the WG group at the end of year 1 did not necessarily remain in that group by the end of year 7, implying that individuals were engaged in the weight-management process throughout their time as a TOPS member. These findings are significant since 62% of individuals were in the SWL category after 7 years.

Weight-loss and weight-maintenance phases of weight-management programs tend to be finite in nature and differ by frequency of participation – for example, weekly during the weight-loss phase and monthly during the maintenance phase. Weight-loss maintenance among TOPS participants may be enhanced by the program's continual support once they reach their goal weight and become "KOPS" members. This aligns with a continuous care model of obesity treatment[18] and has been supported in a review analyzing "extended care" for long-term weight-loss maintenance[19] and national guidelines to manage overweight and obesity.[5]

Several studies have shown that the more program sessions individuals attend or the more time an individual spends in a program, the more weight they lose.[20-22] In this study, it is important to note that when individuals in the SWL category gain weight, they may remain in that category if their cumulative weight loss is ≥5% of their initial weight. While no other national weight-loss program has investigated weight-change categories for all participants in a real-world scenario beyond 1 year, Weight Watchers has twice reported the weight-loss maintenance of a subset of program participants from 1 to 5 years.[23,24] In the first study of 1,002 "lifetime" members – those who achieved and maintained their goal weights for at least 6 weeks – 70%, 60%, 54%, 46%, and 43% maintained significant weight loss at years 1 to 5, respectively. In the second study of almost 699 "lifetime" members, 80%, 71%, and 50% maintained significant weight loss at 1, 2, and 5 years, respectively. Although it is difficult to compare these results with the current study because of the different methodologies and the small subset of Weight Watchers members vs TOPS members with consecutive annual membership renewal, findings indicate that regaining weight is common among those with significant weight loss in a structured program and that individuals are less likely to maintain significant weight loss as times goes on.

This study is important because it examines the weight-change categories of a population of almost 2,400 individuals who participated in a low-cost, peer-led weight-loss program for at least 7 years. TOPS members might experience greater success at maintaining significant weight loss since individuals who reach their goal weights are expected to participate in weekly educational sessions as part of KOPS, the maintenance category for TOPS.

In TOPS, individuals who reach their goal weight are expected to continue to attend weekly meetings indefinitely. This expectation of continuous engagement in the weight-management process may be the key to the successful weight-loss maintenance for many of the individuals in this study.

There are two unexpected results from this study. Individuals who were above their initial weight after one or more consecutive annual renewals continued to renew their annual membership, and some of those individuals eventually lost a clinically significant amount of weight. First, it is surprising that individuals would remain in a weight-loss program where they gained weight over the course of 1 or more years. It is possible that participants enjoyed the social interactions within the TOPS chapter so they continued to participate, even if they did not lose weight. Second, these results contradict other studies and conventional wisdom suggesting that "successful" weight loss is mostly, if not only, associated with "early" weight loss.[25-28] Our results may indicate the value of keeping individuals engaged in the weight-management process, even if they were initially unsuccessful.

One potential limitation is that this analysis represents a small percentage of those who joined the program during its first year because it was limited to individuals who consecutively renewed their annual membership. However, our goal was to determine the long-term weight-change categories of those who were continuously engaged in the program. Second, we do not have data about comorbid conditions, concomitant medication use, diet, physical activity, or weekly participation. While these factors could serve as significant confounding variables that influenced weight change over the study period, the study examines weight-change outcomes in a real-world setting. Third, we do not have data on participants' socioeconomic status. Therefore, we cannot draw any conclusions about whether this program is successful for individuals of varying socioeconomic levels. However, our previous research showed the demographics of the census tracts where TOPS chapters were located: more than 60% were in census tracts where the annual median income was less than $50,000, more than 90% were in predominantly White census tracts, and almost 75% of TOPS chapters were in predominantly urban census tracts.[29] We also have published the average age and weight of female TOPS' participants who achieved significant weight loss.[30]

One practical implication is that insurance coverage for weight-loss programs could be used to a greater extent to assist individuals in managing their weight and, thus, improving their health. However, weight-loss programs for *overweight* patients with comorbidities are not fully covered by Medicare,[5] and the coverage for obesity is restricted. For example, Medicare coverage for treating obesity (not overweight) allows weekly visits for month 1, every other week for months 2 to 6, and monthly for months 7 to 12, although interactions that are more frequent are associated with greater weight loss and weight-loss maintenance.[21,22] Additionally, Medicare continues to pay for individuals in months 7 to 12 only if they lose at least 3 kg within the first 6 months. Although we only have data for individuals at yearly intervals, 67% lost at least 3 kg by the end of the first year while 69% lost ≥ 3 kg by the end of year 7 (when comparing weight at renewal to weight at baseline). Thus, 33% of individuals would not have insurance coverage even though they might successfully lose weight if given more time to do so. Additionally, almost 46% of individuals in either the WG or WS categories at the end of their first year moved to the SWL category by year 7. Finally, Medicare only covers behavioral counseling for 1 year, even if participants lose the requisite 3 kg in the first 6 months. To maintain weight loss, individuals need to continue the behaviors that helped them lose weight. Under Current Procedure Terminology (CPT) G0447, the total Medicare reimbursement for individual behavioral weight-loss counseling is approximately $500 per year. TOPS costs approximately $92 per year.

CONCLUSION

This study shows that continuous engagement in a weight-loss program can lead to sustained positive results for most participants through either significant weight-loss maintenance or weight loss after initial weight gain. Future research should study why individuals who gain weight may choose to remain in these programs and what motivated those who were initially unsuccessful to start losing weight. To promote sustained weight loss, weight-loss programs should incorporate a model that encourages continuous, long-term engagement. Additionally, insurance programs should consider covering those types of programs.

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A Curriculum to Increase Empathy and Reduce Burnout

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ABSTRACT

Purpose: Empathy is essential for good patient care. It underpins effective communication and high-quality, relationship-centered care. Empathy skills have been shown to decline with medical training, concordant with increasing physician distress and burnout.

Methods: We piloted a 6-month curriculum for interns (N = 27) during the 2015-2016 academic year at the University of Wisconsin-Madison. The course included: (1) review of literature on physician well-being and clinical empathy, (2) instruction on the neurobiology of empathy and compassion, (3) explanation of stress physiology and techniques for mitigating its effects, (4) humanities-informed techniques, and (5) introductions to growth mindset and mindful awareness. To measure effectiveness, we compared empathy and burnout scores before and after the course.

Results: The course was well-attended. Intern levels of burnout and empathy remained stable over the study period. In multivariable modeling, we found that for each session an intern attended, their emotional exhaustion declined by 3.65 points ($P = 0.007$), personal accomplishment increased by 2.69 points ($P = 0.001$), and empathic concern improved by 0.82 points ($P = 0.066$). The course was well-liked. Learners reported applying course content inside and outside of work and expressed variable preferences for content and teaching methods.

Conclusion: Skills in empathic and self-care can be taught together to reduce the decline of empathy and well-being that has been seen during internship. In this single-center pilot, resident physicians reported using these skills both inside and outside of work. Our curriculum has the potential to be adopted by other residency programs.

INTRODUCTION

Strong patient-physician relationships are essential for effective communication and support high-quality care. Clinical empathy is a critical skill in the cultivation of effective therapeutic relationships with patients. Empathy includes cognitive and emotional components, as well as intentions and behaviors that seek to alleviate suffering (ie, compassion and compassionate behaviors). There is no consensus definition of clinical empathy, but researchers have studied the impact of physician empathy primarily by assessing communication or relationship variables. These studies demonstrate positive outcomes for both physicians and their patients. For physicians, these outcomes include improved diagnostic accuracy, efficiency, self-efficacy and confidence, job satisfaction, burnout, rate of malpractice claims, and the cost of care.[1–5] Patient outcomes include improved recall, comprehension, loyalty, trust, satisfaction with care, self-efficacy, treatment adherence in chronic disease management, health status, quality of life, safety, symptom management and function.[6–12] In fact, a meta-analysis published in 2014 focused on randomized controlled trials in which the patient-physician relationship was the experimental variable, found a meaningful impact on health care outcomes across multiple disease states.[12]

There is a nuanced relationship between empathy and burnout. High personal distress and identification with a suffering patient can engender stressful or overwhelming suffering within the empathizer, raising the risk for burnout.[13,14] However, research with trauma therapists demonstrates that well-developed empathy helps both patients and clinicians. This work suggests that "exquisite empathy," described as "highly present, sensitively attuned, well-boundaried, heartfelt empathic engagement" is, in fact, sustaining

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and protective against burnout and compassion fatigue.[15,16] Further, a study examining an intervention aimed at reducing personal distress via cognitive reappraisal compared with an intervention to augment compassion found that while both interventions improved subjects' altruistic behaviors, it was the compassion intervention that was more protective against personal distress.[17] These studies support the growing consensus that well-developed empathy protects physicians against burnout.[18] Since progress through medical training consistently has been shown to correlate with reductions in empathy and epidemic levels of distress and burnout, interventions to support empathy skills and personal well-being are a critical necessity in residency programs.[19,20]

Table 1. Curricular Components

Empathy and Compassion	Observation Training Using Art	Behavior Training Using Improvisation	Stress, Resilience, and Self-Awareness
Definitions	Metacognition	Mirroring	Mindful awareness
Relationship between empathy and distress	Emotion recognition	Emotion recognition and response	Meditation
Neurobiology of empathy and compassion	Connecting with one's own humanity	Close listening	Positive emotion cultivation
Evidence base for utility in Medicine	Comfort with ambiguity	Attention	
Compassion meditation Empathic communication	Perspective-taking	Flexibility	

Box. Outcome Measures and Their Domains

Instruments and Domains Measured

Burnout (Maslach Burnout Inventory)
- Emotional exhaustion – Feelings of depletion and exhaustion related to work
- Depersonalization – Feelings of callousness and detachment from patients
- Personal accomplishment – Feelings of effectiveness and meaning in work

Empathy Domains in the Interpersonal Reactivity Index
- Perspective taking – The ability to perceive another's situation within the world (cognitive empathy)
- Empathic concern – Feelings of warmth, compassion, and concern for others
- Personal distress – Feelings of distress when observing another's pain (physical or emotional)
- Fantasy – The tendency to imaginatively project oneself into the emotional life of another, measured by identification with fictitious characters in books or movies

Emotional Styles Domains
- Resilience – Speed of recovery from adversity
- Outlook – Ability to maintain positive emotion
- Social intuition – Adeptness at picking up social cues
- Self-awareness – How well one perceives bodily feelings reflecting emotion
- Sensitivity to context – Self-regulation in light of social context
- Attention – How sharp and clear focus is

METHODS

We developed a 9-session curriculum for internal medicine interns to strengthen empathy skills and reduce burnout. We hypothesized that a multimodal, neuroscience and humanities-informed curriculum would improve measures of empathy and burnout in this population and measured the course's impact by examining burnout and empathy before and after course participation.

Curriculum Development

We performed a literature review to identify pedagogical techniques with relevance to the development of (1) skills in self-care to reduce burnout and emotional distress and (2) skills in effectively caring for others focused on empathic or compassionate care. We reviewed the medical and other health professions literature as well as the education, psychology, and neuroscience literature. Given evidence from prior programs that a one-size-fits-all approach will leave learner subgroups untouched, we decided to employ a multimodal approach.[21] Components ultimately included in the curriculum are shown in Table 1. We also taught the concept of growth mindset at the beginning of the course to increase learner acceptance and uptake of content and bolster their confidence in learning these skills. Growth mindset is a belief that with effort, one can improve in a certain domain (eg, empathy).[22]

Course Logistics

The course included 9 sessions ranging in length from 2 to 4 hours held on Friday afternoons spread over 6 months. We worked with residency program leadership (including program staff, chief residents, and the program director) to determine where in the weekly and daily schedule our curricular sessions would face the least competition and clinical coverage difficulties that could lead to resentment or low attendance. In this pilot year, the intern class was divided into 2 groups so only half of the interns would be gone from rotations at any given time. We randomized men and women separately into the groups to preserve gender balance. The schedule was provided to the interns at the beginning of the year, and we sent email reminders to all clinical teams at the beginning of each rotation with the schedule of sessions. We also sent reminder pages to the interns 1 to 2 hours before sessions. This project was reviewed and exempted by the University of Wisconsin Institutional Review Board as Program Evaluation.

Course and Program Evaluation

All interns (N = 28; 22 men, 6 women) were required to participate in the curriculum, but they could elect whether or not to participate in the curriculum evaluation, which all but 1 intern elected to do (N = 27). We gathered data during their orientation period, after 6 months of internship, and in the last month of internship. To protect interns' privacy, the course creators did not have access to personally identifying information on any of the measures collected; their data were tracked using a nonidentifying study ID. Outcome measures included empathy, using the Interpersonal

Table 2. Changes in Burnout and Empathy Measures Before and After Attendance of the Empathy Course

	Pre-Course [a]	Post-Course [a]	β Coefficient for Attendance [b]	Other Significant Predictors [c]
Burnout				
Emotional exhaustion	22.5 (5.6)	23.0 (8.0)	-3.65 ($P=0.007$)	Sensitivity to context β=3.97 ($P=0.02$)
Depersonalization [d]	8.7 (4.4)	10.6 (4.5)	0.75 ($P=0.40$)	None
Personal accomplishment	39.4 (4.2)	39.6 (4.5)	2.69 ($P=0.001$)	Attention β=0.96 ($P=0.017$)
Empathy				
Perspective-taking	19.9 (4.7)	20.6 (4.4)	-0.06 ($P=0.869$)	Outlook β=0.78 ($P=0.023$)
Fantasy	18.6 (5.3)	17.7 (6.6)	0.79 ($P=0.21$)	None
Empathic concern	21.2 (2.9)	21.6 (3.0)	0.82 ($P=0.066$)	Sensitivity to context β=-1.1 ($P=0.05$)
Personal distress	10.3 (4.2)	9.6 (4.4)	0.56 ($P=0.29$)	None

[a] Expressed as Mean (Standard Error).
[b] Impact of attendance expressed as β coefficient; for instance, for every session attended the outcome changes by β.
[c] Other significant predictors include those with $P<0.05$ in multivariable modeling.
[d] $P<0.05$.

Reactivity Index (IRI), and burnout, using Maslach Burnout Inventory (MBI). Predictors included Mindset Assessment Profile (MAP)[23–25] and an emotional styles inventory (ESI) that was collected during orientation and at the end of internship to understand the relationship among baseline emotional style, burnout, and empathy.[26] The emotional styles inventory measures resilience, outlook, self-awareness, social intuition, sensitivity to context, and attention. Domains included in the outcome measures are summarized in the Box. If our curriculum were effective, we would expect to see stabilization or reductions in the MBI domains of depersonalization and emotional exhaustion and a stabilization or increase in personal accomplishment, as well as the IRI domains of empathic concern and perspective-taking. We tracked attendance at each session. At the end of the course, we also evaluated favored course methods, skills used both inside and outside of work, and ongoing support for the course using free text entry.

Statistical Analysis

All pre- and post-data were analyzed using paired t tests for dependent samples. In order to understand how the course affected burnout and empathy, we performed multivariable modeling including the following predictors: mindset, emotional styles domains, cohort (to capture time of year), and session attendance. Given the correlations between predictors and instruments, collinearity was assessed among the predictor variables and was acceptably low to include all covariates in the model. Although we performed several comparisons between our burnout and empathy outcome variables and our predictors of interest, we did not adjust for multiplicity due to the exploratory nature of those analyses. All analyses were conducted using SAS, version 9.4 and findings were statistically significant at $P<0.05$ (95% CI).

RESULTS

Of 28 interns, all participated in the course and 27 (96.4%) elected to participate in the course evaluation. The reason for the one intern's nonparticipation was unknown. At baseline, the 2 cohorts did not differ significantly with respect to growth mindset, empathy levels, burnout, or emotional style, and burnout was present in 41% of interns (scoring high in emotional exhaustion or depersonalization, or both) with average scores in the moderate range for both. Detailed pre- to post-outcome measures, as well as the impact of session attendance on outcome measures, are shown in Table 2.

Intervention Feasibility and Acceptability

Interns attended a median of 7 of 9 sessions in both cohorts. However, there were more interns who attended fewer than 6 sessions in cohort 2 (attendance range 5-8 in cohort 1 and 3-8 in cohort 2). Most interns (74.0%) felt they had the support of other residents and faculty to attend the class. The other 26% reported feeling moderately supported and, of these, most reported that it was difficult to leave on call days or otherwise particularly busy clinical days. At course completion, interns were asked to rate their anticipated level of support for new interns attending the course the following year. The majority (92.5%) reported a high, unconditional level of support for the course in the future. By contrast, 2 respondents reported contingent support. For example, one intern said they would "do (their) best to get (their interns) to the course though patient care will continue to take precedence."

Use of Concepts and Favored Methods

Interns reported utilizing concepts both in and outside of work. Skills learned in the improvisational theatre sessions, meditation or mindfulness practices, and specific empathic communication techniques were mentioned the most. Approximately 33% of interns specifically commented that naming emotions and the other skills taught as part of the empathic communication mneumonic NURSE (Naming, Understanding, Respecting, Supporting, Exploring)[27] were very helpful, both in their personal and professional lives. One stated that it was "extremely helpful in 'defusing' angry/frustrated patients."

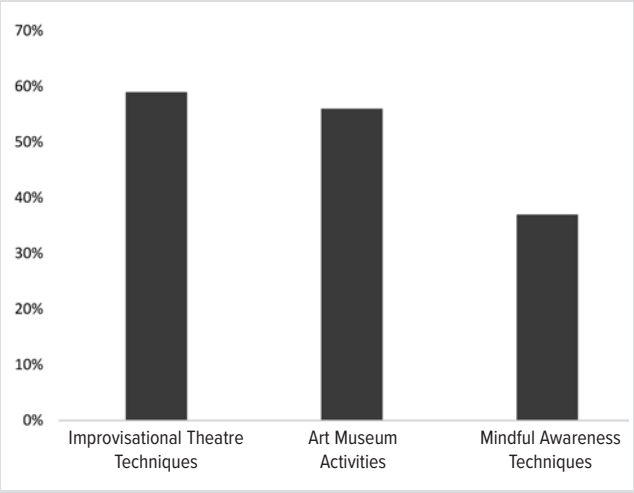
Many interns made comments that meditation and reflection were very helpful, especially with managing their personal emotions: "When I am about to see a presumably 'difficult' patient in clinic, I definitely pause outside the room, take a deep breath, and then knock."

A few interns (14.8%) noted that they started using meditation

and mindfulness more regularly. The fixed versus growth mindset was a new concept to many interns and, at the end of the year, 29.6% noted it as a concept that they either recalled or used during the year. One intern in particular recalled the growth mindset stating, "It took me a really long time to realize that I wasn't alone in feeling kind of overwhelmed and underqualified. I think once I felt okay about not being 100% perfect at my job (and focus on growing, helping patients) I really got a ton better at my job!"

Favored methods in the course also varied, but visiting the art museum and the improvisational theatre sessions were the most enjoyed. Many interns said they appreciated the opportunity to get away from the hospital to visit the art museum. The percentages of interns that reported each method as most enjoyable are shown in the Figure; many interns rated equal enjoyment of more than one method.

Figure. Self-reported Favored Teaching Methods



Empathy and Burnout

The pre- and post-course scores in all burnout and empathy subscales are shown in Table 2. The only measure that changed significantly was depersonalization, which appeared to increase. This could imply a decrease in empathy. However, in the model that included course attendance, there was no signficiant relationship between course attendance and depersonalization (P for beta = 0.40). Course attendance significantly predicted reduced emotional exhaustion (P = 0.007) and improved personal accomplishment (P = 0.001). These findings suggest that without the course, burnout would have worsened over the course of the year, as expected historically. We compared our pilot interns' empathy levels during the fall of their second year of residency to a group of historical second-year residents in our program who had not participated in the course, but were otherwise comparable due to their training level. The 27 residents who had taken our course vs the 34 historical residents showed improved IRI subscale scores in personal distress: 9.26 vs 11.67 (P = .03). All other domains did not reach significance, including perspective-taking: 21.26 vs 19.74 (P = 0.18); empathic concern: 21.33 vs 19.94 (P = 0.12); fantasy: 18.15 vs 16.41 (P = 0.23). Improved empathy is shown on the IRI by increases in perspective-taking and empathic concern accompanied by decreases in personal distress.

DISCUSSION AND CONCLUSIONS

We developed a feasible and well-liked intervention to improve skills in the care of others and self, as measured by improvements in empathy and burnout concordant with course attendance. We found that including multiple modalities supported content delivery. While depersonalization scores, on average, worsened over the course of the year, we found that attendance in our course did not appear to predict this change and was associated with improvements in emotional exhaustion and personal accomplishment, as well as a trend toward improvement in empathic concern. In addition, the course's effect on empathy was sustained after the course ended—as assessed 3 to 9 months after course completion—in comparison to a historical comparison group.

We found that different learners preferred different learning methods. This finding is consistent with the "CHANGES" study,[21] which showed that learner characteristics interact with curricular content in ways that are critical for educators to consider. A "one-size-fits-all" curriculum with a single modality is unlikely to be as effective for all learners as a curriculum that includes different "hooks" and methods. We challenged ourselves to integrate a variety of methods and content into our curriculum, in order to increase the likelihood that any curricular arrow would find a target and stick, allowing us to engage all learners. The methods and concepts interns reported as useful, in both work life and outside of work, clustered around emotional intelligence, empathic communication, and mindfulness in the face of stress or adversity.

We initially were surprised to find worsening depersonalization pre- to post-course, with no apparent effect of course attendance in multivariable modeling, as well as the apparently stable emotional exhaustion pre- to post-course, with an apparently protective effect from course attendance. We did not observe the historically expected increase in burnout over the course of internship in this group of interns.[20] To better understand whether this was simply related to the overall educational environment at our institution, we were able to compare changes in burnout from orientation to mid-academic year for the intern class entering the year after our pilot year to institutional comparisons (other nonprocedural training programs, including pediatrics, emergency medicine, psychiatry, pathology, neurology, radiology, nuclear medicine, and radiation oncology). In this group, we saw that between orientation and mid-year, the internal medicine interns—all of whom received our course—had depersonalization change by -0.11 and emotional exhaustion change by -0.91 (P = 0.92 and P = 0.7, respectively), while in the other nonprocedural interns depersonalization changed

by 1.6 and emotional exhaustion changed by 6.68 ($P = 0.22$ and $P = 0.005$, respectively).

Strengths of this study include excellent course participation, which heightens our confidence in the course's feasibility and acceptability. We also used common and validated outcome measures. Study limitations include the limited power that comes from a small sample size and multiple comparisons made as part of the analysis of this evaluation. The fact that the intervention occurred at a single center by a single teaching team may limit the generalizability of our findings. Finally, we chose for inclusion as predictor variables the subscales of the Emotional Styles Inventory, as published by Richard Davidson, PhD.[26] This inventory was selected because we have found it helpful when coaching residents on doctor-patient relationship issues to identify contributors and potential solutions. While it is not a validated instrument, it contains domains we have found pertinent as educators, and our analysis confirms that it maps to important outcomes. An additional limitation is the potential for reverse causation. For example, perhaps less emotionally exhausted interns were more likely to be able to leave their services to come to the sessions.

Limitations above notwithstanding, our findings suggest that skills in self and others are not mutually exclusive and that, for physicians, these domains can be linked and fruitfully taught together. Future directions include further development of this course to achieve graduated levels of difficulty so that trainees can retrieve and utilize the concepts learned during the most difficult clinical encounters and practice scenarios, in addition to determining whether other learner groups would benefit similarly from this curriculum to assess reproducibility and generalizability.

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A Cross-Sectional Study of Attitudes and Factors That Promote Medical Student Participation in Professional Medical Societies

Michael J. Rigby; Daniel D. Bennett, MD

ABSTRACT

Purpose: Medical student participation in professional medical societies is an understudied extracurricular activity. The purpose of this study is to assess student characteristics associated with participation and their attitudes toward professional medical societies.

Methods: A cross-sectional study using a 21-item survey questionnaire was administered to Wisconsin medical students in the fall of 2019. Regression analysis was used to find factors associated with participation.

Results: A total of 308 questionnaire responses were collected with a response rate of 17.4%. Sixty-three percent of respondents participated in a professional medical society, and the most important reasons for participating included professional development, networking, and advocacy. Participation was positively associated with age (OR = 1.16; 95% CI, 1.01-1.33); years of medical education (OR = 1.4; 95% CI, 1.18-1.69); number of memberships in professional medical societies (OR = 2.02; 95% CI, 1.61-2.53); number of extracurricular advocacy events attended outside of professional medical societies (OR = 1.62; 95% CI, 1.17-2.23); belief that participation is important for professional development (OR = 1.76; 95% CI, 1.39-2.23), patients (OR = 1.51; 95% CI, 1.23-1.86), and medical education (OR = 1.43; 95% CI, 1.19-1.71); and the desire to participate as a physician (OR = 1.53; 95% CI, 1.25-1.88). Participation was negatively associated with male gender (OR = 0.51; 95% CI, 0.27-0.95).

Conclusions: Medical students who participate in professional medical societies believe participation supports their education, their patients, and their professional development. Further study is required to elucidate reasons for nonparticipation.

INTRODUCTION

Physician advocacy is a cornerstone to evoking change in our modern health care system and is recognized as a social responsibility of the profession.[1,2] According to the Principles of Medical Ethics within the American Medical Association (AMA) Code of Medical Ethics, "a physician shall respect the law and also recognize a responsibility to seek change in those requirements which are contrary to the best interest of the patient."[3] The Liaison Committee on Medical Education (LCME) standards for United States medical school accreditation include service-learning and community service (§6.6) as one of many competencies to be achieved by medical students. Furthermore, the LCME calls for curricula to include instruction to address societal problems (§7.5), health care disparities (§7.6), and medical ethics and human values (§7.7).[4] Additionally, the Accreditation Council for Graduate Medical Education (ACGME) common residency program requirements include demonstration of a "commitment to professionalism and adherence to ethical principles" (§VI.B.) as well as "an awareness of and responsiveness to the larger context and system of health care" (§IV.B.1.f).[5] As such, early exposure to and opportunity for advocacy can both help satisfy the LCME standards as well as prepare students for residency training and fulfillment of ACGME requirements.[6-8]

Professional medical societies can provide robust platforms for physician advocacy; these membership organizations aim to address key concerns of the medical profession, including health equity, physician training and wellness, and health care delivery. Many professional medical societies allow and encourage medical student membership and involvement on a variety of levels, allowing for students to both explore the multiple types of physician

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advocacy as well as develop leadership skills in various contexts. A previous study has shown participation in community-based organizations such as professional medical societies can improve student advocacy knowledge and skills.[9] Therefore, student participation in professional medical societies can help achieve the aforementioned LCME standards and prepare for the lifelong role as a physician advocate. While a previous study evaluated medical student extracurricular involvement and attitudes as they pertain to education and professional development,[10] there is a paucity of studies formally examining medical student participation in professional medical societies. Although many of these organizations track and study their own membership to improve their relevance and effectiveness, these results are not often disseminated for consideration by their members or the public. We therefore aimed to survey medical student attitudes towards professional medical societies in order to better understand the major drivers of participation as well as student opinions on the relevance of these organizations for students' professional goals.

METHODS

Respondents

Medical students of all years and program types enrolled in the following Wisconsin medical schools were the target population of this cross-sectional study (number of enrolled students in 2019-2020 academic year):[11] University of Wisconsin (UW) School of Medicine and Public Health (n = 747); Medical College of Wisconsin-Milwaukee, Medical College of Wisconsin-Green Bay, and Medical College of Wisconsin-Central Wisconsin (n = 1022 for all Medical College of Wisconsin campuses).

This study utilized an anonymous questionnaire survey for data collection and was considered quality improvement (QI)/program evaluation by the UW-Madison QI/Program Evaluation Self-Certification Tool (June 10, 2019); therefore, formal institutional review board evaluation was not conducted. The questionnaire was optional, and completion of the questionnaire was taken as consent to participate in the study.

Questionnaire Design

A questionnaire was designed to explore medical student participation and attitudes toward professional medical societies. The questionnaire consisted of 21 items with a variety of multiple choice, 5-point Likert scale, and free text responses (Appendix 1). The questionnaire included branching logic to avoid asking nonapplicable or irrelevant questions. All questions were optional except for questions required for the branching logic. In order to gauge what aspects of professional medical societies are important to medical students, several survey questions were designed with the option to rank the top 3 choices. To parallel these ranking questions, respondents were asked to rank the top 3 greatest challenges expected when they become physicians. Three questions requested a self-reported score ranging from 0 to 100 with 3 descriptive markers placed at 0, 50, and 100 as follows: (1) professional medical society participation score: not involved, somewhat involved, extremely involved; (2) professional medical society satisfaction score: extremely dissatisfied, neither satisfied nor dissatisfied, extremely satisfied; (3) extracurricular participation score: not involved, somewhat involved, extremely involved. Finally, as many medical societies are faced with changes in their internal governance structure to maximize membership engagement, a final set of questions was included to probe beliefs in the way professional medical societies adopt or amend policy that directs their activity.

The questionnaire was reviewed by the UW-Madison Cancer Prevention and Outcomes Data (C-POD) Shared Resource (UW Carbone Cancer Center) and was piloted on several medical students before distribution; the pilot data were excluded from the analysis. The survey time was approximately 5 to 7 minutes.

Questionnaire Administration

Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Wisconsin-Madison.[12,13] REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources.

The questionnaire was distributed by a REDCap weblink via email sent to all enrolled students addressed from the lead author. The email was sent via a listserv containing all enrolled students at their respective institution. No login or password was required to take the survey, and there was no tracking of respondent contact information or unique identifiers during the collection period. No compensation was provided for questionnaire completion. Response collection occurred over a 3-week period from September 17, 2019 to October 4, 2019, with a single email reminder sent to all students on October 2, 2019. Questionnaire results were compiled by REDCap and exported for external analysis.

Statistical Analysis

All questionnaire responses were included for analysis, and no imputation was conducted to fill in missing data. All statistical analyses were conducted using R version 3.6.2 (R Core Team). Respondent characteristics were divided into continuous and categorical variables, and categorical variables were dummy coded for regression analysis. For Likert scale questions used in regression analysis, the following values were used for coding: -4 (strongly disagree), -1 (disagree), 0 (neutral or no opinion/not applicable), 1 (agree), 4 (strongly agree).[14]

Logistic regression was used to determine significant predictors of participation in professional medical societies (binary yes/

Table 1. Wisconsin Medical Student Characteristics Associated With Participation in Professional Medical Societies

Categorical Characteristics	n (%)	Odds Ratio	95% CI	*P* value
Medical School				0.472
University of Wisconsin – Madison (reference level)	128 (46.4)	-	-	
Medical College of Wisconsin – Milwaukee	125 (45.3)	1.00	0.60 – 1.66	
Medical College of Wisconsin – Green Bay	15 (5.4)	0.90	0.30 – 2.69	
Medical College of Wisconsin – Central Wisconsin	8 (2.9)	4.20	0.5 – 35.19	
University of Wisconsin – Madison Program				0.275
Traditional program (reference level)	88 (69.8)	-	-	
Wisconsin Academy of Rural Medicine (WARM)	20 (15.9)	0.81	0.30 – 2.15	
Training in Urban Medicine and Public Health (TRIUMPH)	18 (14.3)	2.31	0.70 – 7.60	
Medical College of Wisconsin – Milwaukee Pathway				0.091
Quality Improvement and Patient Satisfaction (reference level)	28 (23.9)	-	-	
Health Systems Management and Policy	19 (16.2)	3.25	0.86 – 12.28	
Clinical and Translational Research	18 (15.3)	1.08	0.33 – 3.56	
Urban and Community Health	17 (14.5)	2.08	0.58 – 7.49	
Molecular and Cellular Research	12 (10.3)	2.60	0.58 – 11.69	
Global Health	12 (10.3)	1.21	0.31 – 4.76	
Clinical Educator	7 (6.0)	0.14	0.02 – 1.36	
Bioethics	4 (3.4)	2.60	0.24 – 28.14	
Degree Type				0.707
None (reference level)	210 (76.1)	-	-	
MD/PhD	29 (10.5)	1.03	0.46 – 2.29	
MD/MPH	21 (7.6)	2.01	0.71 – 5.70	
Other	10 (3.6)	1.47	0.37 – 5.83	
Extended or split program	6 (2.2)	1.26	0.22 – 7.01	
Gender				0.042
Female (reference)	91 (50.8)	-	-	-
Male	84 (46.9)	0.51	0.27 – 0.95	0.034
Other	2 (1.1)	>100	0 – ∞	0.993
Prefer not to answer	2 (1.1)	>100	0 – ∞	0.993
Ethnicity				0.760
White (reference)	135 (76.7)	-	-	
Other	34 (19.3)	1.27	0.57 – 2.82	
Prefer not to answer	7 (4.0)	1.52	0.28 – 8.11	

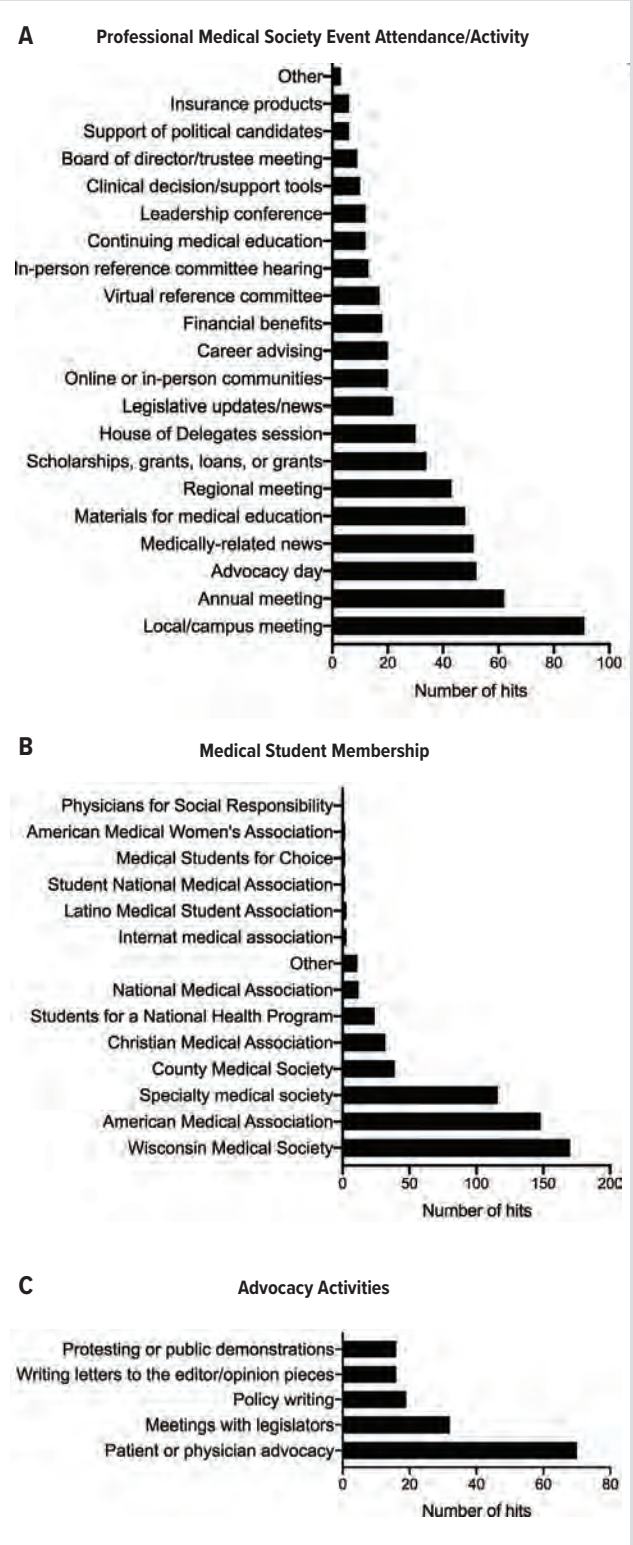
Continuous Characteristics	% Agree	Mean (SD, n)	Odds Ratio	95% CI	*P* value
Years of medical education completed	-	2.75 (1.53, 276)	1.41	1.18 – 1.69	<0.001
Age (years)	-	25.78 (2.57, 172)	1.16	1.01 – 1.33	0.032
Number of memberships	-	2.03 (1.40, 276)	2.02	1.61 – 2.53	< 0.001
Extracurricular participation (self-scored)	-	59.73 (26.26, 195)	1.08	0.97 – 1.19	0.152
Number of extracurricular advocacy activities	-	0.78 (1.09, 195)	1.62	1.17 – 2.23	0.002
"I believe participation is important for my..."					
Professional development	60.5	1.00 (1.77, 200)	1.76	1.39 – 2.23	< 0.001
Patients	50.0	0.57 (1.75, 200)	1.51	1.23 – 1.86	< 0.001
Medical education	54.0	0.70 (1.90, 200)	1.43	1.19 – 1.71	< 0.001
"I plan on participating as a physician"	70.0	1.41 (1.71, 200)	1.53	1.25 – 1.88	< 0.001

Characteristics displayed are divided into categorical (dummy coded) and continuous variables; each characteristic was used as the dependent variable in a logistic regression model to predict the odds of participation in a professional medical society. For extracurricular participation, the odds ratio corresponds to the change in odds for every 10-point change in self-reported score. For Likert-style questions, results are displayed in 2 formats: (1) percent agree that is a combination of agree and strongly agree and (2) the mean and SD using the following scale: -4 = strongly disagree, -1 = disagree, 0 = neutral or no opinion/not applicable, 1 = agree, and 4 = strongly agree.

no response as the dependent variable); a separate model was run for each characteristic, and regression coefficients were converted to odds ratios (OR) with respect to the reference category (if applicable). Since response rates for individual questions varied, each logistic regression model included a different subset (n) of the total questionnaire respondents (N). The overall *P* value of each logistic regression model is reported via the likelihood ratio test comparing the full model to the intercept-only model, and if statistically significant, the *P* values of individual factors are reported.

A general linear model was used to identify significant categorical and continuous predictors associated with the self-reported participation score in professional medical societies. Models relied on an alternative heteroskedasticity-consistent covariance matrix estimator (HCCME)[15,16] to produce standard errors used for sig-

Figure 1. Wisconsin Medical Student Involvement in Professional Medical Societies and Advocacy



1A. Events and activities participated in that are hosted or provided by professional medical societies.
1B. Professional medical society membership by respondents.
1C. Events and activities participated in that are not hosted or provided by professional medical societies.

nificance testing and confidence interval estimation. An F-test for significance of the overall model together with individual regression coefficient *P* values (*t* tests) are reported, with supporting 95% confidence intervals.

Significance for all statistical testing was determined at a threshold of $\alpha = 0.05$.

RESULTS

A total of 308 (N) questionnaire responses were collected, constituting a response rate of 17.4%. Respondent characteristics are displayed in Table 1. Of note, 50.8% of respondents were female and 76.7% were white, which closely matches the demographics of Wisconsin medical students (49.4% and 71.3%, respectively).[11] Additionally, 10.5% of respondents were enrolled in MD/PhD programs, higher than the percentage for Wisconsin medical schools (6.8%).[11]

Sixty-three percent (174 out of 276) of respondents actively participate or have participated in a professional medical society, and the most commonly attended events included local/campus meetings, annual meetings, and advocacy days (Figure 1A). Each respondent was, on average, a member of 2.03 professional medical societies/organizations (SD 1.40) with the Wisconsin Medical Society and American Medical Association being the top 2 most common (Figure 1B). Interestingly, many respondents reported participation in advocacy activities outside of professional medical societies, with patient/physician advocacy and meeting with legislators as the top 2 activities (Figure 1C).

Logistic regression analysis was conducted to elucidate factors that drive participation in professional medical societies (Table 1). Medical school, program type, degree type, ethnicity, and self-scored extracurricular participation (ranging from 0-100; mean 59.73, SD 26.26) did not significantly associate with the odds of participation. For ethnicity, results were aggregated into 3 groups (white only, other, and prefer not to answer) in order to avoid sparsity and instability in the model. The breakdown of ethnicity categories was as follows: White (n = 135; 76.7%), Asian (n = 11; 6.25%), Latino/Spanish/Hispanic (n = 7; 4.0%), White + Asian (n = 6; 3.4%), Black or African American (n = 6; 3.4%), White + Latino/Spanish/Hispanic (n = 2; 1.1%), Middle Eastern or North African (n = 2; 1.1%), and prefer not to answer (n = 7; 4.0%). Male gender, compared to female gender, was associated with decreased odds of participation (OR 0.51; 95% CI, 0.27 - 0.95). Age (OR 1.16; 95% CI, 1.01 - 1.33), years of medical education (OR 1.41; 95% CI, 1.18 - 1.69), number of memberships in professional medical societies (OR 2.02; 95% CI, 1.61 - 2.53), and number of extracurricular advocacy events attended outside of professional medical societies (OR 1.62; 95% CI, 1.17 - 2.23) was associated with a greater odds of participation. Finally, respondents generally agreed that participation in professional medical societies was beneficial for their professional development (60.5% agree or strongly agree), patients (50.0%), and medical education

Table 2. Wisconsin Medical Student Characteristics That Contribute to Self-reported Degree of Participation in Professional Medical Societies

Model: $y=\beta_0+\beta_1 x_1+\beta_2 x_2+\beta_3 x_3+\varepsilon$

Predictors	Estimate (β)	SE	*P* value
Intercept (β_0)	5.69	6.16	0.358
Number of event types attended (x_1)	2.52	0.83	0.003
Leadership experience (x_2)	28.32	7.50	<0.001
Satisfaction with participation (x_3)	2.75	1.04	0.010

F-statistic = 45.05 on 86 observations (*P* value = <0.001); $R^2 = 0.622$

Characteristics were used as dependent variables in a general linear model to predict the self-reported scale of participation (0-100); number of events attended and satisfaction with participation are continuous while leadership experience is binary (yes/no). For participation satisfaction, the regression coefficient corresponds to the change in participation score for every 10-point change in self-reported satisfaction score. SE, standard error.

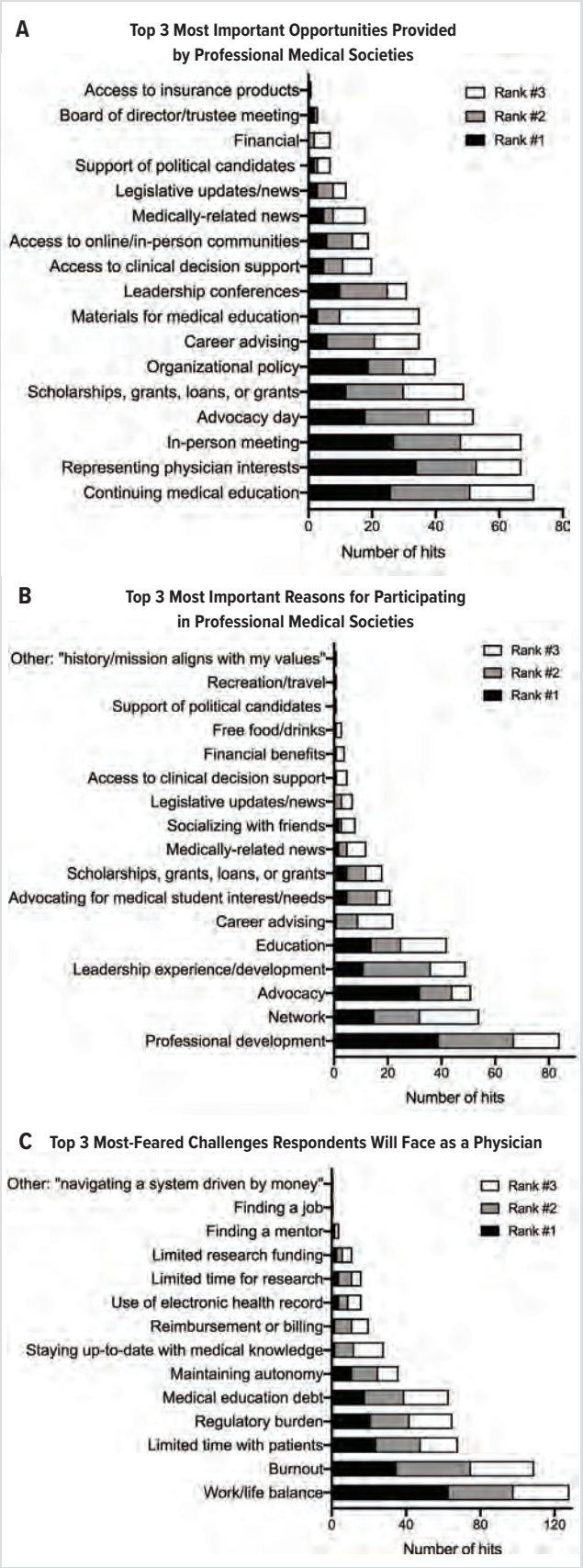
(54.0%). Likewise, respondents generally agreed that they will participate in professional medical societies as physicians (70.0% agree or strongly agree). As such, agreeing with these 4 questions all associated with increased odds of participation: professional development (OR 1.76; 95% CI, 1.39-2.23), patients (OR 1.51; 95% CI, 1.23-1.86), medical education (OR 1.43; 95% CI, 1.19-1.71), desire to participate as a physician (OR 1.53; 95% CI, 1.25-1.88).

Additional analysis was performed on the 174 respondents who actively participate or have actively participated in professional medical societies; for convenience, this subgroup of respondents will be referred to as "participants." These participants provided a self-rated participation score from 0 (no participation) to 100 (maximum participation), which resulted in a mean score of 35.6 (SD 28.9, n = 141). Additionally, these participants attended, on average, 3.33 different event types (SD 3.31, n = 174; see Figure 1A), and overall satisfaction with participation was 67.0 (range 0-100; SD 21.5, n = 101). Of this group, 28.2% (44 of 156) of participants have served in a leadership role in a professional medical society. Using a general linear model, the number of event types attended, holding a prior leadership role, and satisfaction with participation were all significant predictors of participation score (Table 2).

When asked to choose the current most important opportunities provided by professional medical societies, the top 3 responses were continuing medical education, representing physician interest, and in-person meetings (Figure 2A). Furthermore, the most important reasons for participating in professional medical societies included professional development, networking, and advocacy (Figure 2B). Finally, the top 3 choices that are predicted to be the greatest challenges as a physician included work/life balance, burnout, and limited time with patients (Figure 2C).

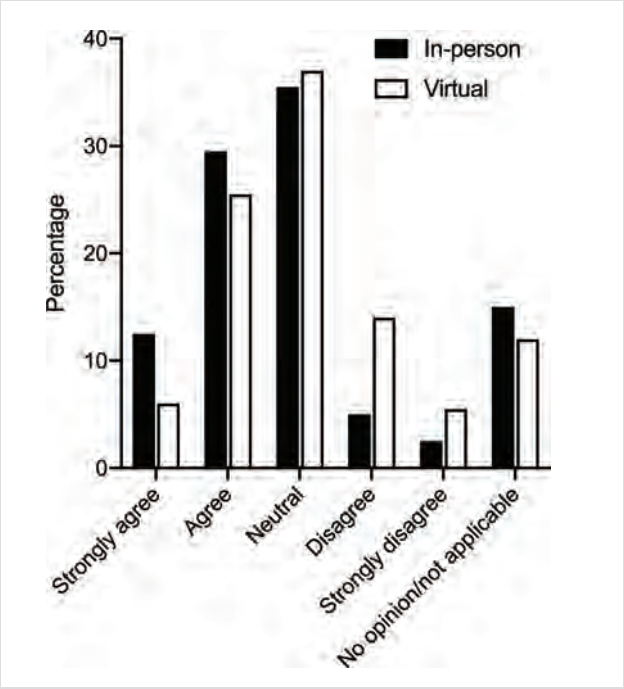
Respondents were mostly neutral on the opinion that an in-person House of Delegates, which serves as a legislative body of the organization, is important to adopt or amend policy (mean 3.00, SD 1.52; 1 = strongly disagree and 5 = strongly agree), but

Figure 2. Attitudes Driving Wisconsin Medical Student Participation in Professional Medical Societies



Data are from 200 respondents.

Figure 3. Wisconsin Medical Student Beliefs in Virtual (White Bars) vs In-person (Black Bars) Policy-Making Processes for Professional Medical Societies



a significant portion of respondents who answered this question (30 of 200; 15%) did not have an opinion (Figure 3). Finally, respondents were also mostly neutral on the opinion that a virtual or online platform to adopt or amend professional medical society policy would be as good as an in-person mechanism (mean 2.77, SD 1.37, n = 200; 1 = strongly disagree and 5 = strongly agree).

Finally, the last item of the questionnaire allowed for free text input on the topic of participation in professional medical societies, of which 18 of 308 respondents (5.8%) added comments. Common concerns mentioned included the following (number of respondents): mismatched political views or values held by the organization (2); feeling unwelcomed or not included within the organization (3); not worth the money (2); and unfamiliarity with the purpose or benefit of participation (6). Additional comments included the following: "they must acknowledge their past and be definitive on a direction;" "I want to see the society put good policy for both patients and physicians over internal politics;" and "professional societies allow me to exert some amount of policy influence despite my relative lack of formal legislative experience."

DISCUSSION

Participation in professional medical societies provides hands-on advocacy skill education for medical students[9] and facilitates professional development and networking. Such extracurricular engagement serves to fulfill medical education LCME standards like service-learning and community service and addresses societal problems and health care disparities, which develops future physicians for a lifelong duty of social responsibility.

Among the first of its kind, our cross-sectional study elucidates medical student attitudes and participation in professional medical societies on a state and national level. Approximately 63% of respondents in our study reported a history of participation in a professional medical society. We found a positive association between participation and female gender, age, years of medical education, number of memberships in professional medical societies, and number of extracurricular advocacy events attended outside of professional medical societies. Additionally, we found that medical students identified professional medical societies as important for professional development, patients, and medical education and that participating students believed that they were likely to participate in the future as a physician. We did not find an association with ethnicity, medical school, program type, degree type, and self-scored extracurricular participation. While many of the positive associations with participation were not surprising, factors such as gender do deserve attention. While the association was only modestly significant ($P = 0.042$), this could represent a shift in participant demographic in these traditionally male-dominated organizations.[17] More robust study would be required to verify this observation. Additionally, assessing the association between participation and ethnicity is severely limited by inadequate sampling of ethnicities beyond white, which is reflective of the Wisconsin medical student population; thus, it is imperative that further study draws from a more diverse population to better assess the impact of ethnicity on participation.

Additional analysis on those participants who gave a self-rated participation score in professional medical societies provided further insight into factors that encourage active engagement with these organizations. As expected, satisfaction with the experience in participating in professional medical societies, which was rated 67 on average (range 0-100), was positively associated with the self-rated participation score. Therefore, it is easy to conclude that appealing to medical student satisfaction can further engage those in professional medical societies. Additionally, while it is not surprising that having a history of holding a leadership position is positively correlated with an increased participation score, it is also plausible that allowing for adequate leadership opportunities within an organization can increase participation.

What remains to be fully elucidated are the characteristics and attitudes of nonparticipants, specifically highlighting the reasons why they choose not to participate in professional medical societies. For example, it is possible that these nonparticipants have differing attitudes about what challenges they are expected to face as a physician; we did conduct an analysis to test this hypothesis, but no significant differences were found between participants and nonparticipants (analysis not shown). Further study would be required to design questionnaire items with the intent of gathering

attitudes and opinions of nonparticipants, specifically probing on why they choose not to participate.

Within the surveyed attitudes toward professional medical societies, there were some comparisons between the top-rated opportunities provided by these organizations, the most important reasons for participating, and the greatest challenges expected as physicians that are worth discussing. Respondents ranked the most important opportunity as continuing medical education; however, education was the fifth reason for participating, and staying up-to-date with medical knowledge was the seventh top fear expected as a physician. Whether this represents a mismatch in expectation versus reality remains to be determined. Additionally, what heavily dominated the top fears included physician health and wellness issues such as work/life balance and burnout. Therefore, a continuing niche of professional medical societies is inclusion of advocacy on these areas, which is in agreement with representing physician interest as the second most important opportunity provided, as well as advocacy as the third highest reason for participating.

Our study includes several limitations. With no prior studies assessing the factors that drive participation in professional medical societies, we constructed 16 different regression models without any corrections for multiple comparisons; these preliminary analyses should serve as a launching point for future study and not be taken as a robust assessment. The relatively low response rate limits the generalizability of these findings to medical students in Wisconsin, as 83% of students did not respond. Additionally, the survey design and administration is not able to fully represent medical students nationally or internationally. Finally, there were no protections against a single respondent submitting multiple questionnaire responses, which could introduce some bias and overrepresentation of certain attitudes.

Nonetheless, we believe our study is the first of its kind to formally report on factors that drive medical student participation within professional medical societies, as well as the attitudes medical students have toward these organizations. As participation in professional medical societies can help achieve LCME and eventually ACGME standards by preparing medical students for lifelong involvement in advocacy, further study is warranted to elucidate the distinction between participants and nonparticipants and tap into this important educational resource.

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Internal Medicine Residents' Perceptions of Writing and Presenting Case Reports

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ABSTRACT

Background: The Accreditation Council for Graduate Medical Education (ACGME) requires all residents participate in scholarly activity during residency. Case reports provide trainees an opportunity to engage in scholarly activities. This study assesses internal medicine residents' perceived benefits of writing and presenting case reports and barriers to this process.

Methods: A survey was disseminated to internal medicine residents at a tertiary academic center. The survey questionnaire aimed to assess residents' perceptions about benefits and barriers to writing and presenting case reports. Responses were obtained on a 5-point Likert scale, and the data were analyzed as respective frequencies and percentages.

Results: Forty-three (34%) of the 125 eligible internal medicine residents completed the survey. Fifty-eight percent reported never having presented a case report. Ninety-six percent believed that finding an interesting case was an important factor in facilitating writing a case report, while 81% perceived finding a good mentor as equally important. Perceived barriers to case report writing included lack of training in reviewing scientific literature (59%), lack of adequate time (58%), lack of formal training in identifying and writing case reports (56%), and lack of a mentor (54%).

Conclusions: Our study showed that the majority of residents had not written or presented case reports. While case reports provide a myriad of educational value, various barriers exist that include lack of proper training, adequate time, and a mentor. Our findings suggest that additional institutional resources should be dedicated to designing a curriculum to address these perceived barriers.

INTRODUCTION

Internal medicine residency training programs are challenged to expose their residents to a myriad of scholarly activities, while also preparing them for rigorous clinical careers and potential subspecialty training. The Accreditation Council for Graduate Medical Education (ACGME) requires all accredited internal medicine residency training programs in the United States to facilitate resident scholarly activities. The Residency Review Committee for Internal Medicine (RRC-IM) established a requirement in 1994 that residents must complete "original research, comprehensive case reports, or review of clinical and research topics."[1] As part of the requirement for resident scholarly activity, the ACGME outlines its criteria to "advance residents' knowledge of the basic principles of research, including how research is conducted, evaluated, explained to patients, and applied to patient care."[2] The ACGME also specifies, "the sponsoring institution and program should allocate adequate educational resources to facilitate resident involvement in scholarly activities."[2]

Currently, there is no standard definition used by RRC-IM to assess scholarship in ACGME-accredited residency programs. Although there is no uniform definition, activities that can be categorized as meeting the criteria for scholarly activity vary widely. Examples include formulation and implementation of an original research question leading to subsequent publication in a peer-reviewed journal; quality improvement projects; composition of review articles; and case report writing and presentation at local, regional, and national conferences.

Case report writing provides educational value with the description of a diagnostic or therapeutic problem experienced by one or several patients and offers an opportunity for the learners to engage in scholarly pursuit. The overarching purpose of these writings is to spread knowledge among medical, scientific, and educational

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groups.[3] Case reports and clinical vignettes are especially useful when considering rare disorders by helping the medical community understand the etiology, pathogenesis, natural history, and treatment of these disorders.[4] In addition to providing a forum for sharing new and unique medical findings, case report writing is a valuable educational exercise. The benefits of writing a case report include sharpening critical thinking skills, improving understanding of patient-centered care, and promoting scientific writings.[5] Additionally, presenting scholarly work provides residents with an opportunity to expand their professional network, improve presentation skills, and engage in discussions with colleagues from around the country, which may foster further expansion of their research. Writing case reports and delivering poster or oral presentations provides opportunities to learn 2 different skill sets. On a broader perspective, they fall into a spectrum of scholarly pursuit that encompasses concept development, presentation in local or national meetings, and manuscript writing. Case reports that have not been presented or published still encourage the development of these same skills. Thus, writing and presenting case reports should not be taken as isolated forms, but rather as a coalescence resulting in a meaningful work or contribution to science.

Although case reports can be an effective teaching tool with multiple potential educational benefits, there is limited knowledge on residents' perceptions regarding writing case reports and presenting them at meetings. This study endeavors to highlight the implications of their perceptions by surveying internal medicine residents and assessing perceived benefits, challenges, and barriers regarding writing and presenting case reports.

MATERIALS AND METHODS

Study Design, Setting, and Participants

A voluntary online survey was conducted between November 1 and November 16, 2017 among internal medicine residents—excluding chief residents—at the Medical College of Wisconsin (MCW), a tertiary care academic medical center in the United States. The study was approved by the MCW Institutional Review Board (IRB), and the survey utilized an informed consent process in which an informational letter was sent to participants via email explaining the nature and expectations of the study and potential risks to the participants, along with a link to the survey. All possible steps were taken by the research team to maintain the anonymity of the participants.

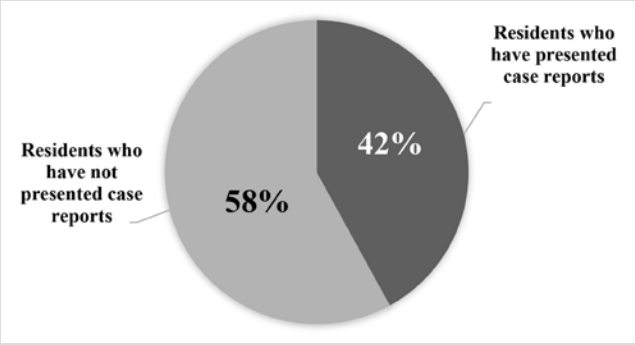
Data Collection, Survey Elements, and Data Analysis

The survey was conducted using the Qualtrics online-based survey platform (www.qualtrics.com). The survey link was sent through an invitation email to 125 internal medicine residents (interns through third-year residents, excluding chief residents). The survey questionnaire aimed to assess whether residents have ever presented case reports, their perceived barriers and potential benefits to writing case reports, and factors that facilitate this process.

Table. Survey Questions and Corresponding Responses From Internal Medicine Residents Regarding Writing and Presenting Case Reports

Survey Questions	Strongly Agree/Agree
Factors that facilitate writing and presenting case reports?	
Finding an interesting case	96%
Finding a good mentor	81%
Having financial assistance	33%
Lectures and workshops	31%
Benefits of writing and presenting case reports?	
Improves presentation skills	100%
Improves scientific writing skills	98%
Enhances CV and secures fellowship position	91%
Improves critical thinking	88%
Networking and collaboration	72%
Barriers to writing and presenting case reports?	
Lack of training in reviewing scientific literature	59%
Lack of adequate time during residency	58%
Lack of formal training in identifying and writing case reports	56%
Lack of mentor(s)	54%
Lack of opportunities/venues to present	46%
Lack of financial assistance	32%

Figure 1. Percentages of Residents Who Indicated They Have and Have Not Previously Presented Case Reports



Responses were obtained on a 5-point Likert scale. Descriptive statistics were used to summarize the responses with the use of respective frequencies and percentages. Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, US).

RESULTS

Forty-three out of 125 residents completed the survey, with a response rate of 34%. The majority of residents who completed the survey (N=25 residents, 58%) indicated they had not previously written and presented a case report (Figure 1). Only 18 residents (42%) indicated they had previously presented a case report at a regional or national meeting.

Ninety-six percent (63% strongly agreed, 33% agreed) indicated that finding an interesting case was an important factor in facilitating writing and presenting a case report, while 81% said finding a good mentor was equally important (Table, Figure 2). Other facilitating factors included financial assistance (33%) and lectures and workshops (31%).

Figure 2. Resident Perceptions Regarding Factors That Facilitate Writing and Presenting Case Reports

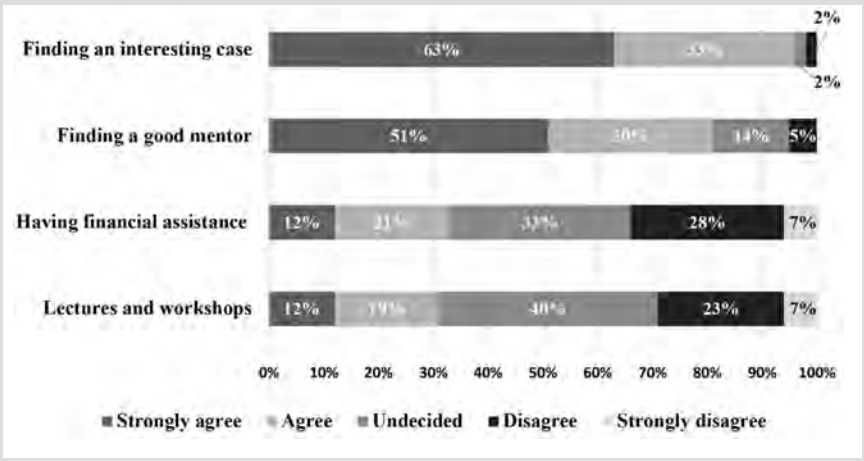


Figure 3. Resident Perceptions Regarding Benefits of Writing and Presenting Case Reports

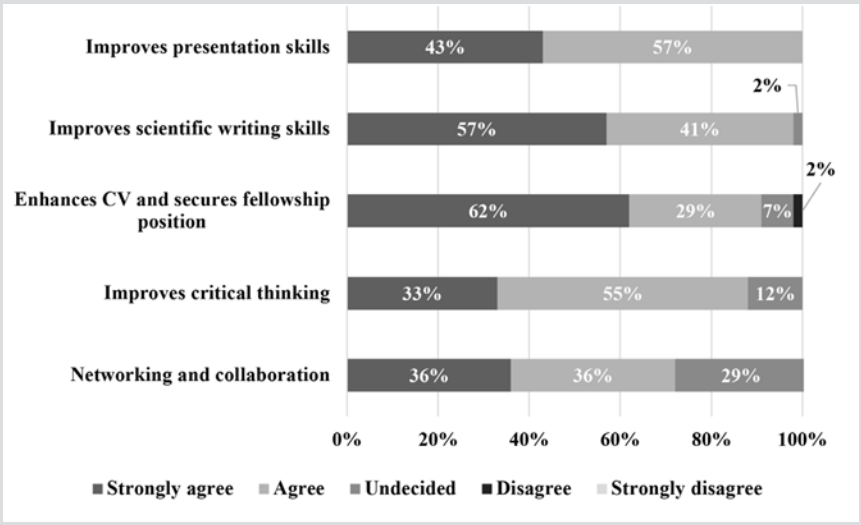
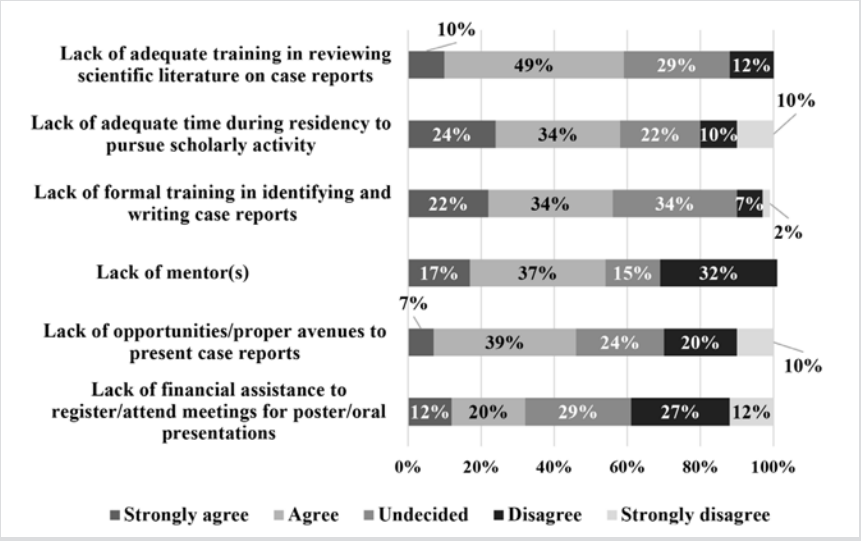


Figure 4. Resident Perceptions Regarding Barriers to Writing and Presenting Case Reports



Regarding benefits, 100% of respondents perceived (43% strongly agreed, 57% agreed) that writing and presenting case reports improved presentation skills (Table, Figure 3). Similarly, 98% said they improved scientific writing skills. Other perceived benefits included enhancing curriculum vitae (CV) and securing fellowship positions (91%), improving critical thinking (88%), and enhanced networking and collaboration (72%) (Table, Figure 3).

The main barrier to writing and presenting case reports, as perceived by 59% of the respondents (10% strongly agreed, 49% agreed), was a lack of adequate training in reviewing scientific literature on case reports (Table, Figure 4). Lack of adequate time during residency to pursue scholarly activity was another commonly perceived barrier (58%). Other perceived barriers to writing and presenting case reports included lack of formal training in identifying and writing case reports (56%), lack of mentor(s) (54%), lack of opportunities/proper venues to present case reports (46%), and lack of financial assistance to register/attend meetings (32%) (Table, Figure 4). On the subgroup analysis, the major barrier perceived by respondents who had not previously presented case reports was a lack of training in reviewing scientific literature on case reports (67%). On the other hand, a lack of financial assistance was the major barrier perceived by residents who had previously presented case reports (59%).

DISCUSSION

Our study shows that the internal medicine residents at a tertiary medical center perceive many benefits of case report writing for both career advancement and advancement of scientific literature. However, this study also identified commonly perceived barriers to case report writing, many of which residency programs can work to address. The majority of survey respondents indicated their belief that scholarly activity through case reports is beneficial, as it improves presentation and critical thinking skills, enhances CVs, and increases chances

of getting into a desired fellowship program. The importance of completing multiple scholarly projects is evident by fellowship match data, which show that those who matched into different subspecialty fellowship positions (allopathic) had a greater number of abstracts, presentations, and publications since their last completed degree compared to those who did not match.[7]

Presenting case reports at regional and national meetings also provides residents an opportunity to network and collaborate. Case reports are particularly important for community-based residency programs with more limited research opportunities. Aside from benefiting the writer, training residents in case report writing serves as a way for residency programs to meet ACGME accreditation requirements and thus avoid citation. Up to 10% of internal medicine residency programs reported being cited for failing to comply with the scholarly activity requirement since it was initiated in 1994.[8] Additionally, citation for the lack of scholarly activity predicts a decreased cycle length between visits by the ACGME.[8,9] This is important to consider as visits by the ACGME require significant preparation and resources.[9] Writing and presenting case reports is a quick, easy way to present and publish scholarly projects to meet ACGME requirements.

Residency programs across many different specialties have attempted to avoid citation for lack of scholarly activity by a variety of methods, and most have centered on improving residents' access to resources and knowledgeable mentors. For example, a family medicine residency program implemented a scholarly activity curriculum that involved allocating contractual time for faculty members to serve as mentors for residents.[10] The program's success is supported by the 24 presentations at national and international meetings and 15 publications in peer-reviewed medical journals by 111 residents who participated in the program.[10] Another residency program implemented a residency research program that involved dedicated research time during ambulatory blocks and access to research assistants, nurses, and biostatistics support personnel, in addition to a resident research director who provided mentorship.[11] Perhaps the most striking benefit of such a program is the impact on fellowship matching. This program saw the percentage of residents who were accepted into fellowships increase from 33% preimplementation to 49% postimplementation.[11]

Despite the clear benefits to writing case reports, only 42% of surveyed residents in our study reported presenting a case report. Reported barriers were a lack of training, adequate time, and a mentor. Fifty-nine percent of respondents reported a lack of training in reviewing scientific literature as a challenge, whereas 58% reported a lack of protected time for scholarship as a barrier. A recent study found strikingly similar results among 4th year medical students: 67% reported not having written or presented a case report, yet felt case reports have many educational and professional benefits.[6] Findings from these studies highlight the need for innovation in curriculum and institutional support to promote scholarly productivity.

Lack of adequate time for scholarship was reported as a barrier to completion of scholarly projects by 58% of the residents in our study. This appears to be a persistent issue, given a prior study reported that 79% of residents deemed lack of time as a barrier.[12] While original research projects traditionally have been seen as superior to other forms of scholarly activity, they take a significant amount of time. Original research conducted by internal medicine residents takes approximately 200 hours to complete, while preparing to present a clinical vignette takes only 50 hours.[12] This time constraint essentially binds the resident to completing only 1 scholarly activity during their residency. Given that lack of adequate time to complete scholarly work was identified as a barrier by the residents in our study, case report writing may be a more time-conscious way for residents to contribute scholarship. It not only affords residents the opportunity to explore multiple areas of interest and scholarly projects, but also supports development of their CV and fellowship application.

Scholarship and mentorship are crucial for academic advancement and professional development for both the learners and teaching faculty members. In our study, 81% of respondents reported that finding a good mentor is an important component for completing a scholarly project, while 96% reported finding an interesting case as a facilitating factor. Faculty experienced in mentoring learners can help residents identify and write up a case for presentation at meetings and possible publication. While mentoring is important, most teaching faculty have received little training in mentoring students and residents and often are challenged by different clinical and nonclinical responsibilities.[13] Prior research has shown that the mentor's research productivity, specifically the number of publications and federally funded grants, is a significant predictor of residents' success in completing a scholarly project.[14] This aligns with our study, which concluded that finding a good mentor was a barrier to case report writing.

Additionally, programs should develop an environment in which residents are encouraged to self-initiate mentorship rather than being assigned a mentor. This has been explored in a recent study that demonstrated that residents had a more positive experience with scholarly projects when they sought out their own mentors.[15] Providing faculty with the necessary training and time to mentor residents is an investment that not only serves the current resident population but can also effect change on future generations of residents. Those who have an influential mentor are more likely to mentor other learners in the future.[16] Young et al found that only 1.5 faculty members per medical school-based program have the necessary protected time for successful research productivity.[17] In order to facilitate mentorship, faculty members must have not only the appropriate training, but also protected time to serve as mentors. Residents who have experience writing case reports are more prepared to take mentorship roles as faculty.

Several limitations of this study should be considered. Our

study had a suboptimal response rate, as is common among survey-based studies. Our survey was limited to a single institution, but larger comparative studies done in multiple institutions would be necessary for the results to be generalizable. Our study findings also may lack direct generalizability to community-based programs. Since access to faculty involved in research highly correlates with resident involvement and publication, residents from community-based programs may have different perceptions on case report writing and publication.[18] These results might only be applicable to academic-based internal medicine residency programs. Our study did not include residents' perceptions on other types of scholarly activity. Additionally, we did not include the respondents' year of residency in our survey. This information would be valuable in future studies as it can help assess the impact longitudinally after adequate curricular changes have been implemented to address reported barriers.

These findings necessitate future studies to determine how perceived barriers may vary by program year, differences in perceived barriers based on specialty, comparisons among multiple academic-based residency programs, and changes in residents' perceptions after adequate changes are made in the curriculum to address various barriers.

CONCLUSION

Our results demonstrate perceived benefits of case report writing by residents and have identified concrete barriers. Residency programs can facilitate an environment conducive to scholarship and mentorship. Structured mentorship, protected time, and appropriate training in scientific writings are specific ways for internal medicine residency programs to prepare residents for success. This may, in turn, reflect positively on the program through increased scholarship and fellowship match rates. Experience in case report writing during residency prepares residents for future scientific writings and serving as a faculty mentor.

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Decrease in Positivity Rate of Influenza Tests Coinciding With Outbreak of SARS-CoV-2: Data From a Southeastern Wisconsin Laboratory

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ABSTRACT

Background: The SARS-CoV-2 outbreak prompted public health interventions and changes in public behavior that may have affected the 2019-2020 influenza season.

Methods: Using data from a laboratory in southeastern Wisconsin, we compared the number of weekly influenza tests and their positivity rates during the 2019-2020 influenza season with the previous 4 seasons.

Results: The number of influenza tests per week at the outset of the SARS-CoV-2 outbreak was higher than the average the previous 4 years, and positivity rates declined to 0% earlier than any of the previous 4 seasons.

Conclusion: The testing trajectory and positivity rate for influenza differed during the part of the 2019-2020 season coinciding with the SARS-CoV-2 outbreak as compared to similar periods during the previous 4 seasons.

BACKGROUND

The outbreak of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in the United States coincided with the latter half of the 2019-2020 influenza season. Several public health interventions were enacted to control the SARS-CoV-2 outbreak. These unprecedented interventions led to mandated changes in public behavior, such as banning large gatherings. Additionally, the SARS-CoV-2 outbreak has received widespread news coverage, leading to high public concern and awareness,[1] which, in turn, has led to voluntary changes in public behavior. An example is a decrease in "non-essential" travel, which has been measurable using mobile phone data.[2] Though these behavior changes are aimed at preventing SARS-CoV-2 transmission, given the similarities in transmission of respiratory viruses, they could also unintentionally affect seasonal influenza.[3]

The change in trajectory of seasonal influenza coinciding with the SARS-CoV-2 outbreak has been described previously. For example, in one of the first such reports, Sakamoto el al reported that the seasonal influenza activity in Japan was lower in 2020 than in previous years.[4] Though there have been several similar reports since, this has not been widely reported in the US, particularly for Wisconsin. Various regions of the world and US states were affected by the SARS-CoV-2 outbreak at different times and may have different baseline influenza activity. They also may have differing baseline public health practices, deployment of mandated public health measures, and public concern and awareness. As a result, the impact of the SARS-CoV-2 outbreak on seasonal influenza may differ by region.

We hypothesized that the 2019-2020 influenza season in Wisconsin was affected by the SARS-CoV-2 outbreak and examined the outbreak's impact on testing for seasonal influenza using data from an academic health system laboratory in Wisconsin.

METHODS

We used data from 2015 to 2020 from an academic health system laboratory in southeastern Wisconsin, which is also a regional reference laboratory serving eastern Wisconsin. The data included tests for both hospitalized and ambulatory patients. We obtained weekly influenza testing numbers and positivity rates (PR), then calculated the tests per week and PR for the 2019-2020 season. We compared

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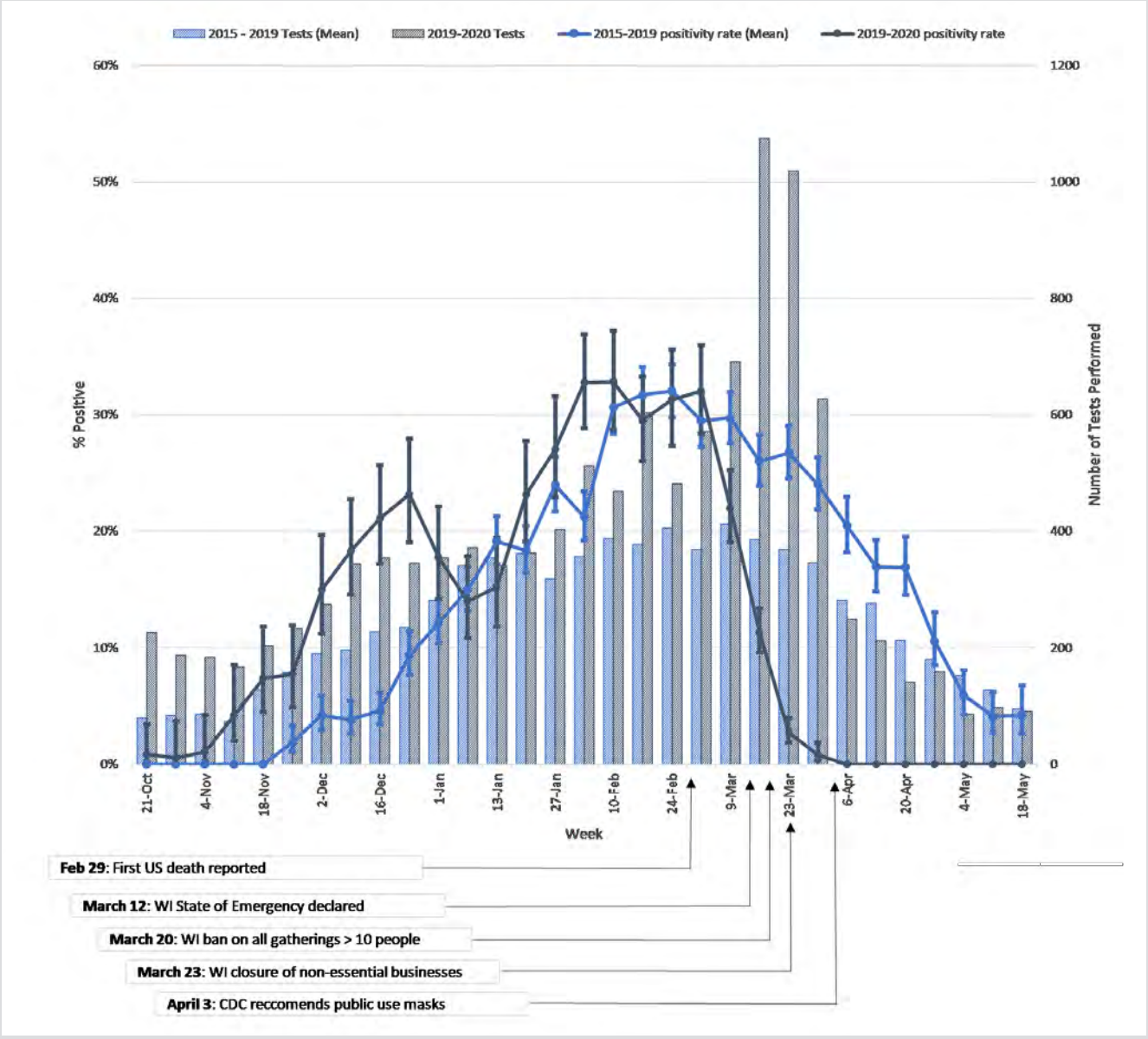
Figure. Number of Influenza Tests Performed and Positivity Rates Per Week During 2019-2020 Season vs Mean Number of Influenza Tests and Positivity Rate for Past 4 Seasons Combined (2015-2019)



Vertical bars represent 95% confidence intervals. The horizontal axis notes the first date of each week for the 2019-2020 season. The horizontal axis is annotated with select events and public health measures enacted during the SARS-CoV-2 outbreak.

them to the mean numbers of samples collected and PR per week for the combined 4 previous seasons using a logistic regression with week and season as categorical variables. We included an interaction so the resulting estimates and confidence intervals correspond to week-by-week model-free binomial analysis.

In accordance with Medical College of Wisconsin's policies, this study was not subject to institutional review board approval because it did not use patient-level data and was not deemed human subjects research.

RESULTS

During the 2019-2020 influenza season, 11,438 tests were performed with 1805 (15.8%) positive results. In the previous 4 seasons, 33,099 tests were performed, with 5,945 (18.0%) positive results. The positive rate in the 2019-2020 season was significantly higher than previous seasons until the second week in January, and it started to decline sharply and significantly in the second week of March (Figure). This decline continued until the second week of April, when positivity reached zero and has remained at zero since. Previously, the earliest zero positivity was during the 2017-2018 season in the last week of May, which is 8 weeks later than what we observed during the 2019-2020 season. In the 3rd and 4th weeks of March 2020, the number of tests performed was

much higher than previous years (1075 and 1019 tests, respectively, compared to an average of 386 and 369 previous years).

DISCUSSION

We noted an initial increase in influenza testing in southeastern Wisconsin followed by a dramatic decline in detection of seasonal influenza coinciding with the outbreak of SARS-CoV-2 and consequent changes in public health policy and public behavior. We also noted the earliest decline to zero influenza cases detected compared to the previous 4 seasons. Prior to this decline, our data show higher positivity rates for influenza tests compared to previous years, consistent with early projections of a severe 2019-2020 influenza season in Wisconsin.[5]

The initial testing increase could have been due to several reasons. For example, because of the high media attention given to the SARS-CoV-2 outbreak, more individuals may have sought care for respiratory symptoms compared to previous years. It is also possible that health care providers were prompted by a shortage of SARS-CoV-2 tests to test more for influenza as a first step to explain a patient's symptoms and conserve SARS-CoV-2 tests for use in patients negative for influenza.

The decline in influenza detection during the 2019-2020 season could have been due to less testing for influenza, which may have happened if clinicians had started testing preferentially for SARS-CoV-2 during this period. Instead, we found that influenza testing was much higher or the same during this period compared to previous years. As influenza and SARS-CoV-2 are symptomatically indistinguishable, it is highly unlikely that patients with influenza self-selected to not seek care. The most plausible hypothesis to explain our finding is that the public health interventions and changes in public behavior in response to the SARS-CoV-2 outbreak unintentionally led to the decreased spread of influenza in 2020.

Our examination is limited by our use of data from a single laboratory. Further, we did not have access to patient-level data that may shed further light on the differences in characteristics of patients tested for influenza in the 2019-2020 season compared to previous seasons. Examining differences in the trajectory of influenza using patient-level data presents an area for future research.

There is concern that the resurgence of SARS-CoV-2 will coincide with the onset of the 2020-2021 influenza season.[6] Together, coinciding influenza and SARS-CoV-2 outbreaks could overwhelm health care facilities much more so than SARS-CoV-2 alone.[7] Apart from the direct health effects of the viruses, this surge in hospitalizations would decrease availability of health care resources for other medical conditions and could lead indirectly to excess morbidity and mortality unrelated to influenza or SARS-CoV-2.[8] An additional intervention to mitigate this will be to increase influenza vaccination rates.[9] This will be important in Wisconsin, as there is considerable room for improvement with vaccination rates across Wisconsin counties between 28% and 54%.[10]

Our examination crucially and additionally shows that persuading the public to change its behavior through policy and information—as was accomplished at the outset of the SARS-CoV-2 outbreak—could again decrease the impact of a "double hit" this fall and winter. These efforts could save lives directly by decreasing the occurrence of seasonal influenza, as well as the occurrence of SARS-CoV-2, and indirectly by decreasing the burden on health care facilities.

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Bridging Undergraduate and Graduate Medical Education: A Resident-as-Educator Curriculum Embedded in an Internship Preparation Course

Jessica S. Tischendorf, MD, MS; Melissa MacDonald, MD; Matthew W. Harer, MD; Christa A. Pittner-Smith, MD; Amy B. Zelenski, PhD; Sara K. Johnson, MD

ABSTRACT

Background: Many graduate medical education programs have implemented curricula to develop trainees into the next generation of medical teachers; however, coordination of in-person teaching curricula is challenging due to full trainee schedules.

Methods: To address limited in-person time, we developed a largely asynchronous resident-as-educator curriculum. Our elective curricular activities are embedded within the fourth-year internship preparation course at the University of Wisconsin School of Medicine and Public Health and include trainees from internal medicine, family medicine, and pediatrics.

Results: Trainee self-assessment of teaching skills improved after our curriculum, and students evaluated resident sessions favorably.

Discussion: Trainees can be effective teachers in an internship preparation course after a brief, asynchronous teaching curriculum. To disseminate our curriculum, we designed a resident-as-educator curriculum website.

INTRODUCTION

At the University of Wisconsin School of Medicine and Public Health (UWSMPH), we developed an asynchronous Resident-as-Educator (RAE) curriculum embedded within our fourth-year medical student Internship Preparation Course (IPC) to promote the professional development of our trainees, the next generation of clinician-educators. In this brief report, we present early outcomes of our pilot RAE curriculum.

In response to perceived lack of preparedness for the residency transition by upcoming interns and program directors alike, IPCs have proliferated.[1] IPCs are resource intensive, often requiring a significant amount of donated faculty time.[2] Our RAE curriculum recruits trainees to fulfill the need for educators in our IPC, while providing a unique near-peer perspective to IPC students.

Many institutions have implemented RAE curricula to meet the call for trainee instruction in teaching.[3] While many of these curricula improve resident teaching skills, most are designed to be delivered in-person, resulting in challenges coordinating busy resident and faculty mentor schedules.[4,5] Our curriculum successfully employs blended learning to overcome this logistical barrier, benefiting the professional development of future clinician-educators while serving the student and institutional needs of a resource-intensive IPC.

METHODS

Setting

We piloted our RAE curriculum concurrent with the UWSMPH IPC in academic year 2014-2015. In 2014-2016, the IPC was an elective for 8, then 15 students entering internal medicine internships. In 2016-2017, the IPC became a requirement for all 148 graduating students. Our IPC addresses essential intern skills, such as management of common acute conditions, communication skills, and awareness of resources for personal well-being and professional development.

Population

We piloted our RAE curriculum with a group of internal medicine residents in 2014-2015 (n = 10) and 2015-2016 (n = 12) in

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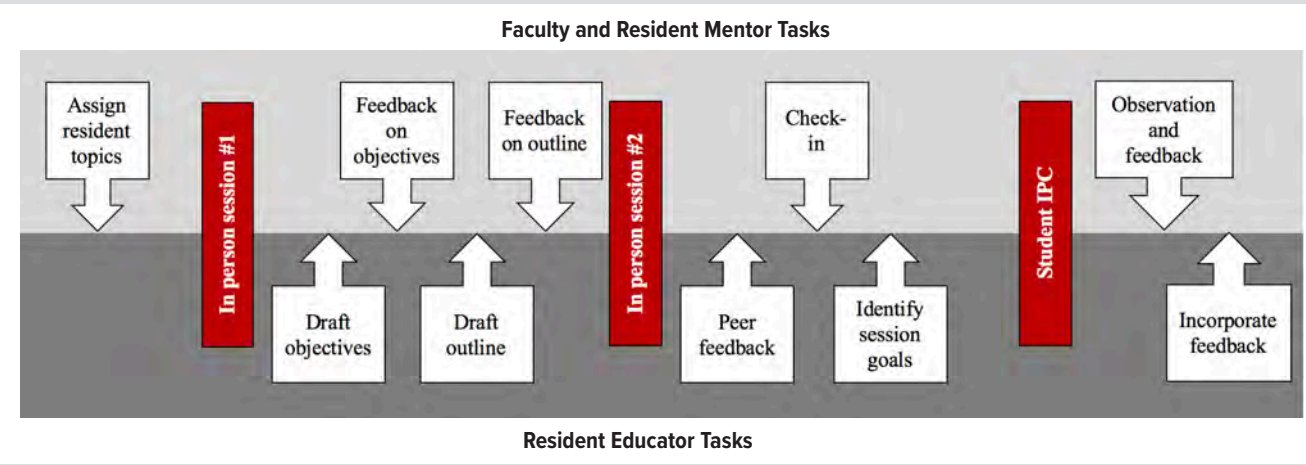
Figure. Resident as Educator Curriculum Timeline



Curriculum occurs in an asynchronous manner focusing on task-based learning, with individualized formative feedback from peers and mentors. Two in-person learning sessions occur before the internship preparation course, with electronic feedback occurring between these meetings and after the internship preparation course.

the Department of Medicine. In academic year 2016-2017, we expanded to family medicine and pediatrics. This expansion was a result of increased trainee interest, adoption of the IPC as a requirement for all graduating medical students, and the addition of pediatric and family medicine faculty mentors.

Program Description

Our RAE curriculum is elective for trainees, and instruction is embedded within IPC preparation at our institution. We designed the curriculum to enhance the classroom teaching skills of trainee educators serving as IPC instructors. We employ the pedagogical principles of situated learning,[6] deliberate practice,[7] task deconstruction,[8] peer feedback,[9] and mentorship. The steps to create an effective classroom teaching session are broken down into discrete tasks. Trainee educators immediately apply learned content to development of their assigned teaching session and receive ongoing peer and faculty feedback. Trainees who have participated in our curriculum in a previous year serve as peer mentors.

Our curriculum emphasizes writing effective learning objectives, structuring teaching sessions to promote engagement, and giving and receiving feedback. We incorporate a scaffolded approach to promote development of trainee educators participating in successive years of our curriculum. The first year focuses on basics of classroom teaching and providing effective feedback. Second-year trainee educators are introduced to more nuanced classroom management skills, such as responding to error, managing interactive activities, and assessment principles. Third-year trainees serve as peer mentors and develop an individual goal pertaining to medical education. Course materials are on our website (see https://rae.medicine.wisc.edu).

Innovative to our curriculum is the largely asynchronous format (Figure). Trainee educators convene for just two 1-hour face-to-face sessions to emphasize key curricular objectives and participate in open discussion. The first session focuses on development of an effective classroom teaching session, including writing learning objectives and incorporating various teaching methods. The second session emphasizes effective feedback and provides time for troubleshooting and generating ideas. The remaining curricular activities occur asynchronously. Time between the sessions is spent developing course materials by applying RAE curriculum lessons and receiving individualized feedback on materials from peer and faculty mentors. The development of course materials is deconstructed into discrete tasks, such as writing learning objectives or developing a session outline (see Figure), with frequent opportunities for feedback.

Ethics

Per the University of Wisconsin-Madison Health Sciences institutional review board (IRB), this program evaluation is exempt from oversight.

Evaluation

We conducted anonymous pre- and post-self-assessments of teaching skills using a locally developed tool (Appendix A and B). Self-assessment data are available for 2016-2017 for 27 of the 40 trainees. A faculty mentor directly observed sessions and provided feedback to trainee educators. Student evaluations of session quality were collected. Students were asked to respond to the following statement on a Likert scale of 1 (strongly agree) to 7 (strongly disagree): "[Session title] was effective." Data from direct observation and feedback were not conducive to robust analysis and are not included in this report.

Statistical Analysis

To evaluate differences in trainee educator self-assessment, data were aggregated and analyzed using the Mann-Whitney test because the participants' identity was hidden. Effect size was cal-

Table. Resident and Fellow Self-Assessment Before and After Participating in the Resident as Educator Curriculum

	Pre-assessment Median (IQR) (n=27)	Post-assessment Median (IQR) (n=26)	*P* value (Mann-Whitney)
I am confident in my teaching skills.	3.5 (3,4)	4 (3,4)	0.09
I can develop focused, relevant goals and learning objectives for a teaching session.	4 (3,4)	4 (4,4)	0.01[a]
I can use learning objectives to structure a teaching session.	4 (3,4)	4 (4,4)	0.001[a]
I appreciate the merits of different teaching formats and when each are appropriate.	4 (4,4)	4 (4,4.25)	0.24
I feel confident in my ability to lead a lecture-style learning session.	4 (3,4)	4 (4,4.25)	0.049[a]
I feel confident in my ability to lead a small group-based learning session.	4 (3,4)	4 (3.75,5)	0.029[a]
I feel confident in my ability to lead a case-based learning session.	4 (3,4)	4 (4,4.25)	0.01[a]
I feel confident in my ability to lead a simulation-based learning session.	3 (3,4)	4 (3, 4.25)	0.003[a]
I can develop printed materials that learners find useful in mastery of a topic I am presenting.	4 (3,4)	4 (3.75,4)	0.043[a]
I have a framework for giving feedback.	3 (2,3)	4 (3,4)	0.0003[a]
I feel comfortable giving positive feedback to my peers.	4 (4,4)	4 (4,4.25)	0.12
I feel comfortable giving constructive feedback to my peers.	3 (3,4)	4 (3.75,4)	0.0009[a]
I can incorporate constructive feedback to improve a presentation or teaching session.	4 (3,4)	4 (4,4)	0.044[a]
I can develop a teaching session that effectively teaches what I think is most important for my learners.	3 (2,3)	4 (3,4)	0.0001[a]
I feel comfortable in acting as a mentor to help others improve their skills as an educator.	3 (2,4)	4 (3,4)	0.007[a]

[a] Indicates significance at the $P \leq 0.05$ level
Data from 2016-2017 (1 = strongly disagree, 5 = strongly agree).

culated and reported with Cliff d values. A Spearman correlation analysis was performed. Student evaluation of session data is presented using descriptive statistics only.

RESULTS

In 2017, our RAE curriculum included trainee educators from our internal medicine residency (n = 17), family medicine residency (n = 5), and pediatrics residency and fellowships (n = 19). These volunteers accounted for 19.1% of the 89 internal medicine residents, 10.4% of the 48 family medicine residents, and 35.8% of the 53 pediatric residents and fellows that academic year. Of these 41 trainee educators, 68% (n = 28) were PGY-2 or 3 level of training (range PGY 1-6), and 27% (n = 11) had participated in RAE the prior year.

Self-assessment of educator skills improved significantly among trainees participating in our RAE curriculum. (See Table). There were multiple associations between topics (Appendix C).

Trainee educators taught 40 sessions in the IPC in the 2016-2017 academic year. Student evaluation data of teaching sessions revealed overall high satisfaction with resident teaching sessions. Of the 40 sessions given by residents, medical students rated 89% (median, interquartile range [IQR] 81%-95%) as a 1 (strongly agree), 2 or 3 (agree) out of 7 on overall session effectiveness, with median Likert score per trainee teaching session of 2.17 (IQR range: 1.78-2.33).

DISCUSSION

Our blended RAE curriculum resulted in enhanced teaching self-efficacy among trainee educators and effective teaching of medical students in our IPC. The success of our largely asynchronous pilot RAE curriculum demonstrates teaching skill development can occur with limited face-to-face instruction by faculty mentors. This structure obviates the barrier of limited time for an in-person RAE curriculum[4,5] while effectively developing a larger pool of effective educators to execute a resource-intensive IPC. In addition, the ongoing RAE participation year after year, in the setting of many time demands, reflects that trainees find this experience valuable.

Similar to other RAE curricula with reports of resident self-assessment, our asynchronous blended curriculum significantly increased residents' perceived preparedness, confidence, and classroom teaching skills.[10]

There are many opportunities for continued innovation building on our curriculum and assessment. First, this curriculum was initially piloted in only 1 clinical department with expansion to 2 additional departments; piloting this curriculum in other departments would be useful to confirm generalizability. Second, our intentional focus on classroom-based teaching does not necessarily develop teaching skills in other venues. Our locally developed assessment plan may limit our ability to draw generalizable conclusions. Given the curriculum is embedded within the IPC and prioritizes high-quality, individualized feedback from trainee and faculty mentors, the number of trainee educators that can fully participate is limited. Given the lack of a comparator group and self-selection of our participants, we cannot make firm conclusions regarding the curriculum's efficacy. Finally, the previous lack of a centralized electronic platform for curriculum delivery, submission of tasks, and feedback limited our ability to disseminate our curriculum widely in a high-fidelity manner.

Many of the identified limitations of the pilot curriculum are being addressed. As highlighted, our RAE curriculum was expanded from including only internal medicine residents to train-

ees from family medicine and pediatrics with similar success in improving the self-efficacy of trainee educators. Assessment revision is ongoing and now dictated largely at the medical school level due to interim adoption of the IPC as a required fourth-year course for all graduating students. Ideally, we would apply a validated instrument to measure success of our RAE curriculum.

A recent advancement of the curriculum is the development of a course website, currently being piloted to supplement the RAE curriculum. The website houses several modules relevant to trainee educators in the IPC with embedded self-assessment activities. We have used the website to disseminate train-the-trainer materials for faculty within and outside our institution interested in implementing our RAE curriculum. (See https://rae.medicine.wisc.edu).

CONCLUSION

Our asynchronous RAE curriculum enhanced self-efficacy in teaching skills among trainee educators. Students find trainee teaching highly effective. We hope to continue to broaden the curriculum's impact and increase its ease of implementation by future groups through a course website that provides a centralized platform for ease of dissemination.

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Appendices: Appendices are available at www.wmjonline.org.

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Parental Perception of Care for Infants With Fever During Hospitalization

Jessica Hayes, MD; Sarah Vepraskas, MD

ABSTRACT

Objective: To assess parental perceptions regarding reason for and length of their infant's hospitalization and to understand family preferences for time of discharge.

Methods: Participants included parents of infants who were noncomplex, well-appearing infants, aged 7 to 60 days, and evaluated for fever without a source. A 5-question structured interview was administered over a 6-month period.

Results: Parents understood that fever necessitated admission for further diagnostic evaluation and that admissions would be no more than 48 hours if bacterial cultures were negative. Over one-third of patients' families preferred overnight discharge.

Discussion: Parents recognize reasons for admission and the rationale for length of stay. Preferences for time of discharge can serve as a starting point for shared decision-making between parents and providers.

INTRODUCTION

Shared decision-making between parents and providers has been used traditionally in management of chronic pediatric illnesses, as it is effective in educating families and incorporating parents' values and preferences into care plans.[1-3] In recent years, there has been increasing discussion about the potential benefits of shared decision-making for the parents of acutely ill children.[4,5] Although there is a growing body of literature on its utility in the management of infants with fever, providers are still determining its role in this population.[6] There are many reasonable approaches to the diagnostic and management decisions surrounding when to hospitalize a well-appearing, febrile infant, what workup to perform, and when to discharge the infant,[7,8] thus providing an opportunity to engage parents by incorporating shared decision-making. To do this effectively, it is essential for providers to understand parental perspectives.

Previous studies have examined febrile infants' parental preferences around parental stress, breastfeeding problems, hospital experience, perception of illness severity, and family and social impact.[9,10] From our literature review, it does not appear that parents of infants with fever have been asked about their understanding of the reason for hospitalization, the expected length of stay or, above all, whether they would prefer nontraditional discharge timing. Furthermore, specific parental discharge timing preferences have not been clarified in the context of current evidence-supported guidelines, which support that neonates hospitalized for a fever with negative bacterial cultures can be safely discharged at 36 hours.[7,8] Consideration of these preferences in this context would allow for implementation of shared decision-making and meaningful input from parents in the discharge planning process after the workup is complete.

We aimed to evaluate parental perceptions surrounding several important decision points in the care of well-appearing, febrile infants, specifically regarding reason for hospitalization, expected length of stay, and discharge timing.

METHODS

Study Design

A 5-question structured interview was developed via consensus of the study group based on clinical experience, literature review,

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and feedback from hospital medicine providers. Questions were formulated to investigate caregiver understanding and preferences regarding the following topics: (A) reason for hospitalization, (B) anticipated length of stay (LOS), (C) timing of discharge, (D) concerns about discharge education, and (E) impact of hospitalization on daily life. For the purpose of this brief report primarily focused on parental perceptions, we will be discussing responses regarding topics A, B, and C (see Box). The structured interview was read aloud to parents of admitted febrile infants by a single study team member at any point during the infant's hospitalization. The language spoken by the family during the interview and the time of interview administration was noted. The responses were summarized in writing during the interview, reviewed immediately after the interview by the same study member to ensure accuracy, and entered into a secure document. For each infant, charts were reviewed to identify time of admission as well as results of urine and blood cultures. These characteristics were recorded alongside parental interviewee responses in the secure document. All tasks were performed by the same study member.

Setting

Study participants were parents of infants who were admitted to the acute care unit of a 300-bed, urban, free-standing tertiary care pediatric hospital in the Midwestern United States from June to November 2017. Our institution was participating in a national quality improvement collaborative through the Value in Inpatient Pediatrics network, Project REVISE (Reducing Excessive Variability in Infant Sepsis Evaluation). The purpose of this project was to reduce variation in the care of febrile infants in aspects ranging from appropriate work-up to reducing LOS. As an example, providers and families of hospitalized, febrile infants with negative bacterial cultures were educated on a new target discharge goal of 36 hours. Our work reported herein was performed independently of Project REVISE but utilized the same patient population.

Caregiver Selection

A convenience sample of parents was interviewed. Participants were selected under the assumption that they all received education from their provider regarding the anticipated hospital course and LOS for febrile infants without urinary tract or invasive infections. They were selected solely based on whether their infant met inclusion criteria (previously healthy, well-appearing, and ages 7 to 60 days) and was admitted for further evaluation of fever without a source. Exclusion criteria were comorbid conditions (such as conditions predisposing to severe or recurrent bacterial illness, including genetic, congenital, chromosomal, neuromuscular, or neurodevelopmental abnormalities), positive bacterial cultures, and/or focal infection or bronchiolitis. Charts of admitted infants were reviewed each morning over a 6-month period to identify eligible infants.

Box. Selected Structured Interview Questions

Interviewer: What is your relationship to the baby? *Interviewee: open-ended response*

A. Can you tell me why your baby is in the hospital? (YES/NO)
- If yes, what is the reason?
- If no,
  - Were you told anything about the age of your child that led to being hospitalized?
  - Were you told anything about your child's lab work that led to being hospitalized?

B. What were you told about approximately how long your baby (in hours) might be in the hospital?

C. *I do not know if this is the case for you, but)* if results were available and indicated that your baby could be discharged in the middle of the night, would you prefer to be discharged home at that time or would you rather be discharged home the next morning?

Ethical Issues

This study was declared exempt by our hospital's Institutional Review Board, as it was considered within the scope of quality improvement work.

RESULTS

Characteristics of Patient and Caregiver Participants

All caregivers approached agreed to and completed the entire interview (N=24 caregivers of 24 admitted infants). Responses from 3 caregivers were excluded from analysis due to their infant's positive urine cultures: 2 *Escherichia coli* and 1 *Streptococcus agalactiae,* or group B Streptococcus. One parent was non-English-speaking (language: Karen); the remaining 20 were English-speaking. Eighty-one percent (17/21) were interviewed within 24 hours of their infant's admission, and 19% (4/21) were interviewed between 24 and 48 hours after admission.

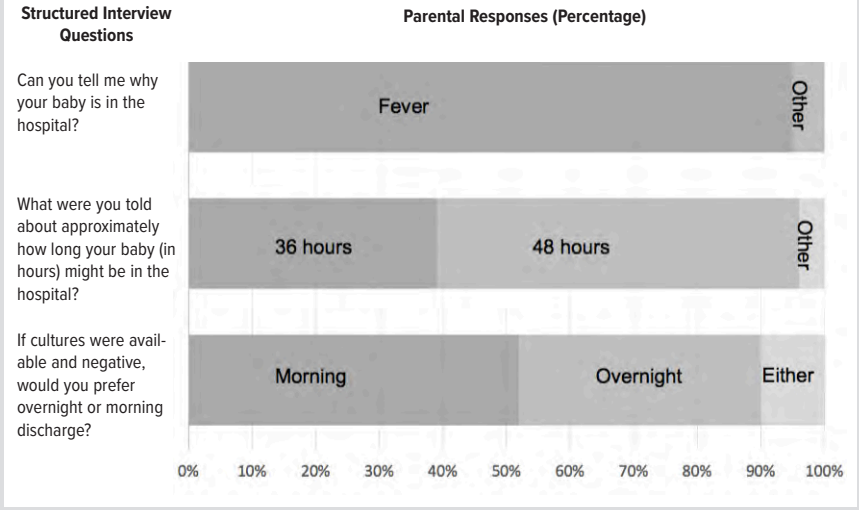
Responses to Structured Interview

The average LOS for all infants meeting inclusion criteria was 42 hours. More specifically, the average LOS for parents who preferred overnight versus morning discharge was 39 hours versus 46 hours, respectively (see Figure). Ninety-five percent (20/21) of parents correctly identified their infant's reason for hospitalization as fever. The remaining parent (1/21) correctly provided the already established diagnosis (viral meningitis). Thirty-eight percent (8/21) of parents anticipated a 36-hour LOS, 57% (12/21) a 48-hour LOS, and 5% (1/21) "other" (response: 24 hours). Fifty-two percent (11/21) of parents preferred morning discharge, 38% (8/21) overnight discharge, and 10% (2/21) had no preference.

DISCUSSION

Shared decision-making (SDM) with parents of febrile neonates offers the opportunity for providers to acknowledge and integrate family values into plans of care. To accomplish this goal, providers must first be able to understand the specific perceptions and preferences of parents regarding their infant's care. The diagnos-

Figure. Parental Responses to Structured Interview



tic evaluation of febrile neonates remains difficult and ambiguous depending on the clinical scenario, which, understandably, confuses parents and limits the utility of SDM. This study adds to the previous literature on parental preferences and perceptions regarding care of febrile infants, while providing additional insight into expected LOS and preferred discharge timing.

Our results demonstrated that parents seem to know that their infant's fever necessitates admission for further diagnostic evaluation. They also understand that their infants will remain admitted for a short amount of time—no more than 48 hours—as long as bacterial cultures are negative. In fact, over one-third of parents appropriately anticipated a 36-hour stay, having discussed with their provider at time of admission that this was a safe, evidence-based hospital duration for infants with negative bacterial cultures. As this study involved parents of well-appearing infants, we expected parents to anticipate a shorter LOS, which is also more appropriate for SDM in a nonemergent setting. Their clear understanding of reason for admission and the rationale for LOS further supports the appropriateness of SDM for this population. Lastly, more than a third of patient's families stated they would like to be discharged overnight. As seen by the differences in mean LOS between the overnight and morning preference groups (39 vs 46 hours, respectively), overnight discharge could not only enhance patient-centered care, but also could improve hospital efficiency and resource use. Providers could, thus, apply SDM by considering a nontraditional discharge time, if able, for this patient and family population. Furthermore, communication between parents and providers about discharge timing could be initiated earlier in the discharge process to accommodate parents' preferences. With that said, it would be important to evaluate for unintended consequences of nontraditional discharge times, such as caregivers feeling they were discharged too soon (if being told they need to be discharged in the middle of the night, lack-of appropriate follow-up being arranged, or readmissions).

This study contributes to the literature as an example of directly eliciting family perceptions and preferences that lend to the application of the SDM model. The knowledge about parental perceptions and preferences makes the proposed 3-step SDM framework more feasible: choice, options, and decision talk.[4] Preferred discharge timing, as shown by the survey results, can serve as an example of SDM implementation. To establish choice, parents can be made aware that more than one option exists, overnight versus morning discharge. The options can be weighed based on associated harms or benefits of each choice. For instance, an overnight discharge would save costs, time, and resources from the hospital system standpoint, but would also decrease the amount of professional observation during what can be an uncertain and stressful time for parents.[9,10] Decision talk can then be implemented, wherein parents' values and preferences allow for a joint decision on the appropriate time for discharge. Alternatively, this model could be applied to evaluate parents' perceptions of earlier discharge criteria, allowing for the earlier discharge of more infants.

This study had certain limitations, such as small sample size and convenience sampling. An interview of caregivers for a larger and more diverse population of parents/caregivers of infants with fever would be necessary to make more global conclusions. The results were also not conducive to a thematic analysis due to limited answer choices. A future survey, however, could include questions that analyze preferences further, such as morning discharge even when discharge criteria are met overnight. Future areas of investigation also could include determining how providers in different fields apply SDM in their practices with infants and parents, such as in family medicine, obstetrics, or even various pediatric subspecialties. This could allow us to identify themes that enhance SDM as a model across pediatric medicine.

CONCLUSION

Overall, this study provides insight into parental perspectives on essential aspects of the care of infants with fever and demonstrates the value of understanding the views of parents with whom collaboration could result in effective shared decision-making.

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Low Rate of SARS-CoV-2 Infection in Adults With Active Cancer Diagnosis in a Nonendemic Region in the United States

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ABSTRACT

Introduction: The mortality rate in cancer patients with SARS-CoV-2 has been cited to be as high as 13% amidst a global pandemic. Here we present the prevalence of SARS-CoV-2 in adult patients with active cancer in a nonendemic cancer center at the time of the study.

Methods: All adult patients with an active history of cancer undergoing any elective surgery were screened for SARS-CoV-2 symptoms, including fever ≥ 38 degrees Celsius, chills, dyspnea, cough, sputum production, pharyngitis, myalgia/arthralgia, headache, anosmia, and nasal discharge. Both symptomatic and asymptomatic patients were tested for SARS-CoV-2 preoperatively via nasopharyngeal swab within 48 hours of surgery using an RT-PCR assay. Active cancer was defined as receipt of chemotherapy and/or radiation within 1 year of the SARS-CoV-2 test. Deidentified, institutional review board-exempt patient data were analyzed with IBM Statistical Package for the Social Sciences (SPSS) Version 26.

Results: Between March 16, 2020 and June 30, 2020, a total of 227 patients were tested preoperatively for SARS-CoV-2. Median age was 64.0 years (range 21 to 90). The majority of the cohort were White. Only 2 patients (0.8%) were positive for SARS-CoV-2. One 73-year-old woman undergoing hip replacement had Stage IV breast cancer and a 75-year-old man undergoing port placement had Stage IV retroperitoneal leiomyosarcoma. Neither patient had symptoms of SARS-CoV-2, underwent hospitalization for SARS-CoV-2, or proceeded to have the scheduled surgery after the positive test results until a 14-day quarantine period and a subsequent negative test result. Both patients subsequently received the procedures they were originally scheduled for with no complications.

Conclusion: Careful consideration of resource allocation and treatment limitations for cancer patients should occur in lower endemic regions.

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INTRODUCTION

An outbreak of the novel coronavirus disease (SARS-CoV-2) occurred in Wuhan, China in December of 2019. Initial studies out of Wuhan warned clinicians of higher morbidity and mortality in those with an immunosuppressed state. Mortality rates in cancer patients with SARS-CoV-2 have been cited to be as high as 13% amidst a global pandemic.[1-4] In addition, postoperative pulmonary complications have been reported to occur in half of patients with perioperative SARS-CoV-2 infections, with high mortality rate.[4]

The University of Wisconsin Carbone Cancer Center instituted universal screening for SARS-CoV-2 on all patients prior to surgery as a method of preserving personal protective equipment and limiting exposures to SARS-CoV-2 for patients and health care workers on March 16, 2020. Here we present the prevalence of SARS-CoV-2 in adult patients with active cancer in an area which was a nonendemic at the time of the study.

METHODS

All adult patients with an active history of cancer undergoing any elective surgery were screened for SARS-CoV-2 symptoms, including fever ≥ 38 degrees Celsius, chills, dyspnea, cough, sputum production, pharyngitis, myalgia/arthralgia, headache, anosmia, and nasal discharge. Both symptomatic and asymptomatic patients were tested for SARS-CoV-2 preoperatively via nasopharyngeal swab within 48 hours of surgery using an RT-PCR assay. Active cancer was defined as receipt of chemotherapy and/or radiation within 1 year of SARS-CoV-2 test. The study population was

representative of the cancer center's typical patient population. Emphasis was made to delay patients with cancer who could have been delayed through use of nonimmunosuppressive medical therapy, but most patients with cancer received their treatment as was scheduled prior to the pandemic.

Deidentified, institutional review board-exempt patient data were analyzed with IBM Statistical Package for the Social Sciences (SPSS) Version 26.

Table. Results of Routine SARS-CoV-2 Testing Prior to Surgery in Patients With Active Cancer History (n=227)

Variable	SARS-CoV-2 Positive (n=2) Median (Range)	N (%)	SARS-CoV-2 Negative (n=225) Median (Range)	N (%)
Age (Years)	74.0 (73.0-75.0)		63.0 (21.0-90.0)	
Sex				
Female		1.0 (50)		127.0 (56.4)
Male		1.0 (50)		98.0 (43.6)
Race				
White		2 (100)		212.0 (94.2)
Black or African American		0 (0)		5.0 (2.2)
Asian		0 (0)		3.0 (1.3)
American Indian or Alaska Native		0 (0)		2.0 (0.9)
Two or more races		0 (0)		1.0 (0.4)
Patient declined to answer		0 (0)		2.0 (0.9)
Body mass index	41.9 (39.3-44.4)	0 (0)	27.6 (13.8-49.4)	
Cancer type				
Bone marrow transplant		0 (0)		3.0 (0.4)
Bone and connective tissue		0 (0)		2.0 (0.9)
Melanoma		0 (0)		5.0 (2.2)
Other		0 (0)		9.0 (4.0)
Breast		1 (50)		25.0 (11.1)
Eye, brain, other nerve cancer		0 (0)		12.0 (5.3)
Gastrointestinal		1.0 (50)		74.0 (32.9)
Genitourinary		0 (0)		24.0 (10.7)
Gynecology		0 (0)		18.0 (8.0)
Head and neck		0 (0)		5.0 (2.2)
Hematologic		0 (0)		11.0 (4.8)
Lung and thoracic		0 (0)		37.0 (16.4)
Surgery type				
Inpatient		2 (100)		144.0 (63.1)
Outpatient		0.0 (0.0)		83.0 (36.9)

RESULTS

Between March 16, 2020 and June 30, 2020, a total of 227 active cancer patients were tested preoperatively for SARS-CoV-2. Median age was 64.0 years (range 21 to 90). The majority of the cohort were White. Only 2 patients (0.8%) were positive for SARS-CoV-2 (Table). One 73-year-old woman undergoing hip replacement had Stage IV breast cancer, and a 75-year-old man undergoing port placement had Stage IV retroperitoneal leiomyosarcoma. Neither patient had symptoms of SARS-CoV-2, underwent hospitalization for SARS-CoV-2, or proceeded to have the scheduled surgery after the positive test results until a 14-day quarantine period and a subsequent negative test result. Both patients subsequently received the procedures they were originally scheduled for with no complications.

DISCUSSION

In December of 2019, there was an outbreak of the novel coronavirus disease (SARS-CoV-2) in Wuhan, China, which has resulted in a global pandemic. Reports from China regarding its cancer patients noted that infection rate of SARS-CoV-2 in patients with cancer is higher than the cumulative incidence of all diagnosed with SARS-CoV-2 cases reported over same time period.[5-7] As a result, many institutions took measures to reduce frequency of hospital visits of patients with cancer during the pandemic.

The incidence rate of SARS-CoV-2 infection in endemic regions ranges widely. In Wuhan, China, the asymptomatic all population rate of SARS-CoV-2 and asymptomatic cancer patient rate was estimated to be approximately 0.4% and 0.8%, respectively.[7] The incidence of SARS-CoV-2 infection in asymptomatic pediatric cancer patients was found to be 2.5% in New York City.[2] In adults, the rate of SARS-CoV-2 infection in asymptomatic adult patients with cancer was found to be 8.2% in the United Arab Emirates.[1]

Cancer patients may be more susceptible to severe outcomes from SARS-CoV-2 infection than individuals without cancer because of their immunosuppressed state due to cancer treatment and/or their malignancy.[3-5,8] The majority of studies report these patients to be actively receiving anticancer therapy, including chemotherapy. As a result, many institutions took measures to reduce frequency of hospital visits of patients with cancer during the pandemic. However, there is little clarification whether or not patients had active cancer versus a history of cancer.

The present data were gathered from a National Cancer Institute (NCI) designated cancer center in Madison, Wisconsin, which at the time of this study had lower rates of SARS-CoV-2 prevalence compared to other states. Universal screening was implemented for SARS-CoV-2 for all patients undergoing any surgery preoperatively as a way to keep health workers safe, since the risk of aerosolized virus in the operating room is unclear. In addition, such a measure would protect the patient against complications from SARS-CoV-2 in the perioperative period, as well as prevent the spread of the infection further.

We elected to analyze this data to obtain the rate of SARS-CoV-2 infection positivity in patients with active cancer undergoing elective surgery. Active cancer was defined as receiving either chemotherapy and/or radiation therapy within 1 year of SARS-CoV-2 test result. To date, this is the only study that clearly defines whether or not the study population had active cancer or just a history of cancer.

Our data analysis showed that only 2 cancer patients out of 227 (0.8%) tested positive for SARS-CoV-2 over a 3.5-month period during the pandemic. This rate is much lower than reported in other higher endemic regions. Both patients were asymptomatic and were not hospitalized for the infection. Interestingly, both patients had disseminated cancer.

Notably, our rate of SARS-CoV-2 positivity in adult patients with active cancer is much lower than that reported in higher endemic regions. While this may suggest decreased susceptibility to infection as previously thought, there are important limitations to our study that must be considered before generalizing this data. These limitations include the retrospective nature of this study, which limits the ability to understand other factors—including other social determinants of health—that may have led this population to take more precautions, leading to a reduced positivity rate. It can be presumed that just knowing about their cancer diagnosis made patients more aware that they may be more susceptible to the virus.

In addition, our physicians and other health care providers frequently counsel patients with cancer to take greater precaution with exposing themselves to the outside environment and other contacts. While these limitations must be considered, our data suggest a relatively low rate of SARS-CoV-2 positivity in adult patients with active cancer in an area that was nonendemic during the study period, which can be used to help plan expectations for cancellations of procedures and hospital resource allocation given the ongoing pandemic.

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Pulmonary Blastomycosis: Pediatric Cases Emphasizing Prompt Identification Using C-Reactive Protein and Procalcitonin to Distinguish Fungal vs Bacterial Origin

Charles A. Gusho, BS; Tannor A. Court, BS

ABSTRACT

Introduction: Pulmonary blastomycosis is a rare fungal disease with increased prevalence in states such as Wisconsin. Clinical manifestations of blastomycosis may vary from asymptomatic infection to multiorgan, disseminated disease.

Case Presentation: We present 2 pediatric patients with blastomycosis who were initially worked up secondary to cough and fever of suspected bacterial origin, though whose subsequent hospital course was notable for deterioration until antifungal treatment was initiated.

Discussion: In each case, the disease burden was monitored concurrently with serum procalcitonin and C-reactive protein levels, the former of which remained relatively normal throughout the hospital course signifying lack of bacterial involvement.

Conclusion: We emphasize the importance of obtaining an early C-reactive protein and procalcitonin, which may distinguish a bacterial from fungal pulmonary infection such as blastomycosis. This, in turn, may shorten hospital stay and reduce hospital inpatient cost, morbidity, and mortality by means of prompt antifungal intervention.

INTRODUCTION

Blastomycosis is a rare, geographically constrained, thermally dimorphic fungi of the genus and species *Blastomyces dermatitidis*. The disease is most prevalent near the Mississippi, Missouri, and Ohio River basins and notably infectious in states such as Wisconsin. The clinical symptomatology is diverse, and according to studies conducted before the development of successful antifungal therapy, more than 70% of a Veteran's Administration cohort with blastomycosis had multiorgan spread, with mortality rates as high as 90%.[1] Therefore, early antifungal therapy is paramount to an appropriate clinical recovery. However, the presenting signs and symptoms may be misattributed to a bacterial pneumonia. Nonspecific symptom, such as fever, cough, and chest pain, and physical exam findings, such as diminished breath sounds, are not reliable in distinguishing the 2 etiologies. When the clinical suspicion for pneumonia is high, results of simultaneous nonspecific inflammatory markers such as C-reactive protein (CRP) and procalcitonin (PCT) may be used to guide empiric antifungal versus antibacterial therapy. While reports from Wisconsin describe a lower frequency of disseminated disease, the primary infection rates are high, and delay in recognition and treatment may significantly prolong hospital stay and increase total charges, morbidity, and mortality.[2]

CASE 1

A 16-year-old Somali male, born to immigrant parents who arrived in Wisconsin 5 years prior, was in his normal state of health until 11 days before admission to the pediatric intensive care unit (PICU), when he was seen at urgent care for a fever and cough. He was diagnosed with left lower lobe pneumonia following radiographic evidence of a consolidation and was prescribed a 5-day course of azithromycin 250 mg/5 ml by mouth and an albuterol inhaler. Two days later, he was brought to the emergency department (ED) with worsening generalized weakness and was sent home.

On return to the ED 1 week later, he had persistent decreased breath sounds in the lower left lung field, diffuse bilateral rhonchi, chest wall tenderness to palpation, and increased work

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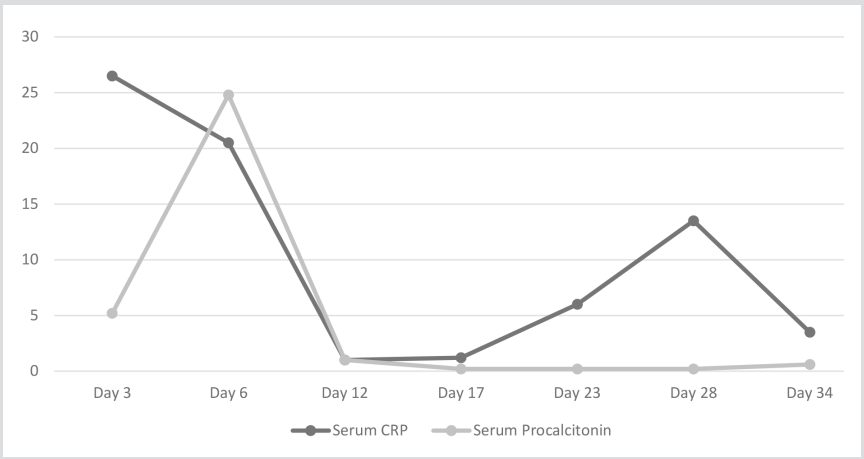
Figure 1. Serum Procalcitonin and C-reactive Protein (CRP) Levels (mg/dL) Recorded Throughout 35-day Hospital Stay of Patient 1



breathing. Vitals were normal at this time. Subsequent computed tomographic imaging revealed prominent bilateral infiltrates with complete opacification of the lower left lobe and a left-sided pleural effusion.

CRP level on admission was 29.60 mg/dL (normal: < 0.8 mg/dL) with a white blood cell (WBC) count of 13.1 x10^3 cells/uL (normal: < 11.0 x 10^3 cells/uL). Tuberculosis QuantiFERON and pneumococcal antigen panels were negative. Additionally, thoracentesis was performed, though pleural fluid bacterial and fungal cultures were negative at this time. On admission day 2 while intubated, the patient underwent bronchoalveolar lavage and bronchoscopy, which were significant for visible hemorrhagic lesions in the left main stem bronchus. Bacterial bronchial aspirate cultures showed no growth, though microscopy of fungal cultures demonstrated broad-based budding yeast. Additionally, *Legionella* urine antigen studies were negative, and *Blastomyces* urine antibodies were nonreactive at this time. He began therapy with intravenous (IV) ceftriaxone (Rocephin) (1000 mg/50 mL/24 hours) and, on admission day 3, therapy with liposomal amphotericin B IV (Ambisome) (300 mg/dextrose 5% 250 mL/24 hours) and piperacillin-tazobactam IV (Zosyn) (4500 mg/daily). The following day, admission day 4, his CRP and PCT were 26.7 mg/dL and 5.29 ng/mL (normal: < 0.25 ng/mL), respectively.

On admission day 6, the patient was deemed critically ill and therapy was initiated with veno-venous extracorporeal membrane oxygenation (ECMO) and mechanical intubation. On admission day 7, urine Histoplasma antigens came back positive, and on day 12, serum *Blastomyces* antigens returned positive, after which he was transitioned from strict ECMO oxygenation-ventilation to a combination of ECMO and mechanical ventilation. On day 23, pulmonary examination was normal on the right with residual decreased breath sounds on the left, and on day 35, he was transferred to a rehabilitation unit with normal vital signs and a benign clinical exam. Throughout the course of his hospital stay, the patient had simultaneously and regularly measured PCT and CRP levels (Figure 1). Upon transfer to the rehabilitation unit, he was weaned off liposomal amphotericin B IV (Ambisome) from a rate of 300 mg/dextrose 5% 250 mL/24 hours and started on oral itraconazole (10mg/kg/24 hours) for an anticipated 12 months duration. Prior to discharge, he underwent magnetic resonance imaging of the head, which was negative for evidence of cerebral blastomycosis. However, he did not receive a bone scan to evaluate for disseminated blastomycosis of the bone.

CASE 2

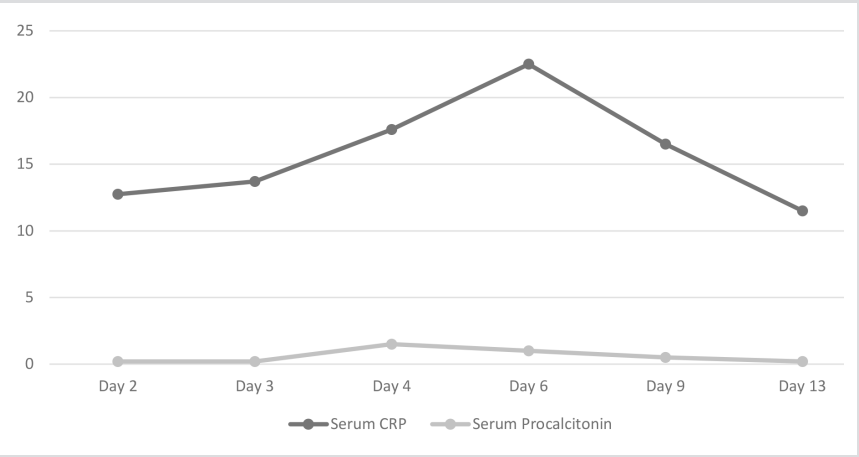
Two years following case 1, an 11-year-old Somali girl, accompanied by immigrant parents who arrived in Wisconsin 2 years prior, presented to the ED with a 3-day history of persistent cough and low-grade fever. Her parents reported a decreased appetite and markedly reduced activity level prior to presentation. Review of systems was negative for rhinorrhea, congestion, ear pain, throat pain, rashes, or dyspnea. She had no history of recent travel outside the Green Bay, Wisconsin area, and past medical history was negative. On admission, her temperature was 38.3°C, pulse 126 beats per minute, 24 respirations per minute, and an SpO_2 of 100% on ambient air. Physical examination was wholly unremarkable. Radiographs of her chest disclosed a dense consolidation in the left suprahilar region with no right-sided disease, and she was prescribed a 5-day course of azithromycin 200 mg/5 ml by mouth. Nine days later she returned to the ED afebrile, though with persistent cough and bilateral facial swelling. Her parents confirmed she completed her course of azithromycin and denied any significant interval history. On return to the ED, her temperature was 37°C, with a pulse of 117 beats per minute, respirations of 18 per minute, and an SpO_2 of 95% on ambient air.

At this time, the physical examination disclosed right periorbital ecchymosis, though was otherwise normal. Chest films demonstrated worsening left lobe opacification with a new right middle lobe consolidation. PCR nasal swab for viral antigens was negative, and she was started on ceftriaxone IV (Rocephin) (1620 mg/24 hours) and diphenhydramine IV (Benadryl) (12.5 mg as needed) and admitted to the PICU.

On admission day 2, the patient's CRP was 11 mg/dL (normal: < 0.8 mg/dL) and PCT was negligible (normal: < 0.25 ng/mL); she was started empirically on IV vancomycin (320 mg/6 hours) and liposomal amphotericin B IV (Ambisome) (160 mg/dextrose 5% 100 mL/24 hours). Serum antibody and urine antigen studies were nonreactive, and bronchial aspirate was negative for growth at that time. On admission day 5, serum *Blastomyces*

antibodies returned positive and ceftriaxone was discontinued. By day 7, her CRP began to fall (Figure 2), her vancomycin was discontinued, and she was thereafter started on levofloxacin (Levaquin) (319 mg/12 hours). On day 9, urine *Blastomyces* antigen test returned positive and by day 13, she was presumed to have been infected with blastomycosis and was discharged. During the course of her hospital stay, she neither exhibited signs nor symptoms of focal neurologic deficit, and imaging of the head, as well as a bone scan, were not performed. Prior to discharge, she was advised to return to the hospital for regularly scheduled liposomal amphotericin B IV therapy (160 mg/dextrose 5% 100 mL/24 hours) for 1 week, with an anticipated 6-months duration of oral itraconazole (10mg/kg/24 hours) thereafter, in addition to lactobacillus capsules by mouth twice daily. Chest radiography on discharge was negative and showed resolution of intrapulmonary disease.

Figure 2. Serum Procalcitonin and C-reactive Protein (CRP) Levels (mg/dL) Recorded Throughout 13-day Hospital Stay of Patient 2



DISCUSSION

Blastomycosis is an often-misdiagnosed fungal disease as its initial symptom profile may be nonspecific. Additionally, *Blastomyces*—as opposed to other fungal pathogens—has a proclivity of affecting healthy, immunocompetent patients.[3] While the usual presentation of blastomycosis involves pneumonitis in a patient within a certain geographical area that does not respond to typical antibacterial therapy, the subsequent course ranges from primary pulmonary disease, to fulminant hypoxic respiratory failure and acute respiratory distress syndrome, to extra pulmonary complications commonly involving the skin and bones.[4] As emphasized in the previous 2 cases, the initial presenting symptoms—here occurring in 2 immunocompetent patients—often mimic a routine bacterial infection. Without prompt recognition, the delay in diagnosis and treatment of blastomycosis leads to poor clinical outcomes, including increased morbidity and mortality, greater length of hospital stay, and increased inpatient costs.[5]

In the presence of nonspecific symptoms not relieved by antibiotics, the best initial test to identify blastomycosis is through microscopic examination of pulmonary (lower respiratory tract) secretions, obtained either by induced sputum production or pulmonary endoscopy. While some clinical data suggest fungal growth is insidious, often taking as long as 5 weeks to appear on microscopy, an induced sputum sample or one properly obtained from pulmonary endoscopy should show fungal growth within a few days.[6] Therefore, given the potentially broad time-course of growth, clinical suspicion is paramount to prompt recognition and treatment. We suggest that the early gathering and interpretation of nonspecific inflammatory markers that reveal a low PCT and elevated CRP may help promote subsequent distinguishing of a bacterial from fungal pneumonia by way of targeted diagnostic tests. This practice ultimately would permit a more expeditious antifungal treatment course and overall reduction in antibiotic exposure. The dissociation of PCT and CRP should stimulate the treating physician to rapidly obtain tests to confirm blastomycosis, such as microbiologic studies, urinary antigen testing, or cultures of pulmonary secretions. The benefit of early interpretation of these markers stems not only from antibiotic dismissal, but also from confirmation of the fungal pathogen via diagnostic testing before initiation of toxic antifungal therapy.

Serum CRP and PCT concentrations are of a relatively new clinical benefit used as an adjunct in the diagnosis and treatment of infections due to their accessibility and high specificity and sensitivity.[7,8] CRP is an acute phase reactant synthesized by the liver in response to inflammatory cytokines, and its rise is proportional to the severity of the inflammatory process, making CRP a reasonable proxy for identifying both a worsening or resolving bacterial or fungal infection.[9] PCT, another inflammatory marker, is a hormone secreted by parafollicular C-cells of the thyroid gland in response to hypercalcemia or systemic inflammation caused by infection. While the CRP has great sensitivity in identifying inflammatory conditions, it is often considered nonspecific for infectious disease as it may be elevated in response to various noninfectious stimuli, including trauma and inflammation.[10] Therefore, PCT is of great clinical significance for differentiating bacterial versus fungal infection, such as blastomycosis. Studies suggest that infections caused by a fungal pathogen do not elicit as great an increase in serum PCT (range, 0.69–1.23) compared to its conventional rise in patients who have an infection of confirmed bacterial origin (range, 4.18–12.9).[11]

In Case 1, we cannot explain the rapid increase in serum PCT

from admission day 3 (5.29 mg/dL) to admission day 6 (24.48 mg/dL), though in a previous study by Markova et al, the overall trend of elevated CRP concentrations with low PCT levels indicates invasive fungal infection, thereby warranting early initiation of antifungal therapy.[12] Due to ambiguities between invasive fungal and bacterial infections, however, blastomycosis is often treated initially as a bacterial infection until the course of the disease is markedly worse (inpatient stay, use of ECMO, etc) than were its presenting symptoms. *Blastomyces* can infect immunocompetent hosts and may occur as a cluster of outbreaks within a specifically populated area. For example, in the summer of 2015, individuals visiting the Little Wolf River were exposed to *Blastomyces*, with a subsequent infection rate of 59 confirmed and 39 probable cases.[13] Similarly, a large-scale outbreak in Marathon County, Wisconsin in 2009-2010 resulted in 55 confirmed cases.[14] Therefore, in states like Wisconsin where its prevalence is increased, or within which outbreaks are rare but not entirely uncommon, early use of serum PCT as a marker to promote further differentiation of bacterial from fungal infection may certainly decrease the prejudicial use of the antibiotics in patients with underlying fungal disease such as blastomycosis, as well as reduce cost, hospital stay, and inpatient morbidity and mortality.

CONCLUSION

Blastomycosis is a potentially fatal fungal disease that can be difficult to differentiate clinically from bacterial pneumonia. Prompt treatment and diagnosis, which can be persuaded by early dissociation of PCT and CRP, is undoubtedly associated with a better prognosis, less antibiotic resistance, and reduced costs.

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The Eyes Cannot See What the Mind Does Not Know: Endocrinological Side Effects of Ibrutinib

Nikhitha Chandrashekar, MD; Rachel McKenney, MD

ABSTRACT

Introduction: Over the last 7 years, ibrutinib has been given US Food and Drug Administration approval for a rising number of indications ranging from chronic lymphocytic leukemia (CLL) and marginal zone lymphoma to Waldenstrom macroglobulinemia.

Case Presentation: An 85-year-old man with a history of CLL who had been treated with ibrutinib over 6 weeks developed a rash and progressive weakness, and he was ultimately admitted to the hospital for obtundation. He was hypotensive, hyponatremic, and hypothyroid. Despite extensive testing and treatment for syndrome of inappropriate antidiuretic hormone (SIADH), he remained unimproved. Results of an adrenocorticotropic hormone stimulation test indicated secondary adrenal insufficiency. He was treated with hydrocortisone, and his symptoms subsequently resolved.

Discussion: Previous studies have demonstrated the presence of endocrine dysfunction, such as adrenal insufficiency, thyroid dysfunction, hyperparathyroidism, and gonadal failure in some tyrosine kinase inhibitors (TKI). To our knowledge, no previous literature has reported this association specifically with the TKI ibrutinib. The case highlights the importance of spreading awareness amongst clinicians of potential side effects that can occur with targeted therapy such as ibrutinib. This, in turn, will facilitate prompt recognition and early management when such cases arise in a hospital setting.

INTRODUCTION

Tyrosine kinase inhibitors (TKI) are key regulators of signaling pathways involving cellular proliferation, differentiation, and apoptosis and affect TK-dependent oncogenic pathways.[1] Ibrutinib is the first drug approved by the US Food and Drug Administration (FDA) that is designed to target Bruton tyrosine kinase (BTK)—a key protein in the B cell.[2,3] Ibrutinib first received FDA approval for treatment of mantle cell lymphoma and since that time has been approved for numerous other indications. In 2016, it was approved as a frontline chronic lymphocytic leukemia (CLL) treatment, in 2017 for marginal zone lymphoma (MZL), in 2018 for Waldenstrom macroglobulinemia, and most recently—in 2019—for small lymphocytic lymphoma (SLL) along with obinutuzumab.[4] TKIs potentially provide a relatively low toxicity in comparison with conventional cytotoxic chemotherapy. However, with their increasing use, we are becoming aware of important side effects.

CASE PRESENTATION

An 85-year-old man with a history of CLL (diagnosed in 2013 and under observation until 2019) had been started on ibrutinib after development of an enlarged mass in the parotid and submental lymph nodes. He had an excellent response to therapy, with a reduction in the size of his lymph nodes and splenomegaly. After 2 weeks of therapy, he developed mucocutaneous bleeding; a purpuric rash over his scalp, neck, upper lip; and diffuse petechiae along his bilateral lower extremities. He also experienced arthralgias in the right knee and hip. Concern for worsening bleeding prompted discontinuation of ibrutinib, but it was later restarted at a lower dose. A week later, he developed symptomatic sinus bradycardia and weakness, and ibrutinib was again discontinued. Ten days later, he was admitted to the hospital for multiple syncopal episodes with increasing fatigue and obtundation. His only other medications were allopurinol, gabapentin, tamsulosin, omeprazole, and furosemide. Laboratory evaluation was significant for hypokalemia (potassium,

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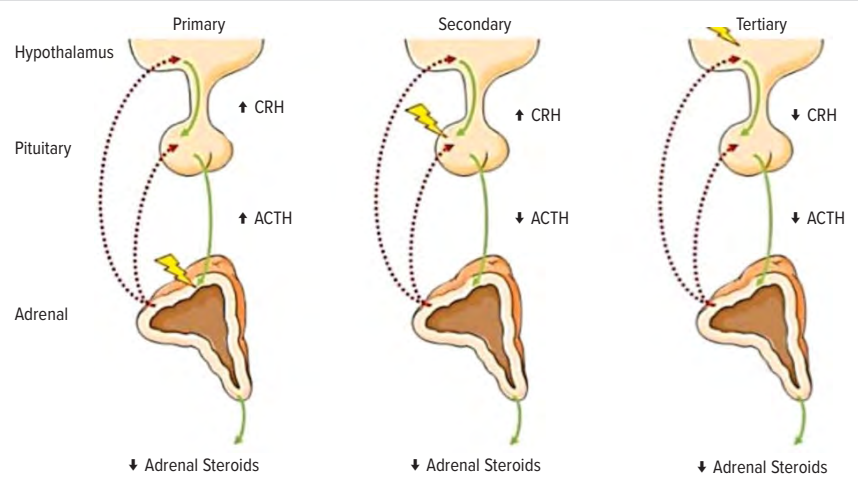
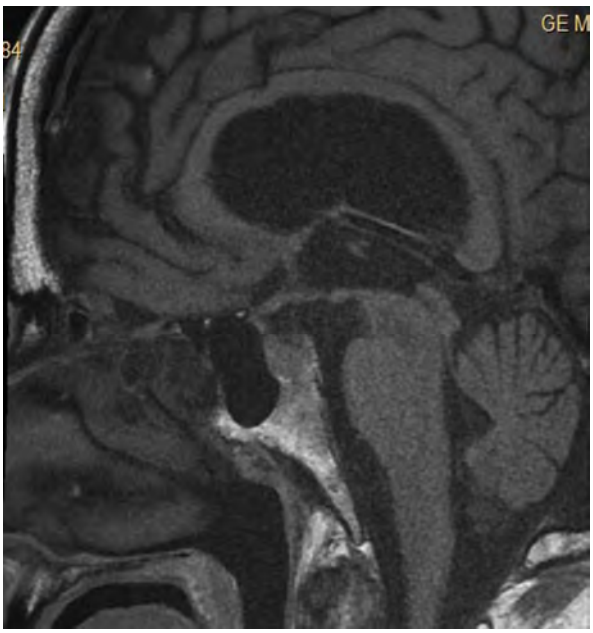
Figure 1. Types of Adrenal Insufficiency



Abbreviations: RH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone.

Figure 2. Normal Magnetic Resonance Imaging of Pituitary Sella



+3.4 mmol/L), hyponatremia (sodium, 123 mmol/L), and thyroid-stimulating hormone (TSH) (0.48 uU/mL, normal range 0.40-5.50 uU/mL). Workup for hyponatremia showed a low serum osmolarity 268 mosm/kg, urine osmolality of 240 mosm/kg, and a high urine sodium of 73 mmol/L (26 mmol/L after recheck post discontinuation of diuretic). Given the patient's recent ibrutinib use, chronic diuretic use, and laboratory values, there was a strong suspicion for syndrome of inappropriate antidiuretic hormone (SIADH). However, with fluid restriction, there was only a marginal improvement of his sodium levels. He was treated empirically for urosepsis with intravenous cefepime, but urine and blood cultures ultimately returned negative for growth and antibiotics were discontinued.

On hospital day 5, the patient experienced a near syncopal episode with systolic blood pressure of 60 mm Hg. An adrenocorticotropic hormone (ACTH) stimulation test resulted in a baseline cortisol of 10.04 µg/dL and levels at 30 and 60 minutes of 14.01 µg/dL and 14.89 µg/dL, respectively, after 250 mcg of cosyntropin was administered. A baseline ACTH was not obtained; however, the 21-hydroxylase antibody returned normal. Given the serum cortisol concentration <18 mcg/dL to 20 mcg/dL before and after corticotropin (ACTH), the patient was diagnosed with secondary adrenal insufficiency.[5] (See Figure 1.) At this time, a free thyroxine (T4) concentration also was measured and returned low (0.45 ng/dL). This, along with a low-normal TSH, was in line with a diagnosis of central hypothyroidism. Oral hydrocortisone was started immediately, but levothyroxine was not administered until 7 days later to avoid potential adrenal crisis. After initiation of hydrocortisone, the serum sodium concentration rose from 129 mmol/L to 134 mmol/L, with marked improvement in mentation to near baseline. Magnetic resonance imaging (MRI) of pituitary sella was performed 3 days after discharge and showed a normal pituitary gland with no evidence of pituitary masses, infiltrates, or lesions, thus confirming that there was no preexisting pituitary disease attributing to the patient's low cortisol levels (see Figure 2). On outpatient follow-up, he was noted to have maintained normal electrolyte levels, and his overall functioning continued to improve.

DISCUSSION

Previous studies have demonstrated the presence of endocrine dysfunction, such as adrenal insufficiency, thyroid dysfunction, hyperparathyroidism, and gonadal failure in some TKIs like sunitinib, imatinib, sorafenib, pazopanib, and axitinib.[6-12] However, to our knowledge there are no prior case reports or studies that have demonstrated this relationship specifically with the TKI ibrutinib. According to Kust et al, no papers have been published linking the ibrutinib to hypothyroidism as a side effect of therapy, even as an individual case report.[13]

In order to stipulate that hypopituitarism in this patient was related to ibrutinib therapy, other causes of potential pituitary insufficiency were assessed. The presence of underlying structural pituitary lesions was rebuked given that the outpatient MRI of the pituitary sella showed a normal-appearing pituitary gland with no

discrete masses. Functional hypogonadotropic hypogonadism also was ruled out as the serum testosterone (2.8 ng/dL) and luteinizing hormone (4.9 IU/L) were normal. Prolactin levels (18 ng/mL) were elevated.

A limitation of this study is that no ACTH level was obtained prior to the cosyntropin stimulation test, which would have given us more certainty in making the determination about whether this was a primary or secondary adrenal insufficiency. Additionally, renin and aldosterone levels were not obtained, therefore limiting our ability to definitively rule out a primary destructive adrenal etiology. That being said, the patient's 21 hydroxylase antibodies were normal and would have been elevated in the case of an underlying autoimmune process involving the adrenal glands. Therefore, we ruled out autoimmune adrenalitis, which is the most common cause of primary adrenal insufficiency in the United States. Another piece of evidence that goes against a primary adrenal process is that computed tomography (CT) of abdomen and pelvis performed 3 weeks after discharge showed the presence of normal adrenal glands. One also would expect to see much lower cortisol values in a primary process. Our patient's symptoms were likely a direct side effect of ibrutinib, as they developed after roughly two-and-a-half weeks of use and he was on no other concurrent or prior medications that might have caused these endocrine side effects.

We can refute the possibility that the initial thyroid dysfunction noted on admission was illness related (euthyroid sick syndrome), as the patient continued to require levothyroxine after discharge to maintain normal T4 and TSH levels. A repeat cosyntropin test (after holding the evening dose of hydrocortisone) was not performed in an outpatient setting to demonstrate persistent cortisol deficit. The patient has been continued on both levothyroxine and hydrocortisone since discharge with no dose adjustments and has been doing well.

This case illustrates endocrine-related side effects of ibrutinib, namely secondary adrenal insufficiency and central hypothyroidism. Although an association between TKIs and TSH and parathyroid hormone elevation has been established, the etiology behind these associations has not been elucidated. Multiple mechanisms for thyroid dysfunction have been postulated, including direct toxicity of TKI on follicular cells, induction of destructive thyroiditis, increased hormone clearance, thyroid capillary regression by vascular endothelial growth factor receptor (VEGFR) inhibition, and impaired iodide uptake.[14] Interestingly, a study by Lechner et al showed that new hypothyroidism in cancer patients treated with TKIs is associated with improved overall survival and, therefore, should not necessitate TKI dose reduction or discontinuation.[15] Understanding the clinical significance of thyroid dysfunction and with TKI therapy is important because it may alter decisions regarding discontinuation or dose reduction.

CONCLUSION

A paucity of literature reports the correlation of endocrinological adverse outcomes specifically with ibrutinib. As the use of ibrutinib continues to rise, early recognition of such potential side effects is important to prevent delays in prompt treatment and will help reduce morbidity and mortality in these patients. This report underscores the need for a retrospective study to determine the prevalence of endocrinological side effects of ibrutinib. Adverse effects like adrenal insufficiency can be potentially fatal if left untreated. Cases like these bring awareness about dangerous side effects of TKIs and help clinicians understand the association between the two, thereby reducing unnecessary testing and facilitating prompt management when such cases arise.

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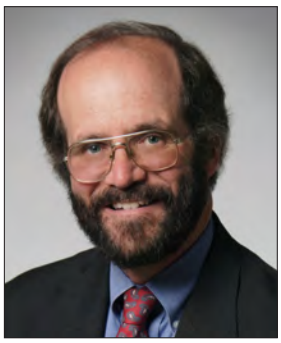

Robert N. Golden, MD

Jonathan Temte, MD, PhD

It's Not Enough

Jonathan Temte, MD, PhD; Robert N. Golden, MD

As 2020 dawned, we were greeted with fair skies and unseasonably warm (18° F) temperatures across southern Wisconsin,[1] along with the promise of a new year. According to the Chinese Zodiac, it was to be the Year of the Rat. In traditional Chinese culture, rats are seen as a sign of wealth and surplus. Due to their high reproduction rate, married couples pray to them for children. Little did we know or suspect, however, that this high reproductive rate would apply to a novel virus.

A Brief History

The first documented case of SARS-CoV-2 in the United States was recorded in Washington state on January 19, 2020.[2] Seventeen days later, Wisconsin reported its first case—arriving by airline from Beijing—on February 5. By late February, non-travel-related, person-to-person transmission had been confirmed in the United States.[3] In response to rising cases in Wisconsin, Governor Tony Evers issued Executive Order #72, declaring a public health emergency on March 12, followed the next day by a mandate for closure of all public and private schools in Wisconsin no later than March 18.[4] At that time, Wisconsin had recorded 10 cases. In addition, on March 13, University of Wisconsin (UW) System President Ray Cross announced that in-person instruction would not resume after spring break to help protect the health and safety of UW students, their families, UW employees, and communities.[5]

On March 25, Governor Evers issued the "Safer at Home" order with a planned expiration on April 25. Due to a growing case burden, on April 16 this order was extended to May 26, prompting the Wisconsin Legislature to file legal action against the "Safer at Home" order in the Wisconsin Supreme Court on April 21. In a 4-3 ruling on May 13, the Court blocked the "Safer at Home" extension, essentially lifting caps on the size of gatherings, allowing people to travel as they please, and businesses—including bars and restaurants— to reopen.[6]

As of December 21, 2020, Wisconsin has accumulated 457,177 cases and nearly 4,417 deaths.[7] Our state is currently ranked 11th in terms of cases across the United States. Looking back across 10 months at the cumulative curve of SARS-CoV-2 cases, one sees a perfect example of exponential growth, with occasional deviations. One can pick out the end of "Safer at Home" and Memorial Day weekend, as well as the Fourth of July holiday, as "flash points" fueling accelerated growth. In general, however, Wisconsin has experienced a persistent doubling of cases every 16.3 days.

> With the advent of highly effective vaccines, multiple therapeutics, and a plethora of testing modalities, we now find cause for hope. But no single intervention is going to save us or return us to normalcy.

What Have We Done to Combat This?

The UW School of Medicine and Public Health has been at the forefront in fighting SARS-CoV-2. On January 29, during a seminar slot made available by the sudden cancellation of a planned visit by Centers for Disease Control and Prevention (CDC) Director Robert Redfield, MD, we brought together eight experts from across the school and campus for one of the nation's first symposia on the novel coronavirus. From early on, our faculty and graduates have taken leadership and consultative roles in

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the Wisconsin Department of Health Services, UW-System, UW-Madison campus, and UW Health, as well as with national vaccine advisory committees. But, it's not been enough. Our physicians and their teams have placed themselves in harm's way to provide vital and innovative patient care. Our researchers have been on the cutting edge of developing care pathways, recommending infection control practices, evaluating therapeutics, and testing candidate vaccines. But, it's not been enough. Our public health faculty have contributed to modeling the outbreak, highlighting health disparities, and advising best practices. Across our school and through collaborative efforts with other partners, we have provided countless hours of teaching, media interviews, and outreach—all aimed at encouraging the statewide adoption of public health mitigation strategies. But, it's not been enough.

A testament to Wisconsin's heritage, the "Swiss cheese" model of SARS-CoV-2 mitigation efforts has emerged as a useful metaphor.[8] The model shows how multiple layers of protection—even though each layer has "holes"—reduce disease transmission. The composite of multiple interventions is necessary. Applied a different way, however, every single COVID-19 death is a failure of our tertiary health care system, our therapeutics, and our supportive care. Every hospitalization reflects the limitations of our primary care system, our inconsistent access to care, and our lack of health equity. Every single new case is a failure of our public health infrastructure, our lack of adequate testing and contact tracing, and our lack of community outreach and engagement. And even if we had it all, it would not be enough. Every single case, every hospitalization, and every death is the direct consequence of an initial acquisition of SARS-CoV-2 virus from another person.

It's On Us

With the advent of highly effective vaccines, multiple therapeutics, and a plethora of testing modalities, we now find cause for hope. But no single intervention is going to save us or return us to normalcy. In his assessment of the 1918 influenza pandemic, historian Alfred Crosby wrote:

"Studying the record of the American people in 1918 and 1919 is like standing on a high hill and watching a fleet of many vessels sailing across a current of terrible power to which the sailors pay little attention. They grip their tillers firmly, peer at their compasses, and hold faithfully to courses, which, from their vantage, seem to be straight, but we can see that the secret current is sweeping them far downstream. The immense flow swamps many of the ships, and their sailors drown, but the others take little notice. The others are intent on maintaining their own unwavering courses."[9]

The words of a 74-year-old, semiretired family doctor from a small town in South Dakota could not be more profound at this time.[10] Dr Tom Dean is one of three physicians in the county where he has devoted his career. He has experienced the devastation of the pandemic, recently losing both parents at the nursing home that he directs:

"My parents lived a good life, and they were at the end of their road. They got married 76 years ago during World War II once they'd finally saved up enough of their sugar rations to bake a proper wedding cake. They loved telling that story. Everybody was sacrificing for the war. It was a national effort. They were proud of it. The country had bigger problems, and their wedding cake could wait.

"How can we get back to that? What happened to us? My hope now that this election is over is maybe we can take a break from tearing each other apart. The virus is still raging, and there's no magic solution. It doesn't just go away unless we stop it."

From nearly the beginning of this pandemic, the secret to transiting and surviving COVID-19 has been known and repeatedly made available to everyone. The secret involves the oft-repeated mantra of distancing, masking, maintaining hand hygiene, staying home while ill, isolating if infected, and quarantining if exposed. We all know this. But, it's not enough. ***It's on each of us to live this.***

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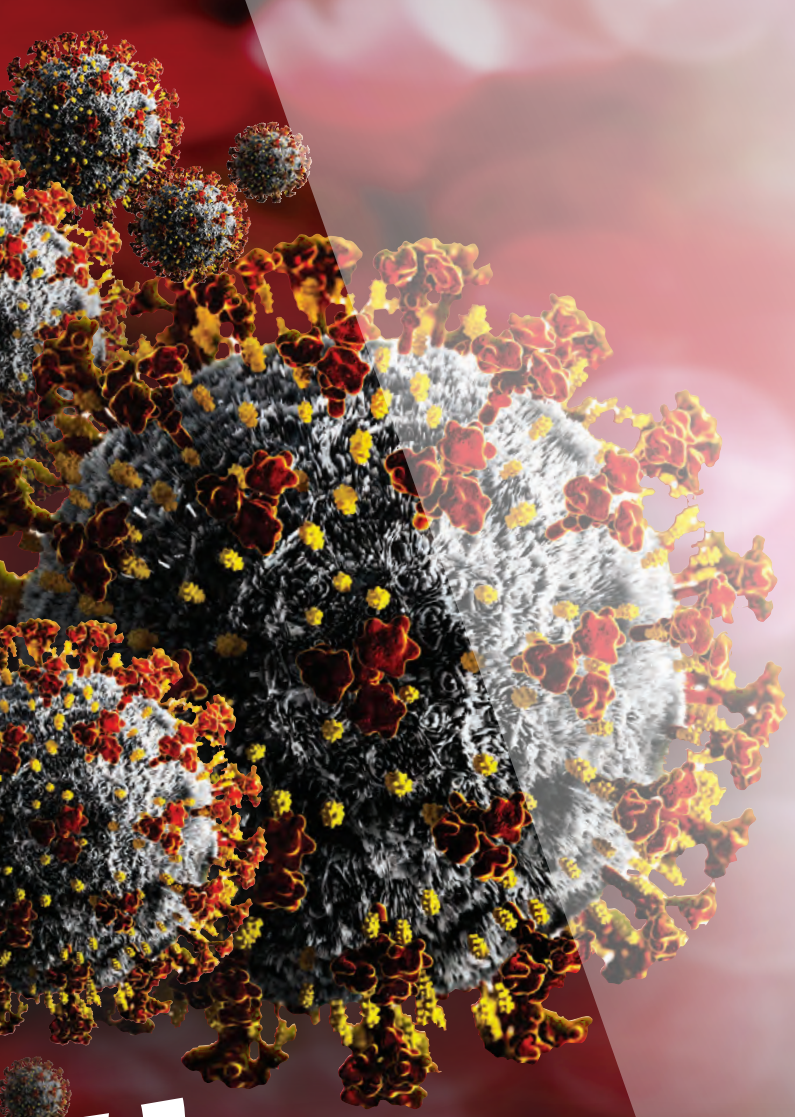

Keep up with the challenges facing good medicine...

the new normal

What if a patient claims they got COVID-19 from our office?

What do we do if a doctor or staff member tests positive?

Where do I find out if I have immunity from COVID-19 claims?

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What do you do to help burned out physicians?

How do we keep our practice safe?

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